Bijlage 8 Evidence tabellen en GRADE Profielen

Richtlijnen palliatieve zorg voor kinderen

1 ORGANISATIE VAN ZORG

Inhoudsopgave

1 Uitgangsvragen

Zie: Appendix – interactieve werkconferentie organisatie van zorg voor meer informatie over de totstandkoming van de uitgangsvragen.

Vraag 1: Wat is de rol van de huisarts en hoe kan deze het best voor continuïteit van zorg, in de 4 domeinen (lichamelijk, sociaal, psychologische en spiritueel) inclusief nazorg – in de thuissituatie zorgen?

Vraag 2: Hoe kunnen we de continuïteit van zorg inclusief nazorg bij de overdracht van het ziekenhuis naar thuis, hospice of instelling verbeteren in de vier domeinen?

Vraag 3: Hoe zorgen we ervoor, dat anticiperende zorgplanning vanuit het ouder- en kindperspectief standaard wordt in de kinderpalliatieve zorg? (d.w.z. zorgplanning die rekening houdt met symptomen en situaties die zich kunnen voordoen).

Vraag 4: Hoe kunnen we de coördinatie van zorg zo organiseren, dat ouders en kind zoveel mogelijk worden ontlast met behoud van regie?

Vraag 5: Op welke wijze kan een casemanager het beste worden ingezet?

Vraag 6: Wat zijn de belangrijkste drie onderdelen van de module kinderpalliatieve zorg in de opleiding van toekomstige zorgverleners?

Vraag 7: Wat is de grootste hindernis om ons werk kwalitatief goed te kunnen doen, die we zelf kunnen verminderen of helemaal uit de weg ruimen, en hoe doe we dat?

2 Resultaten van het literatuuronderzoek

Jaar	Bibliografie	Studie karakteristieken
1: Wat is de rol van de huisarts en hoe kan deze het best voor continuïteit van zorg, in de 4 domeinen (lichamelijk, sociaal, psychologische en spiritueel) inclusief nazorg – in de thuissituatie zorgen?* **2:** Hoe kunnen we de continuïteit van zorg inclusief nazorg bij de overdracht van het ziekenhuis naar thuis, hospice of instelling verbeteren in de vier domeinen?* **3:** Hoe zorgen we ervoor, dat anticiperende zorgplanning vanuit het ouder- en kindperspectief standaard wordt in de kinderpalliatieve zorg? (d.w.z. zorgplanning die rekening houdt met symptomen en situaties die zich kunnen voordoen). * **4:** Hoe kunnen we de coördinatie van zorg zo organiseren, dat ouders en kind zoveel mogelijk worden ontlast met behoud van regie? * **5:** Op welke wijze kan een casemanager het beste worden ingezet?* **6:** Wat zijn de belangrijkste drie onderdelen van de module kinderpalliatieve zorg in de opleiding van toekomstige zorgverleners?* **7:** Wat is de grootste hindernis om ons werk kwalitatief goed te kunnen doen, die we zelf kunnen verminderen of helemaal uit de weg ruimen, en hoe doen we dat?*		
Geen literatuur beschikbaar		

*Systematisch gezocht naar effectiviteit van interventies over organisatie van zorg, zie: bijlage 7 zoekverantwoording–search 1

3 Evidence tabellen

Niet van toepassing. Uit de systematische zoekstrategie resulteerden geen gerandomiseerde studies over organisatie van zorg.

4 Samenvatting en gradering van bewijs

Niet van toepassing. Uit de systematische zoekstrategie resulteerden geen gerandomiseerde studies over organisatie van zorg.
Om antwoord te geven op de vragen, bovenstaande vragen is een ideafactory georganiseerd.

5 Aanbevelingen uit richtlijnen

Table 1 Assessment of concordance and discordance between existing guidelines for organization of pediatric palliative care

	Richtlijn palliatieve zorg voor kinderen 2013	National Institute for Health Care Excellence	National Coalition for Hospice and Palliative Care (aanbevelingen voor volwassenen en kinderen)	Concordance/discordance
Recommendations on teams of professionals providing pediatric palliative care				
Multidisciplinary teams				
- Provision of care through multidisciplinary team	Yes	Yes	Yes	Concordance
- Identified members of a multidisciplinary team	eindverantwoordelijke hoofdbehandelaar; coördinerend verpleegkundige evt. aanvullende leden: Huisarts AVG; kinderarts, kinderthuiszorg, fysiotherapeut, logopediste, ergotherapeut, diëtiste, maatschappelijk werker, psycholoog, rouwtherapeut, leerkracht, ambulant begeleider, geestelijk verzorg	healthcare professionals from primary, secondary or tertiary services (including specialists in the child's, condition, hospice professionals and members of the specialist palliative care team); social care practitioners; education professionals; chaplains; allied health professionals (for example physiotherapists)	Physicians; nurses; advanced practice providers; social workers; chaplains; clinical pharmacists; other professionals to meet the needs of the patients.	Concordance
- Members of the team can change dependent on the needs of the patient	Not specified	Yes	Yes	Discordance
- Lead clinician coordinating care	Yes, hoofdbehandelaar	Yes, a named medical specialist	Not specified	Discordance
- First point of contact	Yes, coördinerend verpleegkundige	Yes, a named member of the multidisciplinary team	Not specified	Discordance
- Involvement of parents in multidisciplinary team meetings	Not specified	Yes, if appropriate	Not specified	Discordance
Specialist palliative care teams				
- Presence of a specialist palliative care team	Not specified	Yes, involve when child has unresolved distressing symptoms	Yes	Discordance
- Identified members of a specialist palliative care team	Not specified	a paediatric palliative care consultant; a nurse with expertise in paediatric palliative care; a	A palliative care specialty team includes a certified palliative care specialist. The setting of care or	Discordance

		pharmacist with expertise in specialist paediatric palliative care experts in child and family support who have experience in end of life care	reimbursement may further dictate which clinician must be certified.	
Recommendations on provision of pediatric palliative care				
24-hour care	Yes Hoofdbehandelaar en coördinerend verpleegkundige zijn 24 uur per dag bereikbaar	Yes Advice from a consultant in pediatic palliative care by telephone; Pediatric nursing care	Yes Family has access to palliative care staff 24 hours a day, seven days a week by phone	Concordance
Use of Palliative care plan	Yes Hoofdbehandelaar bespreekt regelmatig en in alle beslissende fase het zorgplan met kind en/of ouders	Yes	Yes, The team facilitates the implementation and ongoing refinement of the palliative care plan	Concordance
(Rapid) Transfer to preferred place of death	Not specified	Yes; update advance care plan with: intended changes to care; care plans that cover (final hours of life; what happens when child lives longer then expected; family support after death of child; care of the child's body); involved responsible professionals; professionals that help with arrangements after death	Not specified	Discordance
Recommendations on care settings				
- *Discussion of preferred place of care/death*	Not specified	Yes, children and young people and their parents or carers, provide information about: the various care settings (for example home, hospice or hospital care); the care and support available in each setting practical and safety issues.	Yes, care is provided in the setting preferred by the patient and family, if feasible or the team helps the patient and family select an alternative setting.	Discordance
- *Information about practical considerations such as home adaptations*	Not specified	Yes, If the child or young person and their parents or carers prefer	The IDT shares information and resources regarding palliative care	Discordance

		care at home, take into account and discuss the practical considerations with them	with clinicians and other professionals involved in the patient's plan of care.	
- *Services/providers should be able to support parenteral drug administration (opioids)*	Not specified	Yes, Services for children and young people who are approaching the end of life and are being cared for at home should be able to support parenteral drug administration (for example continuous subcutaneous opioid or anticonvulsant infusions).	Yes, Providers in all settings address the unique needs of children, whether they are patients, family members, or visitors	Discordance
Recommendations on continuity of care/care transitions				
Medical Patient file which is accessible by health professionals, parents and patients	Yes, dossier met een zorgplan en informative over alle dimensies van zorg	Not specified	No All taken steps should be well documentated, especially in case of transition in care.	Discordance
Recommendations on education				
Development of learning modules	Yes, symptoombestrijding, voeding, PAZO richtlijn, communicatie, eindigheid en sterven, zorgcoördinatie, mogelijkheden van respijtzorg, sociale kaart, zorg voor de zorgenden, kinderhospices, rouwbegeleiding, palliatieve zorg voor verstandelijk beperkte kinderen	Not specified	Yes, All palliative care clinicians receive training regarding the use of opioids, including: Safe and appropriate use of opioids; Risk assessment for opioid substance use disorder; Monitoring for signs of opioid abuse and diversion; Managing pain for patients at risk for substance abuse; Safe disposal of opioids in home and community settings	Discordance

2 ADVANCE CARE PLANNING EN GEZAMENLIJKE BESLUITVORMING

Inhoudsopgave

1 Uitgangsvragen

1.1 Effectiviteit van ACP interventies

Vraag 1: Wat is het effect van advance care planning (ACP) bij kinderen tussen 0 en 18 jaar in de palliatieve fase en hun familie/verzorgers op besluitvorming en kwaliteit van leven?

P: Kinderen in de palliatieve fase tussen 0 en 18 jaar
Familie/verzorgers van kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Advance Care Planning
C: Geen interventie/standaard zorg
O: Effect op besluitvorming en kwaliteit van leven

1.2 Belemmerende en bevorderende factoren van ACP en gezamenlijke besluitvorming

Vraag 2: Wat zijn de bevorderende en belemmerende factoren voor Advance Care Planning en gezamenlijke besluitvorming in de palliatieve fase bij kinderen tussen 0 en 18 jaar, familie/verzorgers en het multidisciplinaire team ?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
Familie/verzorgers van kinderen tussen 0 en 18 jaar in de palliatieve fase
Multidisciplinaire zorgteam van kinderen tussen 0 en 18 jaar in de palliatieve fase
I: (1) Advance Care Planning, het ontwikkelen, beoordelen en evalueren van een gepersonaliseerd parallel zorgplan. (2) Gezamenlijke besluitvorming
C: -
O: Belemmerende en bevorderende factoren

2 Resultaten van het literatuuronderzoek

Jaar	Bibliografie	Studie karakteristieken
1: Wat is het effect van ACP op besluitvorming en kwaliteit van leven?*		
2016	***National Institute for Health and Care Excellence (NICE).*** End of life care for infants, children and young people with life-limiting conditions: planning and management. 2016	Richtlijn kinderen
2010	***Lyon ME et al.*** Is it safe? Talking to teens with HIV/AIDS about death and dying: a 3-month evaluation of Family Centered Advance Care (FACE) planning - anxiety, depression, quality of life. HIV/AIDS Research and Palliative Care. 2010;2:27-37.	RCT kinderen
2017	***Lyon ME et al.*** A randomized clinical trial of adolescents with HIV/AIDS: pediatric advance care planning. AIDS Care. 2017;29(10):1287-96.	RCT kinderen
2013	***Lyon ME et al.*** Family-centered advance care planning for teens with cancer. Jama, Pediatr. 2013;167(5):460-7.	RCT kinderen
2014	***Lyon ME et al.*** A longitudinal, randomized, controlled trial of advance care planning for teens with cancer: anxiety, depression, quality of life, advance directives, spirituality. J Adolesc Health. 2014;54(6):710-7	RCT kinderen
2: Wat zijn de belemmerende en bevorderende factoren voor kinderen tussen 0 en 18 jaar, familie/verzorgers en het multidisciplinaire team bij gezamenlijke besluitvorming (o.a. ACP) in de palliatieve fase?**		
2016	***National Institute for Health and Care Excellence (NICE).*** End of life care for infants, children and young people with life-limiting conditions: planning and management. 2016	Richtlijn kinderen
2017	***Cicero-Oneto et al.*** Decision-making on therapeutic futility in Mexican adolescents with cancer: a qualitative study. BMC Med Ethics 2017;18:74.	Kwalitatieve studie SDM
2018	***Day et al.*** "We just follow the patients' lead": Healthcare professional perspectives on the involvement of teenagers with cancer in decision making. Paediatric Blood Cancer 2018;65.	Kwalitatieve studie SDM
2017	***Henderson et al.*** Preparing Pediatric Healthcare Professionals for End-of-Life Care Discussions: An Exploratory Study. J Palliat Med 2017;20:662-6.	Kwalitatieve studie SDM
2017	***Kelly et al.*** Identifying a conceptual shift in child and adolescent-reported treatment decision making: "Having a say, as I need at this time". Pediatr Blood Cancer 2017;64.	Kwalitatieve studie SDM
2020	***Mekelenkamp et al.*** Parental experiences in end-of-life decision-making in allogeneic pediatric stem cell transplantation: "Have I been a good parent?". Pediatr Blood Cancer 2020;67:e28229.	Kwalitatieve studie SDM
2018	***Murrell et al.*** Identifying Opportunities to Provide Family-centered Care for Families With Children With Type 1 Spinal Muscular Atrophy. J Pediatr Nurs 2018;43:111-9.	Kwalitatieve studie SDM
2019	***Sasazuki et al.*** Decision-making dilemmas of paediatricians: a qualitative study in Japan. BMJ Open 2019;9:e026579.	Kwalitatieve studie SDM
2020	***Sisk et al.*** Communication in Pediatric Oncology: A Qualitative Study. Pediatrics 2020;146:e20201193.	Kwalitatieve studie SDM
2018	***Superdock et al.*** Exploring the vagueness of Religion & Spirituality in complex paediatric decision-making: a qualitative study. BMC Palliat Care 2018;17:107.	Kwalitatieve studie SDM
2016	***Zaal-Schuller et al.*** How parents and physicians experience end-of-life decision-making for children with profound intellectual and multiple disabilities. Res Dev Disabil 2016;59:283-93.	Kwalitatieve studie SDM
2017	***Beecham et al.*** Keeping all options open: Parents' approaches to advance care planning. Health Expect 2017;20:75-684.	Kwalitatieve studie ACP
2020	***Edwards et al.*** Decisions for long-term ventilation for children: perspectives of family members. Ann Am Thorac Soc 2020;17:72-80.	Kwalitatieve studie ACP
2017	***Edwards et al.*** Decisions around Long-term Ventilation for Children. Perspectives of Directors of Pediatric Home Ventilation Programs. Ann Am Thorac Soc 2017;14:1539-47.	Kwalitatieve studie ACP
2021	***Fahner et al.*** Evaluation showed that stakeholders valued the support provided by the Implementing Pediatric Advance Care Planning Toolkit. Acta Paediatr 2021;110:237-46.	Kwalitatieve studie ACP
2020	***Fahner et al.*** Towards advance care planning in pediatrics: a qualitative study on envisioning the future as parents of a seriously ill child. Eur J Pediatr 2020;17:1461-68.	Kwalitatieve studie ACP
2017	***Odeniyi et al.*** Communication Challenges of Oncologists and Intensivists Caring for Pediatric Oncology Patients: A Qualitative Study. J Pain Symptom Manage 2017;54:909-15.	Kwalitatieve studie ACP
2020	***Hein et al.*** Identifying key elements for paediatric advance care planning with parents, healthcare providers and stakeholders: A qualitative study. Palliat Med 2020;34:300-8.	Kwalitatieve studie ACP
2018	***Jack et al.*** A qualitative study of health care professionals' views and experiences of paediatric advance care planning. BMC Palliat Care 2018;17:93.	Kwalitatieve studie ACP
2020	***Lord et al.*** Assessment of Bereaved Caregiver Experiences of Advance Care Planning for Children With Medical Complexity. JAMA Netw Open 2020;3:e2010337.	Kwalitatieve studie ACP
2017	***Lotz et al.*** "Hope for the best, prepare for the worst": A qualitative interview study on parents' needs and fears in paediatric advance care planning. Palliat Med 2017;31:764-71.	Kwalitatieve studie ACP

2019	***Mitchell et al.*** Parental experiences of end of life care decision-making for children with life-limiting conditions in the paediatric intensive care unit: a qualitative interview study. BMJ Open 2019;9:e028548.	Kwalitatieve studie ACP
2020	***Orkin et al.*** Toward an Understanding of Advance Care Planning in Children With Medical Complexity. Pediatrics 2020;145:e20192241.	Kwalitatieve studie ACP

*Systematisch gezocht, zie: bijlage 7 zoekverantwoording – search 1
**Systematisch gezocht, zie: bijlage 7 zoekverantwoording – search 2

3 Evidence tabellen

3.1 Effectiviteit van ACP interventies

Effectivity of Advance Care Planning Interventions				
Lyon ME et al. Is it safe? Talking to teens with HIV/AIDS about death and dying: a 3-month evaluation of Family Centered Advance Care (FACE) planning - anxiety, depression, quality of life. HIV/AIDS Research and Palliative Care. 2010;2:27-37.				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: 2-armed, randomized controlled clinical trial Setting: 2 hospital-based outpatient clinics, USA Duration: 3-month follow-up Study years: 2006-2008 Protocol published in register: Protocol of the trial has been registered at www.clinicaltrials.gov	Number and type of participants: *(diagnosis)* • Intervention group: 20 HIV-infected adolescents and 20 adult surrogates • Control group: 18 HIV-infected adolescents and 18 adult surrogates Age (adolescents) – 3-month post intervention: • Intervention group: Mean (SD): 16.65 (2.11), Range: 14-21 yr. • Control group: Mean(SD): 16.58 (2.38), Range: 14-21 yr. Sex (adolescents) – 3-month post intervention: • Intervention group: M:8 (40%). F: 12 (60%)	Type of intervention: Three weekly 60-90 minute sessions in family format. Session 1- Lyon Advance Care Planning Adolescent and Surrogate Versions Session 2 - The Respecting Choices Interview Session 3 - Completion of The Five Wishes Type of control: Three weekly 60-90 minute sessions in family format. Session 1- Developmental History. Session 2 - Safety Tips Session 3- School and Career Planning interview	Outcome measures: **Completion of legal document with treatment preferences:** Completed legal five-wishes document that facilitates the expression of treatment preferences. **Decision to stop extraordinary treatment:** Adolescent state in the Statement of Treatment Preferences, a document in which treatment preferences of patients and their surrogates are specified. The SoTP documents states what the adolescent/family would want in three situations: 1. Situation 1 – long hospitalization: If I have serious complications from AIDS, such as an overwhelming infection or pneumonia, so that I was facing a long hospital stay, with many medical treatments AND my chance of living through this complication is low (for example, only 5 out of 100 kids will live), I would choose the following: (Whatever my choice, I want to be kept as comfortable as possible). 2. Situation 2 – functional impairment: If I have AIDS and a serious complication, such as an overwhelming infection or pneumonia and have a good chance of living through this complication, but it was expected that I would never be able to walk or talk again, and I would need 24 hour nursing care, I would choose the following. (Whatever my choice, I want to be kept as comfortable as possible) 3. Situation 3 – mental impairment: If I have AIDS and a serious complication, such as an overwhelming infection or pneumonia and have a good chance of living, but it was expected that I would never know who I was or who I was with and would need 24 hour nursing care, I would choose the following. (Whatever my choice, I want to be kept as comfortable as possible). Patients and surrogates chose one of the three options. • continue all treatment to keep me alive as long as possible • to stop all efforts to keep me alive; • don't know. **Anxiety:** Prevalence of anxiety among patients and surrogates. Prevalence was measured using Beck Anxiety Index (BAI) , score ranging from 0 to 63, higher scores represent higher symptom level. Score of 0 to 7 is minimal anxiety. **Depression:** Prevalence of depression among patients and surrogates. Prevalence was measured using) Beck depression Inventory-II (BDI-II). Range of scores was 0-63; a score of 0-13 equals minimal depression. **Quality of life:** Quality of life of adolescents and surrogate perception of adolescent quality of life. This was measured by using 23-item questionnaire: The paediatric Quality of life inventory Results (per outcome) **Completion of legal document with treatment preferences at 3 month follow-up (intervention vs. control):**	Strengths: Limitations: **Risk of bias** A. Selection bias: Unclear Reason: Dyads were randomly assigned to one of the gropes using permuted block design. Allocation concealment was not reported B. Attrition bias: low risk Reason: Loss to follow-up was less than 90% in both intervention and control group. In case, of follow-up or drop-out the reason was mentioned. C. Performance bias High risk Reason: Personnel and participants were not blinded D. Detection bias Unclear

	• Control group: M: 7 (39%) F: 11 (61%)		90% (N= 19) vs. 11% (n = 2), (p<0.001) SoTP at 3-month follow-up **Decision to stop extraordinary treatment at 3 month follow-up (intervention vs control)** Percentage of dyads (adolescents and adult surrogates) that decided to stop treatment 'stop all efforts to keep me alive'. Situation 1 - Long hospitalization: 15% (n = 3) vs 6% (n = 1), p = 0.187 Situation 2 - Functional impairment: 25% (n = 5) vs 28 % (28%), p = 1.000 Situation 3 - Mental impairment: 30% (n = 6) vs 17% (n- = 3), p = 0,528). Majority chose to continue all treatment. **Anxiety** Mean anxiety scores at baseline (intervention vs control) *Adolescents:* 2.76 (95%CI 1.38–4.60) vs 1.38 (95%CI 0.44–2.84), p = 0.170 *Adult surrogates:* 1.64 (95%CI 0.62–3.14) vs 2.51 (95%CI 1.14–4.41), p = 0.*394* Mean anxiety scores at 3-month follow-up (intervention vs control) *Adolescents:* 2.48 (95%CI 1.14–4.34) vs 1.06 (95%CI 0.24–2.45), p =0.149 *Adult surrogates:* 2.48 (95%CI 1.20–4.22) 2.35 (95%CI 1.06–4.15), p = 0.901 **Depression** Mean depression scores at baseline (intervention vs control) *Adolescents:* 7.8 (95%CI 4.73–11.69) vs 1.27 (95%CI 0.22–3.17), p = 0.001 *Adult surrogates:* 2.0 (95%CI 0.66–4.09) vs 3.65 (95%CI 1.62–6.50), p = 0.261 Mean depression scores at 3-month follow-up (intervention vs control) *Adolescents:* 5.06 (95%CI 2.57–8.39) vs 3.43 (95%CI 1.35–6.45), p = 0.432 *Adult surrogates:* 2.73 (95%CI 1.26–4.77) vs 3.29 (95%CI 1.57–5.65), p = 0.676 **Mean Quality of Life scores at 3-month follow-up (Intervention vs. control):** Total: *Adolescents:* 338.5 (95%CI 321-355) vs. 345.6 (95%CI 327.3-363.1), p = 0.568 *Surrogate perception of adolescent quality of life:* 324.8 (95%CI 308.4-340.4) vs. 349.3 (95%CI 333.4-364.6), **p = 0.032** Physical: *Adolescents:* 93.1 (95%CI 89.4–96.6) vs 93.8 (95%CI 91.3–96.3), p = 0.692 *Surrogate perception of adolescent quality of life:* 92.3 (95%CI 89.3–95.1) vs 93.0 (95%CI 89.7–96.1), p = 0.692 School: *Adolescents:* 75.0 (95%CI 68.4–82.0) vs 77.7 (95%CI 70.7–85.2), p = 0.589 *Surrogate perception of adolescent quality of life:* 66.9 (95%CI 60.0–74.1) vs 80.0 (95%CI 72.1–88.3), **p = 0.018** Emotion: *Adolescents:* 82.0 (95%CI 74.8–88.6) vs 82.5 (95%CI 74.4–90.0), p = 0.921 *Surrogate perception of adolescent quality of life:* 74.8 (95%CI 67.2–81.6) vs 85.7 (95%CI 78.9–92.0), **p = 0.029** Social: *Adolescents:* 90.3 (95%CI 86.5–93.9) vs 92.0 (95%CI 88.6–95.2), p = 0.297 *Surrogate perception of adolescent quality of life:* 91.0 (95%CI 88.0–93.8) vs 92.7 (95%CI 89.2–95.9), p = 0.297	Reason: Blinding of outcome assessors was not reported in the article

Effectivity of Advance Care Planning Interventions				
Lyon ME et al. A randomized clinical trial of adolescents with HIV/AIDS: pediatric advance care planning. AIDS Care. 2017;29(10):1287-96.				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: Longitudinal, single-blinded, multi-site randomized controlled trial. Setting: 6 pediatric hospital-based HIV-clinics, located in high HIV mortality cities, USA Duration: Outcome was assessed uring treatment, session 2 and at 3 month follow-up Study years: *July 2010 – June 2014* Protocol published in register: Not reported	Number and type of participants: • Intervention group: 54 adolescents with HIV/AIDS and their surrogates or families • Control group: 51 adolescents with HIV/AIDS and their surrogates or families Baseline characteristics are only measured for adolescents. Age (adolescents): • Intervention group: Mean (SD): 17,9 (1,88), Range: 14-21 yr. • Control group: Mean(SD): 17,7 (1,99), Range: 14-21 yr. Sex (adolescents): • Intervention group: M: 29 (53,7%). F: 25 (46,3%) • Control group: M: 26 (51,0%). F: 25 (49,0%) No significant differences existed between intervention	Type of intervention: Three sixty minute sessions scheduled one week apart. *Session 1 - Lyon Family Centered ACP Survey:* Assessment of values, beliefs, and life experiences with illness and EOL care. *Session 2 - Respecting Choices:* A facilitated pACP conversation with the adolescent and family about the medical condition, complications, fears, hopes and experiences. SoTP is used to encourage dialogue about goals and values. *Session 3 – five wishes:* A legal advanced directive document was placed in the medical record. Type of control: *Session 1 - developmental history:* Structured interview on the developmental history of the adolescent. *Session 2- Safety tips:* Counselling on safety information for the adolescent and family such as using a seat belt and having a smoke detector at home. *Session 3 - Nutrition and exercise*: Counselling on nutrition and exercise	Outcome definitions **Congruence in EOL treatment preferences** Treatment preferences were determined in the Statement of Preference (SoTP). This document was used both intervention and control group immediately following the pACP conversation in week 2 and 3 months post-intervention. The SoTP documents what the adolescent/family would want in three situations 1. Long hospitalization with many procedures and low survival 2. Functional impairment, never able to walk and talk 3. Mental impairment, never knowing who you are There were three answer options for each situation: • continue all treatment to keep me alive as long as possible • to stop all efforts to keep me alive; • don't know. **Agreement to give family leeway** Adolescents were asked if they wished to grant their family leeway: 'strictly follow my wishes' or 'do what the family thinks is best at the time. Results (per outcome) PABAK (prevalence Adjusted bias adjusted kappa) was used to assess adolescent/family congruence in EOL treatment preferences (see 3 answer options) by situation (see 3 situations). 0: no agreement 0-0.19: slight agreement 0.2-0.39: fair agreement 0.4-0.59: moderate agreement 0.6-0.79: substantial agreement 0.8-1: almost perfect agreement **Congruence in EOL treatment preferences post-session 2** • Situation 1: Intervention: PABAK = 0.688, Control: PABAK = 0.335, • Situation 2: Intervention = PABAK = 0.687, Control: PABAK = 0.029 • Situation 3: Intervention = PABAK = 0.717, Control: PABAK = 0.341 Congruence in EOL treatment preferences was substantial (PABAK was approximately 0.70) among pACP dyads for all three disease-specific situations immediately post-intervention and negligible among control dyads. **Congruence in EOL treatment preferences at 3 month follow-up** • Situation 1: Intervention = PABAK =0.599, Control: PABAK = 0.34 • Situation 2: Intervention = PABAK = 0.318, Control: PABAK = 0.031 • Situation 3: Intervention = PABAK = 0.419, Control: PABAK = 0.328 Though the congruence level decreased 3-months post intervention, PABAK values still remained at moderate level (40< = PABAK < 60) for the high burden and mental	Strengths: Randomization minimized the risk of selection bias SoTP is a useful tool for stimulating adolescent to engage in conversations Limitations: Selection bias may exist with those enrolled in the study likely representing individuals most comfortable discussing HIV and pACP.. Sample size was too small to identify any patterns in the change in congruence over time. The black and white p ACP choices on the SoTP do not reflect the more nuanced choices. **Risk of bias** A. Selection bias: Unclear Reason: Unclear how dyads were randomized and whether allocation was blinded B. Attrition bias: High risk

	and control adolescents. '		impairment situations, while it was fair (PABAK = 0.32) for the functional impairment situation. In contrast, congruence among control dyads was fair for the high burden and mental impairment situations (PABAK < 0.35) immediately post-intervention, and remained at the same level three months later. There was almost no congruence (PABAK was about 0.03) among the control dyads for the functional impairment situation at both time points. **Agreement per answer option (Intervention vs control):** **<u>Post-Session 2</u>** • Situation 1 – long hospitalization Total agreement: N(%): 38 (79.2%) vs 25 (55.5%) o 'continue treatment: N(%): 28 (58.3%) vs 24 (53.3%) o 'discontinue treatment': N(%): 7(14.6%) vs 0 (0%), p = 0.013 o 'don't know': N(%):3 (6.3%) vs 1 (2.2%) • Situation 2 – functional impairment Total agreement: N(%): 38 (79.2%) vs 16 (35.5%) o 'continue treatment: N(%): 30 (62.5%) vs 10 (22.2%) o 'discontinue treatment': N(%): 6 (12.5%) vs 2 (4.4%), p = 0.269 o 'don't know': N(%):2 (4.2) vs 4 (8.9%) • Situation 3 – mental impairment Total agreement: N(%): 39 (81.2%) vs 25 (55.5%) o 'continue treatment: N(%): 24 (50.0%) vs 19 (42.2%) o 'discontinue treatment': N(%): 11 (22.9%) vs 2 (4.4%), p = 0.015 o 'don't know': N(%):4 (8.3) vs 4 (8.9%) **Agreement per answer option (Intervention vs control):** **<u>3 month follow-up</u>** • Situation 1 – long hospitalization Total agreement: N(%): 29 (70.8%) vs 22 (53.7%) o 'continue treatment: N(%): 25 (61%) vs 20 (48.8%) o 'discontinue treatment': N(%): 4(8.9%) vs 0 (0%) o 'don't know': N(%):0 (0%) vs 2 (4.9%) • Situation 2 – functional impairment Total agreement: N(%): 22 (55.0%) vs 18 (44.0%) o 'continue treatment: N(%): 13 (32.5%) vs 12 (29.3%) o 'discontinue treatment': N(%): 8 (20.0%) vs 2 (4.9%) o 'don't know': N(%):1 (2.5) vs 4 (8.9%) • Situation 3 – mental impairment Total agreement: N(%): 25 (61.0%) vs 22 (53.7%) o 'continue treatment: N(%): 14 (34.2%) vs 17 (41.5%) o 'discontinue treatment': N(%): 8 (19.5%) vs 3 (7.3%) o 'don't know': N(%):3 (7.3) vs 2 (4.9%) **Agreement to give family leeway (intervention vs control)** Agreement to give family leeway was higher in intervention than control-arm **<u>Post-Session 2</u>** 62.5% vs. 45.7%, p=0.1012 **<u>3 month follow-up</u>** 68% - 51%, p=0.13	Reason: 3-month follow-up was assessed for less than 90% in each treatment arm (75-80%). <u>C. Performance bias</u> High Risk Reason: Personnel and participants were not blinded <u>D. Detection bias</u> Unclear Reason: Blinding of outcome assessors was not reported in the article

Effectivity of Advance Care Planning Interventions				
Lyon ME et al. Family-centered advance care planning for teens with cancer. Jama, Pediatr. 2013;167(5):460-7.				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: Two-group randomized controlled trial Setting: Not reported Duration: Outcomes were assessed at 5 time points: baseline, Sessions 1 through 3, and 3-month follow-up Study years: January 17, 2011 – March 29, 2012 Protocol published in register: (*clinicaltrials.gov / WHO register*)	Number and type of participants: • Intervention group: 17 adolescents with cancer and 17 surrogates or families • Control group: 13 adolescents with cancer and 13 surrogates or families Age • Adolescents (n = 30) Mean: 16.3 yr., Range: 14-21 • Surrogates (n=30) Mean: 46.0 yr., Range: 22-62) Sex: • Adolescents (n = 30) M: 18 (60%), F: 12 (40%) • Surrogates (n=30) M: 2 (7%), F: 28 (93%)	Type of intervention: Three weekly 60 minute sessions in family format. *Session 1 - Lyon Family-Centered ACP Survey:* Assessment of values, beliefs, and life experiences with illness and EOL care. *Session 2 - Respecting Choices:* A facilitated ACP conversation with the adolescent and family about the medical condition, complications, fears, hopes and experiences. SoTP is used to encourage dialogue about goals and values *Session 3 - Completion of The Five Wishes:* Adolescent completed Five wishes a legal advanced directive. Type of control: Standard Care + information Participants received a brochure with information on ACP at baseline. Assessment were administered at the same time 5 points in time (baseline, session 1, session 2, session 3, 3-month follow-up.	Outcome definitions: **Treatment preference congruence** Treatment preferences were determined in the Statement of Preference (SoTP). This document was used both intervention and control group immediately following the pACP conversation in week 2 and 3 months post-intervention. The SoTP documents what the adolescent/family would want in six situations 1. Long hospitalization stay with many treatments and chance of living through this complication is low. 2. Cancer has spread and treatments will extend my life by no more than 2 to 3 months, side effects of treatment are serious 3. Functional impairment, never able to walk and talk, need of 24h nursing care 4. Mental impairment, never knowing who you are, need of 24h nursing care 5. I want cardiopulmonary resuscitation attempted unless my physician determines any one of the following: I have an incurable illness or injury and am dying 6. Mechanical ventilation There were three answer options for each situation: 1 continue all treatment to keep me alive as long as possible 2 to stop all treatment to prolong my life; 3 don't know. **Decisional conflict** Degree of uncertainty about course of action. This was assessed by the decisional conflict scale which consists of 3 subscales on a 5-point Likert scale ranging from 1 (strongly disagree) to 5(strongly agree). **Quality of Participant-Interviewer Communication** This was measured during session 2,3 and 4 for both adolescents and families independently. Items were scored on a on a 5-point Likert scale ranging from 1 (definitely no) to 5(definitely yes). Results (per outcome) **Treatment preference congruence (Intervention vs control):** Ƙ coefficients assessed chance-adjusted agreement between surrogate and adolescent responses, and difference in Ƙ coefficients between conditions was tested. • Situation 1: Ƙ = 0.59 vs Ƙ = -0.13; p = 0.001 • Situation 2: Ƙ = 0.6 vs Ƙ = -0.06; p < 0.001 • Situation 3: Ƙ = 0.89 vs Ƙ = 0.11; p < 0.001 • Situation 4: Ƙ = 0.63 vs Ƙ = 0.19; p < 0.001 • Situation 5: Ƙ = 0.34 vs Ƙ = -0.03; p = 0.12; • Situation 6: Ƙ = 1.00 vs Ƙ = -0.00; p < 0.001 **Agreement per answer option (overall agreement, continue treatment/discontinue treatment, don't know (Intervention vs control):** • Situation 1 – long hospitalization Overall agreement: N (%), 14 (82%) vs 9 (69%), p = NS, OR = 2.1	Strengths: Randomized controlled trial of a reproducible EOL intervention. Limitations: *(Study funding/ Conflict of interest reported)* **Risk of bias** A. Selection bias: low risk Reason: Computer triggered randomized was used to create groups. Both participants and personnel were blinded until baseline assessment were completed. B. Attrition bias: Low risk Reason: Outcome was assessed for 100% of participants in the intervention and control group. C. Performance bias High risk Reason: Personnel and participants were not blinded D. Detection bias

			○ 'continue treatment': N(%): 11 (65%) vs 9 (69%) ○ 'Limit treatment': N(%): 1 (6%) vs 0 (0%) ○ 'don't know': N(%):2 (12%) vs 0 (0%) • Situation 2 – treatments would extent my life Overall agreement: N (%): 14 (82%) vs 4 (31%), p < 0.05, OR = 10.5 ○ 'continue treatment': N(%): 10 (59%) vs 3 (23%) ○ 'Limit treatment': N(%): 3(18%) vs 0 (0%) ○ 'don't know': N(%): 1 (6%) vs 1 (6%) • Situation 3 – functional impairment Overall agreement: N (%): 16 (94%) vs 7 (54%), p < 0.05, OR = 13.7 ○ 'continue treatment': N(%): 10 (59%) vs 7 (54%) ○ 'Limit treatment': N(%): 2(12%) vs 0 (0%) ○ 'don't know': N(%): 4 (24%) vs 0 (0%) • Situation 4 – mental impairment Overall agreement: N (%): 13 (76%) vs 6 (46%), p = NS, OR = 3.8 ○ 'continue treatment': N(%): 7 (41%) vs 4 (31%) ○ 'Limit treatment': N(%): 2 (12%) vs 2 (15%) ○ 'don't know': N(%): 4 (24%) vs 0 (0%) • Situation 5 – attempting cardiopulmonary resuscitation Overall agreement: N (%): 11 (65%) vs 7 (54%), p = NS, OR = 1.6 ○ 'continue treatment': N(%): 5 (29%) vs 2 (15%) ○ 'Limit treatment': N(%): 6 (35%) vs 5 (38%) ○ 'don't know': N(%): 0 (0%) vs 0 (0%) • Situation 6 – mechanical ventilation Overall agreement: N (%): 17 (100%) vs 10 (83%), p = NS, OR > 20 ○ 'continue treatment': N(%):16 (84%) vs 10 (83%) ○ 'Limit treatment': N(%): 1 (6%) vs 0 (0%) ○ 'don't know': N(%): 0 (0%) vs 0 (0%) **Agreement to give family leeway (intervention vs control)** After completing the statement of treatment preferences, adolescents were asked how strictly they wanted their surrogate to follow their wishes. , "Do what he/she thinks is best at the time, considering my wishes," 100% vs 62%, p 00.009 **Decisional conflict** Adolescents in the intervention group thought they were better in formed about EOL decisions than the control group. **Quality of Participant-Interviewer Communication during intervention** In both groups there was no change in quality of communication occurred. There was no significant difference between the intervention and control group	unclear Reason: Blinding of outcome assessors was not reported in the article

			No adverse events occurred.	

Effectivity of Advance Care Planning Interventions				
Lyon ME, Jacobs S, Briggs L, Cheng YI, Wang J. A longitudinal, randomized, controlled trial of advance care planning for teens with cancer: anxiety, depression, quality of life, advance directives, spirituality. J Adolesc Health. 2014 Jun;54(6):710-7. doi: 10.1016/j.jadohealth.2013.10.206. Epub 2014 Jan 7. PMID: 24411819.				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: Two-group randomized controlled trial Setting: Not reported Duration: Outcomes were assessed at 5 time points: baseline, Sessions 1 through 3, and 3-month follow-up Study years: January 17, 2011 – March 29, 2012 Protocol published in register: (*clinicaltrials.gov / WHO register*)	Number and type of participants: *(diagnosis)* • Intervention group: 17 adolescents with cancer and 17 surrogates or families • Control group: 13 adolescents with cancer and 13 surrogates or families Age • Adolescents (n = 30) Mean: 16.3 yr., Range: 14-21 • Surrogates (n=30) Mean: 46.0 yr., Range: 22-62) Sex: • Adolescents (n = 30) M: 18 (60%), F: 12 (40%) • Surrogates (n=30) M: 2 (7%), F: 28 (93%)	Type of intervention: Three weekly 60 minute sessions in family format. *Session 1 - Lyon Family-Centered ACP Survey:* Assessment of values, beliefs, and life experiences with illness and EOL care. *Session 2 - Respecting Choices:* A facilitated ACP conversation with the adolescent and family about the medical condition, complications, fears, hopes and experiences. SoTP is used to encourage dialogue about goals and values *Session 3 - Completion of The Five Wishes:* Adolescent completed Five wishes a legal advanced directive. Type of control: Standard Care + information Participants received a brochure with information on ACP at baseline. Assessment were administered at the same time 5 points in time.	Outcome definitions: **Satisfaction** Satisfaction was assessed using the Satisfaction Questionnaire (developed and pilot-teted for the FACE protocol with HIV-positive adolescents). Questionnaire consisted of 13 items, answered on a 5-point Likert scale (strongly disagree to strongly agree). Higher scores indicate higher satisfaction. **Anxiety** (adolescents): Beck Anxiety Inventory (21 item questionnaire rated with 4 point Likert scale) was used to assess presence of symptoms of anxiety over the past week. Clinical score interpretation of levels of anxiety: • 0 – 7: minimal anxiety; • 8 – 15: mild anxiety; • 16 – 25: moderate anxiety; • 26 – 63: severe anxiety **Depression (**adolescents): Beck Depression Inventory - II, (21 item questionnaire rated with 4 point Likert scale) was used to assess presence of symptoms of depression over the past week. Clinical score interpretation of levels of anxiety: • 0 – 13: minimal depression; • 14 – 19: mild depression; • 20 – 28: moderate depression; • 29 – 63: severe depression **Health-Related Quality of life** Pediatric Quality of Life Inventory 4.0 Generic Core Scales (23 item questionnaire) was used to measure health related quality of life on physical, emotional, social and school domain). The Integrated Pediatric Quality of Life Cancer-specific Module measured cancer symptoms. Higher scores indicated better quality of life. **Spiritual wellbeing** Spiritual Well-Being Scale of the Functional Assessment of Chronic Illness Therapy Version 4 (23 item questionnaire) was used to assess existential aspects of spirituality. Two subscales were meaning/peace and faith. The higher the score, the better the spiritual well-being. **Advance directive** Filling in Five wishes Advance Directive Results (per outcome) **Feasibility** 72% of eligible families enrolled (Note Marijke: those whom declined were not included in this sum) Attendance all there sessions:: 100% of include participants Retention 3 months:; 93% Completeness of data 3 months: 100% of 56Participants who completed follow up.	Strengths: Limitations: No conflict of interests **Risk of bias** A. Selection bias: low risk Reason: Computer triggered randomized was used to create groups. Both participants and personnel were blinded until baseline assessment were completed. B. Attrition bias: low risk Reason: outcome assessment >90* C. Performance bias High risk Reason: Personnel and participants were not blinded D. Detection bias unclear Reason: Blinding of outcome assessors was not

			Satisfaction (intervention) Adolescents: Adolescent: Adolescents worthwhile ratings increased over time: Session 1 = 65%, Session 2 = 71%, Session 3 = 88-94% Adult surrogates: All adult surrogates (100%) rated the three sessions as worthwhile **Mean (SD) anxiety scores (intervention vs control)** *(according to generalized estimating equation model)* Baseline *Adolescents: 6.8 (8.2) vs 9.8 (10.0)* *Adult surrogates: 3.4 (3.4) vs 4.3 (8.6)* 3 month follow-up *Adolescents: 2.6 (2.2) vs 4.0 (3.20)*, β = *- 3.1, p = 0.3542)* There was no significant difference in anxiety scores of adolescents over time between intervention and control group *Adult surrogates: 4.0 (5.1) vs 3.5 (8.7),* β = *- 0.9, p = 6973)* There was no significant difference in anxiety scores of adult surrogates over time between intervention and control group **Mean (SD) anxiety scores (Baseline vs 3-month follow-up)** *(according to generalized estimating equation model)* *Adolescents* Intervention: 6.8 (8.2) vs 2.6 (2.2), β = -5.6; p = 0.0212 Control: 9.8 (10.0) vs 4.0 (3.2), β = -5.6; p = 0.0212 Anxiety scores of adolescent (3 month follow up - baseline) Anxiety scores of adolescents significantly decreased in both intervention and control group over time. *Adult surrogates* Intervention: 3.4 (3.4) vs 4.0 (5.1), p = NS Control: 4.3 (8.6) vs 3.5 (8.6), β = -1.2, P = 0.0314 The anxiety of surrogates score dropped significantly in the control group but increased in families in the intervention group **Mean (SD) depression scores (intervention vs control)** *(according to generalized estimating equation model)* Baseline *Adolescents: 5.5 (4.8)vs 10.9 (8.1)* *Adult surrogates: 5.4 (6.6) vs 5.8 (5.8)* 3 month follow-up *Adolescents: 6.3 (5.3) vs 4 7.4 (4.3),* β = *- 5.4, p = 0.0268* Intervention group had a significantly lower depression score at baseline and 4 month follow-up as compared with controls. *Adult surrogates: 5.3 (7.7) vs 5.3 (8.0)*, β = *- 0.4, p = 0.8424* There was no significant difference in depression scores of adult surrogates between intervention and control group. **Mean (SD) depression scores (baseline vs 3 month follow-up)**	reported in the article

			(according to generalized estimating equation model) *Adolescents* Intervention: 5.5 (4.8) vs 6.3 (5.3), Control: 10.9 (8.1) vs 7.4 (4.3) There was no significant difference in depression scores over time between intervention and control group β = -3.0, p = 0.1007 *Adult surrogates* Intervention:: 5.4 (4.8 vs 5.3 (7.7), p = NS Control: 5.8 (5.8) vs 5.3 (8.0), P = NS There was no significant difference in depression scores over time between intervention and control group β = -0.9 p = 0.5357 **Mean (SD) Quality of life scores (intervention vs control)** *(according to generalized estimating equation model)* <u>Baseline</u> *Adolescents: 71.9 (17.4) vs 68.7 (17.4)* *adult surrogates perception of adolescents' QoL:* *68.9 (18.9) vs 61.7 (16.3)* <u>3 month follow-up</u> *Adolescents: 77.2 (13.4) vs 4 76.2 (10.4)),* β = 3.1, *p = 0.6123* There was no significant difference in Quality of life scores of adolescents at baseline and 3 month follow-up between intervention and control. *Adult surrogates perception of adolescents' QoL:* *74.7 (15.8) vs 66.9 (11.1)*, β = 7.2*, p = 0.2475* There was no significant difference in Adult surrogates perception of adolescents' QoL at baseline and 3 month follow-up between intervention and control. **Mean (SD) Quality of Life scores (baseline vs 3 month follow-up)** *(according to generalized estimating equation model)* *Adolescents* Intervention: 71.9 (17.4) vs 77.2 (13.4), P = NS Control: 68.7 (17.4) 76.2 (10.4), p = NS Intervention vs control (over time): β = 5.9, p = 0.1123 There was no significant difference in Quality of Life in adolescents scores over time between intervention and control group *Adult surrogates perception of adolescents' QoL* Intervention: 68.9 (18.9) vs 74.7 (15.8) Control: 61.7 (16.3) vs 66.9 (11.1) Intervention vs control (over time): β = 7.2, P =.2475 There was no significant difference in adult surrogates perception of adolescents' QoL over time between intervention and control group **Mean (SD) spirituality scores in adolescents** (baseline vs 3-month follow-up) *Total* Intervention: 78.9 (13.1) vs 78.2 (8.1), Control: 70.8 (7.8) vs 67.2 (14.3) Intervention vs control (over time): β = 8.1, p =.0296. Intervention group was higher at baseline and 3 month follow-up, compared to control.	

			Peace subscale Intervention: 28.2 (3.8) vs 27.6 (3.6), p = NS Control: 24.4 (5.5) vs 25.4 (4.0), P = NS Intervention vs control (over time): β = 3.9, p =.0239 Intervention group was higher at baseline and 3 month follow-up, compared to control. *Faith subscale* Intervention: 13.2 (4.0) vs 12.2 (4.4), p = 0.466 Control: 11.8 (3.7) vs 9.9 (4.9), p = 0.446 Faith subscale scores dropped significantly from baseline to 3 month follow-up Intervention vs control (over time): β = 3.1, p =0.3286, there's no difference between intervention groups. **Completion of legal document with treatment preferences at 3 month follow-up (intervention vs. control):** 100% vs 0%	

3.2 Belemmerende en bevorderende factoren van ACP en gezamenlijke besluitvorming

3.2.1 Advance Care Planning

Barriers and facilitators of shared decision-making and Advance Care Planning			
Beecham et al. Keeping all options open: Parents' approaches to advance care planning. Health Expect 2017;20:75-684.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
Study design Open-ended, semi-structured interviews. All parents were invited for a second interview, 12 weeks later. Main study objective To investigate how parents of children and young people with LLCs approach and experience ACP. Additional study characteristics UK; 2012-2013; principles of grounded theory, including both inductive and deductive coding	Number and type of participants: 18 parents • 9 parents whose child was currently receiving palliative care • 9 bereaved parents whose child had received palliative care Children had following diagnoses: o 10 neurologic o 2 metabolic o 2 oncologic o 1 gastroenterological o 1 immunologic o 1 respiratory o 1 chromosomal abnormality Age: *(mean, median, range)* Parents: not reported Children of interviewed parents • 0-1 years (n=2)	Outcome definition: Outcome 2: periods in the illness and child's condition when decisions were made Outcome 3: involvement in decision making Outcome 4: factors identified by parents as contributing to decisions about the child's care and treatment Outcome 5: helpful ways to support parents when making decisions about the child's care and treatment Results **Outcome 2: periods in the illness and child's condition when decisions were made** *Facilitators perceived by parents* • Many parents' narratives indicated a desire to keep options open. Stating they would decide at the time or by agreeing to limit treatment with the knowledge they could change their mind later. *Barriers perceived by parents* • Parents reported that it was difficult to visualize the likely consequences of limiting treatment. • Parent mentioned that making decisions about future treatment was difficult because their way of thinking care or treatment were	Strengths: • Inclusion of perspectives from parents of children with a range of LLCs, both deceased and alive • The follow-up interview allowed researchers, guided by emerging data, to explore and understand the decision making process in more depth Limitations: • Sample was limited to the families of 18 children, and in most cases only the mother participated • Selection bias due to non-invitation of eligible families, because clinicians were more likely to invite families they knew well and have a "good" relationship with • Sample has been drawn from a caseload of a specialist paediatric palliative care team for whom ACP is a recognized aim of their practice; this may not be so in different settings

	• 1-4 years (n=2) • 4-12 years (n=6) • 12-17 years (n= 8) <u>Sex:</u> *(N (%))* Parents Mother=13 (72.2%); father=2 (11.1%); both=3 (16.7%) Children of interviewed parents F=9 (50%); M=9 (50%) <u>Ethnicity:</u> Not reported <u>Religious preference:</u> Not reported <u>Level of education:</u> Not reported <u>Other:</u> *Number of interviews with researcher* • 1 interviews (n=6) • 2 interviews (n=11) • 3 interviews (n=1)	hypothetical, and their preferences might change in the future as circumstances altered. **Outcome 3: involvement in decision making** *Barriers perceived by parents* • Parents mentioned that sometimes HCPs asked them to make a particular decision, but parents did not always want the HCP to involve them in decision making. • Sometimes parents were happy to go along with the recommendation given by the HCP(s), or the HCP(s) went along with the parents' preference. Other times, parents and HCPs jointly weighed the benefits and risks of different options. **Outcome 4: factors identified by parents as contributing to decisions about the child's care and treatment** *Barriers perceived by parents* • Parents reported conflicted feeling about decisions about limitation of treatment, since they did not want their child to suffer, but also wanted to do everything possible to try to increase the length of their child's life. • 8/18 parents feel like they did not had much choice with regard to feeding options (e.g. because their child had a NG tube fitted directly after birth) *Facilitator perceived by parents* • 8/18 parents reported accepting clinicians advice after receiving a strong advice from them regarding limiting treatment, despite misgivings. **Outcome 5: helpful ways to support parents when making decisions about the child's care and treatment** *Facilitators perceived by parents* • All parents prominently mentioned the interaction between clinicians and parents, including the need for clinicians to understand the bigger picture of the life of the child and the wider family, rather than simply focusing on treating a particular symptom. • Parents stated the importance of clinicians understanding the need for them to take professional control at certain times and provide practical help. • Parents suggested the need for clinicians to give parents sufficient time to make decisions, allowing them time to adjust to their child's diagnosis and prognosis. • Parents mentioned it would be helpful to have more information about treatment options and likely outcomes.	*Study funding* No specific grant, but was supported by the National Institute for Health Research Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London **Risk of bias** <u>Aim and appropriateness of qualitative evidence:</u> Low risk Reason: Aim is clearly described, qualitative method is appropriate. <u>Rigour in study design or validity of theoretical approach</u> Low risk Reason: Study uses principles of grounded theory as described by Hennink, Hutter and Bailey as a theoretical approach. <u>Sample selection</u> High risk Reason: Purposive sampling was used to select participants. Influence of an interviewer-participant relationship is minimal. <u>Data collection</u> Low risk Reason: Method of data collection is clearly described and adequate. <u>Data analysis</u> Unclear Reason: Analytical process was described. It is unclear whether theme saturation was achieved. <u>Results</u> Low risk Reason: Reasoning behind results is given. Results are credible.

Barriers and facilitators of shared decision-making and Advance Care Planning			
Edwards et al. Decisions for long-term ventilation for children: perspectives of family members. Ann Am Thorac Soc 2020;17:72-80.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**

Study design
Semi-structured interviews using an open-ended interview guide in-person or over-the-phone
 	
Main study objective
Assess what families with children with chronic respiratory failure and life-limiting conditions need and want for informed decision-making
 	
Additional study characteristics
United States; 2015-2017; thematic approach based on framework analysis
	Number and type of participants:
	44 parents of 43 children:
	• 18 contemporaneous invasive LTV decision-makers
	• 10 contemporaneous non-invasive LTV decision-makers
	• 8 former invasive LTV decision-makers
	• 8 former non-invasive LTV decision-makers
	
	1 young woman using invasive LTV
	1 adolescent girl being initiated on non-invasive LTV
	
	Age:
	(mean, median, range)
	Parents
	Median: 35.5 years (IQR: 29-41.5)
	
	Children of parental decision-makers (median (range))
	• Contemporaneous invasive LTV: 11 months (2 months-16 years)
	• Contemporaneous non-invasive LTV: 4.5 years (5 months-16 years)
	• Former invasive LTV: 4 years (6 months-20 years)
	• Former non-invasive LTV: 8.5 years (22 months-18 years)
	
	Sex:
	(N (%))
	Parents
	F=34 (77.3%), M=10 (22.7%)
	
	Children of parental decision-makers
	• Contemporaneous invasive LTV: F=10 (58.8%), M=7 (41.2%)
	• Contemporaneous non-invasive LTV: F=4 (40%), M=6 (60%)
	• Former invasive LTV: F=5 (62.5%), M=3 (37.5%)
	• Former non-invasive LTV: F=3 (37.5%), M=5 (62.5%)
	
	Ethnicity:
	Parents:
	• White (n=28)
	• Black or African American (n=8)
		Outcome definition:
		Outcome 1: Parents' emotional and psychological experience with decision-making
		Outcome 2: Parents' informational needs
		Outcome 3: Parents' communication and decision-support needs
		Outcome 4: Parents' views on the option not to initiate
		
		Results
		Outcome 1: Parents' emotional and psychological experience with decision-making regarding LTV
		Barriers
		• *7/44 parents* felt that there was no decision to be made because supporting their child's breathing or preserving their life was the "only" option to them, and not doing so was unimaginable.
		• *15/44* parents describe as difficult, as if there were no great options and they had to choose between substantial downsides.
		• 3 parents said that their first response was to reject LTV and/or deny their child's situation.
		• Majority of the parents felt devastated by their child's condition and/or tremendously stressed about their decision on LTV because:
		  ○ they felt like they did not receive the desired information
		  ○ they worried about downsides of LTV for their child
		Facilitators
		Parents had various approaches to manage stress in decision-making
		• 5/44 parents put their faith in a higher power. This higher power would guide their decision-making or dictate how things should be
		• 4/44 parents wanted providers' opinions and suggestions about everything, including what would be the best option for their child
		• Several parents drew emotional support from other family members
		• 4/44 parents recommended that other parents trust their own intuition and experience regarding their child, even sometimes over those of medical professionals.
			Strengths:
			• This study is the first to interview parents of children with CRF and life-limiting conditions to assess their decisional needs regarding LTV.
			
			Limitations:
			• We used convenience sampling and, while we tried to recruit all eligible parents, 16% of those approached could not be interviewed.
			
			• Despite achieving thematic saturation for decision-makers who would choose LTV, our sample may not be representative of all caregivers in this group.
			
			• We were only able to interview one parent who declined LTV, so it is highly likely that additional information could be gleaned from interviewing more such parents.
			
			• It was not possible to interview all contemporaneous decision-makers at the same stage of decision-making. We did interview them either before their child underwent tracheotomy or discharge of their child using non-invasive LTV.
			
			• While a sizeable number of children are represented in the study and all had CRF and a life-limiting condition, they were heterogeneous in terms of their conditions, severity, and functional abilities. Such characteristics may affect decisional needs and how parents view and approach their decisions.
			
			• We did not address the informational needs of parents with children with CRF but without life-limiting conditions.

	• Asian(n=5) • Native Hawaiian or other Pacific Islander (n=1) • Hispanic/Latino (n=21) <u>Religious preference:</u> Parents: • Christianity (n=28) • Judaism (n=5) • Islam (n=4) • Hinduism (n=2) • Buddhism (n=1) • Wiccan (n=1) • None (n=3) <u>Level of education:</u> Parents: • Some high school (n=7) • High school/GED degree (n=12) • Associate's degree (n=6) • Some undergraduate (n=7) • Bachelor's degree (n=9) • Some graduate (n=1) • Master's/PhD/professional degree (n=2) <u>Other:</u> *Primary reason for CRF* Contemporaneous invasive LTV: • Central hypoventilation (n=6) • Ventilatory muscle weakness (n=4) • Chronic pulmonary disease (n=7) (Previously used NIV LTV (n=3)) Contemporaneous non-invasive LTV: • Central hypoventilation (n=3) • Ventilatory muscle weakness (n=6) • Chronic pulmonary disease (n=1) Former invasive LTV: • Central hypoventilation (n=5) • Ventilatory muscle weakness (n=2) • Chronic pulmonary disease (n=1) (Previously used NIV LTV (n=1)) Former non-invasive LTV: • Central hypoventilation (n=5) • Ventilatory muscle weakness (n=3)	**Outcome 2: Parents' informational needs** *Facilitators* • 40/44 emphasized the importance of knowing everything about their child's condition(s) and LTV, regardless if the information was upsetting or not. As they needed this to make a well-informed decision for their child and to be prepared for the future • *4/44* parents acknowledged that they preferred to receive only positive messages (e.g., the benefits of LTV) or did not want to hear negative information (e.g., the risks of LTV) unless it was specifically relevant to a decision at hand. **Outcome 3: Parents' communication and decision-support needs** *Facilitators* Following provider practices/qualities regarding communication were considered helpful by contemporaneous decision makers (n =28) • Being honest. 9/28 • Allowing time for processing information and asking questions. 9/28 • Being tactful and using sensitive language. 9/28 • Being supportive. 5/29 • Share information before decisions or crises. 4/28 • Using lay language 4/28 • Using interpreters for non-English speakers 3/28 3/16 former decision makers wanted their child to be informed as much as possible *Barriers* Following communication practices were considered unhelpful by contemporaneous decision makers. • Information concerning child's diagnosis or prognosis was insufficient, lacked detail on LTV or was not provided timely. 14/28 • Pressure to make a decision. 9/28 • Frequent changing of medical providers hindered communication or decision-making. 4/28 • Some parents felt their child was depersonalized because of negative attitudes and statements about the child. **Outcome 4: Parents' views on the option not to initiate** • All families should be offered the full range of options, also to not initiate LTV. 1/16 former decision-makers	• While two investigators performed thematic coding independently, we did not assess interrater reliability as discrepancies were rare and neither coder emerged as dominant. *Study funding* National Institutes of Health K23 grant. **Risk of bias** <u>Aim and appropriateness of qualitative evidence:</u> Low risk Reason: Aim is clearly described, qualitative method is appropriate. <u>Rigour in study design or validity of theoretical approach</u> Low risk Reason: Theoretical framework is based upon knowledge on LTV for children with chronic respiratory failure identified in previous studies. <u>Sample selection</u> Unclear Reason: Convenience sampling was used to select participants. Interviewer-participant relationship unclear. <u>Data collection</u> Low risk Reason: Data collection method i.e. place, interviewer were described. Duration of the interview was not reported. <u>Data analysis</u> Low risk Reason: Data analysis was described in detail and done using framework analysis. Thematic saturation was reached. <u>Results</u> Low risk Reason: Reasoning behind results is given. Results are credible.

Barriers and facilitators of shared decision-making and Advance Care Planning			
Edwards et al. Decisions around Long-term Ventilation for Children. Perspectives of Directors of Pediatric Home Ventilation Programs. Ann Am Thorac Soc 2017;14:1539 47.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
Study design In-depth, semi-structured interviews over the phone using an open-ended interview guide Main study objective Assess how directors of paediatric home ventilation programs facilitate shared decision-making with families facing decisions of whether to initiate or forgo long-term ventilation (LTV) for their children with life-limiting conditions, and assess directors' perspectives on these families' decisional needs Additional study characteristics United states and Canada; 2015-2016; thematic approach based on framework analysis	Number and type of participants: *(diagnosis)* 15 directors/codirectors of paediatric home ventilation programs at children's hospital of following expertise: • 11 paediatric pulmonologists • 2 paediatric intensivists • 2 specialized in both paediatric pulmonology and critical care Children treated in children's hospital: Children with Chronic Respiratory Failure (CRF) Age: Not reported Sex: Not reported Ethnicity: Not reported Religious preference: Not reported Level of education: Not reported Other:	Outcome definition: Outcome 1: Information Outcome 2: Decision-making process Results **Outcome 1: Information** *Facilitators perceived by directors* • Beyond explaining the child's condition and (when possible) prognosis with and without LTV, all directors highlighted the need to inform families of potential benefits, risks, and burdens, and financial impact of LTV for the child and family. *Barriers perceived by directors* • 13/15 directors conceded that using the internet was inevitable, and that it was a helpful source of information/support. However, they added that it could be obstructive, recommending caution, and that families talk to them about what they find. **Outcome 2: Decision-making process** *Facilitators perceived by directors* *Setting the stage for decision-making* • Directors emphasized that the decision-making process around LTV should be unhurried and that it should start as soon as CRF is anticipated or diagnosed—either early during the hospitalization or, ideally, during a period of relative wellness before acute illness pushes the susceptible child into CRF. • Directors stressed that providers should be transparent, candid and consistent when conveying information to families and addressing barriers and worries. • Directors encourage lay appropriate language without euphemisms. • Providers should be compassionate and supportive which means being receptive to what families are saying/not saying. *Parent and child involvement: Facilitators* • All directors felt that families should be the final decision-makers. • All directors insist that cognitively capable older children be involved in discussions and even decision-making around LTV *Barriers to decision-making perceived by directors* Potential barriers to decision-making around LTV stemmed from families, providers, and other sources: *Family*	Strengths: • This study is the first to assess how directors of paediatric home ventilation programs, whose role is to longitudinally care for these children and to be routinely involved in these decisions, facilitate decision-making around LTV. Limitations: • Recruitment was not random nor exhaustive. • In the absence of a comprehensive list of home ventilator programs, identification of potential participants was based on the investigators' knowledge of such programs supplemented by a review of recent literature and a Web-based searc4 directors were invited to participate, but did not ultimately do so • We did not query families to learn if what and how directors tell them is hearkened or appreciated. • We did not interview other providers who play integral roles in helping families facing these decisions (e.g., intensivists, otolaryngologists, ventilator program managers, respiratory therapists, and nurses). • Only North American directors were interviewed, so our findings may not be generalizable to other regions. • Although two investigators did perform coding independently, we did not assess interrater reliability, as discrepancies were rare and neither coder emerged as dominant. • Some of the burdens of LTV mentioned may be just as, or more, attributable to other chronic conditions (severe neurodevelopmental disabilities) than LTV; others may be irrelevant to families who decide to place their children in chronic care facilities. *Study funding* National Institutes of Health K23 grant and a Columbia University John M. Driscoll, Jr., M.D., Children's Fund Award. **Risk of bias** Aim and appropriateness of qualitative evidence: Low risk Reason: Aim is clearly described, qualitative method is appropriate.

	Years of experience caring for children using long-term ventilation Median: 19 years (interquartile range: 12-27; range: 2-38 years)	• Inability to really grasp the information provided or the "big picture" (7/15) • Unrealistic expectations (5/15) • Focusing on the here and now to the detriment of the long term (3/15) • Stress/fear of making any decision (3/15) • Denial or lack of readiness/willingness to hear information (3/15) • Theological fatalism (1/15) • Unrelated family stressors (1/15) • Fear that they are being discriminated against because of their socioeconomic status (1/15) *HCPs* • Not fully informing families (14/15) • Mixed or inconsistent messages (3/15) • Inability to provide prognosis (and sometimes diagnosis) (4/15) • Negative biases regarding the quality of life and abilities to many children on LTV (3/15) • Rushing families to make decisions (3/15) • Not willing to broach difficult topics (2/15) • Focusing on the here and now to the detriment of the long term (2/15) • Changing inpatient providers (2/15) • Not engendering a sense of trust in families (1/15) • Inability to surmount cultural or language differences (1/15) • Setting unrealistic expectations (1/15) *Other* • Influence from outside sources/people (6/15) • Misinformation from outside sources/people (5/15) • Disagreement/discord between family and providers (1/15)	Rigour in study design or validity of theoretical approach Low risk Reason: The thematic framework was developed based on a priori hypotheses of the importance of informed, shared decision-making. Sample selection High risk Reason: Purposive sampling was used as a method to select participants. It is unclear whether an interview-participant relationship influences results. Data collection Unclear Reason: Data collection method is described. However i.e. place, duration and interviewer were not reported. Data analysis Low risk Reason: Data analysis was described in detail and done using framework analysis. Thematic saturation was reached after 15 interviews. Results Low risk Reason: Reasoning behind results is given. Results are credible.

Barriers and facilitators of shared decision-making and Advance Care Planning			
Fahner et al. Evaluation showed that stakeholders valued the support provided by the Implementing Pediatric Advance Care Planning Toolkit. Acta Paediatr 2021;110:237-46.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
Study design Qualitative interviews; focus group interviews and individual interviews Main study objective Describe the development, and pilot evaluation, of the Implementing Pediatric Advance Care Planning Toolkit (IMPACT)	Number and type of participants: 18 healthcare professionals (1 nurse, 17 physicians) of following expertise: • 1 cardiology • 1 gastroenterology • 1 general paediatrics • 1 haematology • 2 hereditary and congenital disorders • 2 intensive care • 3 metabolic diseases	Outcome definition: Outcome 1: Key paediatric ACP elements from the stakeholders' perspectives Results **Outcome 1: Key paediatric ACP elements from the stakeholders' perspectives** *Facilitators* • *Holistic approach:* Patients wanted paediatricians to explore what their lives	Strengths: • The thorough developmental process. Clinicians, children with life-limiting conditions and parents, were all involved during the entire process. This encouraged researchers to stay close to clinical practice and facilitated further implementation of the intervention. • Needs in the field could be addressed, increasing the relevance of the intervention for current daily practice. Limitations:

<u>Additional study characteristics</u>
The Netherlands; 2016-2018; thematic analysis
	• 1 nephrology
	• 1 neurology
	• 2 oncology
	• 3 pulmonology
	
	20 parents of 17 children with life-limiting conditions (10 bereaved parents of 6 children who died) with following diagnoses:
	• 7 chromosomal anomaly
	• 4 congenital heart disease
	• 2 CNS tumour
	• 1 cystic Fibrosis
	• 1 neuromuscular disease
	• 1 epilepsy syndrome
	• 1 perinatal asphyxia
	
	13 children with following diagnoses:
	• 1 auto-immune disorder
	• 1 congenital heart disease
	• 2 hematologic disease
	• 1 metabolic disease
	• 3 neuroendocrine disease
	• 2 pulmonary disease
	• 1 renal disease
	• 2 siblings of a child with life-limiting condition
	<u>Age:</u>
	(mean, median, range)
	Healthcare professionals
	• 30-40 years (n=1)
	• 40-50 years (n=6)
	• 50-60 years (n=8)
	• ≥ 60 years (n=3)
	
	Parents
	• 30-40 years (n=9)
	• 40-50 years (n=8)
	• ≥ 50 years (n=3)
	
	Children
	• 10-12 years (n=1)
	• 12-14 years (n=2)
	• 14-16 years (n=4)
	• 16-18 years (n=3)
	• ≥ 18 years (n=3)
	
	<u>Sex:</u>
	(N (%))
		were like from a psychological, social and spiritual point of view.
		
		• *Importance of child's perspective:*
		  ○ Paediatricians, parents and children all emphasised the importance of the child's perspective.
		  ○ Strategies to elicit the voice of the child are needed, either through direct communication with the child or by trying to understand the child's perspective.
		
		• *Caring attitude*
		  ○ Paediatricians and parents expressed the need for a caring attitude and attention when sharing future perspectives.
		  ○ Paediatricians need to feel confident to ask families about sensitive themes.
		  ○ Parents stated that their paediatrician's acknowledgement of their child as an individual, and their tasks and expertise as parents, would be a precondition for sharing their deepest thoughts regarding their child's future.
		
		Barriers
		• *Holistic approach:*
		  ○ Paediatricians rather talk about medical themes relating to ACP than exploring individual family values.
		  ○ Education is required about the holistic nature of ACP.
		
		• *Importance of child's perspective:*
		  ○ Paediatricians reported challenging experiences when trying to approach children and communicate adequately with them.
		  ○ Parents saw themselves as the best advocates for their child, yet they struggled to define their child's best interests.
			• System factors were not integrated into the developmental process or the intervention.
			
			• The stakeholders involved in the developmental process and the participants of the pilot study were mainly highly educated people with an open attitude towards ACP. This might have positively skewed their perspectives.
			
			• The children included had varying diseases, prognoses and were in different stages of disease, which might result in different needs.
			
			• We could not specify the child's disease progression. That means we could not specify whether the perspectives, as presented by families, corresponded to a position early or later in a disease trajectory. We collected data about the time since diagnosis, but this did not reflect the stage of disease, its burden or length of time until end of life.
			
			• We translated the perspectives of parents and children into a general approach, but it would be valuable to evaluate whether the individual needs of specific groups were sufficiently addressed by this approach or whether specific groups need a more tailored approach.
			
			Study funding
			ZonMw, Grand/Award
			
			Risk of bias
			<u>Aim and appropriateness of qualitative evidence:</u>
			Low risk
			Reason: Aim is clearly described, qualitative method is appropriate.
			
			<u>Rigour in study design or validity of theoretical approach</u>
			Low risk
			Reason: Study uses The Framework for the Development and Evaluation of Complex Interventions.
			
			<u>Sample selection</u>
			High risk
			Reason: Purposive sampling was used to select participants. Interviewer-participant relationship unclear.
			
			<u>Data collection</u>
			Unclear

	Healthcare professionals F=12 (66.7%), M=6 (33.3%) Parents F=15 (75%), M=5 (25%) Child of participating parents F=5 (29.4%), M=12 (70.6%) Children F=8 (61.5%), M=5 (38.5%) <u>Ethnicity:</u> Not mentioned <u>Religious preference:</u> Not mentioned <u>Level of education:</u> Not mentioned <u>Other:</u> *Age of children of participating parent at death/at interview* • < 1 year (n=3) • 1-5 years (n=6) • 5-12 years (n=5) • 12 years (n=3) *Age at diagnosis of participating children* • < 1 year (n=6) • 1-5 years (n=1) • ≥5 years (n=4)		Reason: Data collection method i.e. place, duration and interviewer were not reported. <u>Data analysis</u> Unclear Reason: Data analysis was done using thematic analysis. Saturation was not reported. <u>Results</u> Low risk Reason: Reasoning behind results is given. Results are credible.

Barriers and facilitators of shared decision-making and Advance Care Planning			
Fahner et al. Towards advance care planning in pediatrics: a qualitative study on envisioning the future as parents of a seriously ill child. Eur J Pediatr 2020;17:1461-68.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
Study design Interpretive qualitative study, with individual face-to-face interviews and two focus group interviews Main study objective To identify how parents envision the future when caring for their seriously ill child Additional study characteristics The Netherlands; 2018-2019; inductive thematic analysis	Number and type of participants: 20 parents of 17 seriously ill children with following diagnoses: • 7 chromosomal anomaly • 4 congenital heart disease • 2 CNS tumour • 1 cystic fibrosis • 1 neuromuscular disease • 1 epilepsy syndrome • 1 perinatal asphyxia 6 children are deceased. 10 parents participated in a focus group interview. Age: *(mean, median, range)* Parents • 30-40 years (n=9) • 40-50 years (n=8) • >50 years (n=3) Children's age at death/interview • <1 years (n=3) • 1-5 years (n=6) • 5-12 years (n=5) • >12 years (n=3) Sex: *(N (%))* Parents F=15 (75%), M=5 (25%)	Outcome definition: Outcome 1: Intertwinement of future perspectives with experiences in the present and the past Outcome 2: Future perspectives range from a disease-related orientation to a values-based orientation Outcome 3: No sharing without caring Results **Outcome 1: Intertwinement of future perspectives with experiences in the present and the past** *Facilitators* Parent perspectives on the future were influenced by their attitudes towards the current situation; • Struggling and suffering parents saw the future as a black box. • Parents with consistent and balanced views could more easily look forward. • Perspectives did not seem to be related to better or worse prognosis. In case of more prognostic certainty, parents showed more ability to elaborate on the future. • Parents were more tempted to reflect on future scenario's if they seemed realistic, even when it confronted them with unfavourable outcomes. Parent perspectives on the future were influenced by the past • Some parents mentioned that feeling at peace with the past made them more open-minded towards thinking and discussing about the future, where similar scenarios could happen. • Few parents envisioned the future in relations to decisions made in the past. To see if they had made different choices in the past. These elaborations were followed by thoughts about the good things being a parent of a seriously ill child had brought and these positive thoughts supported them to face the future **Outcome 2: Future perspectives range from a disease-related orientation to a values-based orientation** *Talking about hopes and fears: Facilitators* • Most parents did not spontaneously talk about underlying views, values, hopes, fears, and worries. Recognizing or discussing parent's fears confronted them with worst-case scenarios as a reality. It enabled them to prevent or prepare themselves for a feared situation and left them with greater peace of mind in the present. • Some parents mentioned that they would have valued more attention to their fears, because it made them feel overwhelmed and unprepared when a worst-case scenario occurred *Talking about future care goals: Facilitators* When asked about future care goals, a distinction between disease-related and value-based aims was seen.	Strengths: • Includes non-bereaved and bereaved parents (most studies are often based on experiences of bereaved parents alone) • The knowledge of how parents envision the future might support future research to develop strategies to implement ACP in paediatrics and align ACP to parental needs. Limitations: • Current perspectives of non-bereaved parents could be influenced by current coping strategies. • Recall bias and coping could influence the reflection on the child's end of life in bereaved parents. • Findings might be limited by the diversity of interview settings, and durations of the interviews. • Bias in the results due to predominantly participation of highly educated mothers, and the recruitment of some parents by peer supporters. *Study funding* The Netherlands Organisation for Health Research and Development **Risk of bias** Aim and appropriateness of qualitative evidence: Low risk Reason: Aim is clearly described, qualitative method is appropriate.

	Children F=5 (26.3%), M=14 (73.7%) <u>Ethnicity:</u> Parents • Caucasian (n=20) <u>Religious preference:</u> Parents • Protestant (n=11) • Non (n=9) <u>Level of education:</u> Parents • Secondary school (n=1) • Vocation education (n=4) • High school (n=6) • University (n=9) <u>Other:</u> *Children's age at diagnosis* • <1 year (n=12) • 1-5 years (n=3) • >5 years (n=2)	• Parents who clear short-term disease-related aims; e.g. correction of tracheostomy, could more easily formulate goals of future care. • Parents who had broader, all-encompassing, value based aims; e.g. being happy or try to live an ordinary life, had more difficulty to demonstrate how these aims could guide them to formulate goals of future care. • Some parents mentioned taking their child's perspective helped them define goals of care and treatment; "what would my child value most?" *Talking about treatment limitations: Facilitators* • Some parents addressed treatment limitations themselves because they considered this as an essential part of what they valued as good care. They emphasized they would prefer clinicians to initiate these discussions, because the accompanying emotional distress could be a parental barrier to initiate these conversations. **Outcome 3: No sharing without caring** <u>Facilitators for sharing future perspectives with clinicians;</u> • Parents mentioned the need for acknowledgment for their challenging context, and expressed they felt that clinicians have no idea how caring for a seriously ill child impacts their daily life. • Parents want their growing expertise to be acknowledged and taken into account when it comes to medical decision making, and felt a struggle to be treated as the expert of their child. • Parents reported little room to share perspectives outside the medical domain, but would appreciate it. And expressed to value clinician's awareness of the child's identity apart from their disease. • Parents expressed a need for a consistent approach of clinicians regarding future care and treatment over time and among different disciplines. They reported to struggle to get all clinicians on the same page. If parents felt a shared goal within the team and felt part of the team, this positively influenced their openness to share perspectives.	<u>Rigour in study design or validity of theoretical approach</u> Low risk Reason: Theoretical framework is based upon knowledge on future care planning identified in previous studies. <u>Sample selection</u> High risk Reason: Purposive sampling was used to select participants. Interviewer-participant relationship unclear. <u>Data collection</u> Low risk Reason: Data collection method i.e. place, duration and interviewer were clearly described. <u>Data analysis</u> Low risk Reason: Data analysis was done using thematic analysis. Code saturation was reached on a conceptual level <u>Results</u> Low risk Reason: Reasoning behind results is given. Results are credible.

Barriers and facilitators of shared decision-making and Advance Care Planning			
Odeniyi et al. Communication Challenges of Oncologists and Intensivists Caring for Pediatric Oncology Patients: A Qualitative Study. J Pain Symptom Manage 2017;54:909-15.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
<u>Study design</u> Qualitative study using semi-structured interviews <u>Main study objective</u> To describe experiences and challenges faced by paediatric oncologists and	<u>Number and type of participants:</u> *(diagnosis)* 10 healthcare professionals of following expertise: • 2 intensivist attendings • 1 intensive care fellow • 4 oncologist attendings • 3 oncologist fellows	<u>Outcome definition:</u> Outcome 1: Barriers Outcome 2: Facilitators <u>Results</u> **Outcome 1: Barriers** • Intensivists and oncologists experienced personal conflicts about addressing goals of care and shared decision-making.	<u>Strengths:</u> - <u>Limitations:</u> • Sample recruited from a single institution

intensivists and how the oncologist-intensivist relationship impacts communication and initiation of goals of care discussions (GCDs) <u>Additional study characteristics</u> USA; study years not reported; qualitative analysis utilizing consensus-based findings	<u>Age:</u> Not reported <u>Sex:</u> *(N (%))* F=5 (50%), M=5 (50%) <u>Ethnicity:</u> Not reported <u>Religious preference:</u> Not reported <u>Level of education:</u> Not reported <u>Other:</u> Not reported	*1. Who should initiate the conversations* • Intensivist and oncologists were unsure whether increased intimacy with patients made them more or less successful at engaging in challenging conversations. • Intensivist and oncologists agreed that oncologist had longer relations and stronger ties with the patients; however, they were concerned that the parents would feel that they were 'giving up' if they initiated GCD. • Intensivist felt at times uncomfortable broaching sensitive discussions when they had a less intimate relationship with the family. • Intensivist felt responsible for parents understanding the child's prognosis and treatment choices, but struggled with making recommendations about what was best for the child. *2. Level of parent involvement* • Intensivists and oncologist struggled with placing the burden of major decisions on parents, because parents have to live with the consequences of their decisions, and because they might not have the medical knowledge to understand the implications of certain conditions. • Oncologist acknowledged that attempts to place decisions solely in parents' hands were unfair and place an undue burden on them, especially when the child was likely to die. *3. Timing* • Both groups of providers struggles with the timing and mechanics of communicating bad news to families, e.g. when to shift to palliative care, and providing support. • Oncologist were often uncertain about continuing offering additional treatments when cure was unlikely, and struggled with if they should recommend a shift in goals-of-care. *4. Lack of training* • All providers reported lack of formal training in communication. **Outcome 2: Facilitators** *1. Level of parent involvement* • Intensivists described the central importance of listening to parents and respecting their wishes. • Both specialties expressed the sentiment that 'parents are always right' in terms of their ultimate decision for their child's care, and acknowledged the need to respect parental beliefs and decisions because they felt that parents knew their child best. • Providers prepared families by giving them "permission" to consider limitations of interventions.	• Relatively small sample size with fewer intensivists than oncologists *Study funding* The Robert Wood Johnson Clinical Scholars Program **Risk of bias** <u>Aim and appropriateness of qualitative evidence:</u> Low risk Reason: Aim is clearly described, qualitative method is appropriate. <u>Rigour in study design or validity of theoretical approach</u> Low risk Reason: Grounded theory approach was used in this study (enables researchers to extract a new theory through the repeated process of making an inquiry) <u>Sample selection</u> Unclear Reason: Convenience sampling was used to select participants. Interviewer-participant relationship unclear. <u>Data collection</u> Unclear Reason: Data collection method i.e. duration and interviewer were clearly described. Place of interviews is not described. <u>Data analysis</u> Low risk Reason: Data analysis was clearly described and analysed utilizing consensus-based findings to develop themes. Saturation was achieved. <u>Results</u> Low risk Reason: Reasoning behind results is given. Results are credible.

		• Providers directed parents to “listen” both literally and figuratively to their children and consider the burdens of aggressive support and the suffering they may experience.	

Barriers and facilitators of shared decision-making and Advance Care Planning			
Hein et al. Identifying key elements for paediatric advance care planning with parents, healthcare providers and stakeholders: A qualitative study. Palliat Med 2020;34:300-8.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
Study design Qualitative design with a participatory approach, with two transdisciplinary workshops. First workshop: discussion groups, with aim to explore experiences with paediatric advance care planning Second workshop: dialogue groups, with as topics: participation of children and adolescents, paediatric advance care planning documentation, implementation and supplementary written materials Main study objective Identifying key components of paediatric advance care planning through direct discussions with all involved parties Additional study characteristics Germany; 2018; content analysis, using descriptive, content-based analysis following a data-driven strategy	Number and type of participants: 9 bereaved parents of 9 children with following diagnoses: • 3 metabolic • 2 oncological • 2 perinatal • 1 cardiological • 1 neuromuscular 14 healthcare providers and stakeholders: • 4 paediatricians • 1 emergency physician • 1 psychologist • 1 chaplain • 3 nurses (intensive care, out-patient) • 2 social workers • 2 special education teachers Age: *(mean, median, range)* Children: 2-16 years Sex: *(N (%))* Parents F=6 (66.7%), M=3 (33.3%) Professionals • First workshop: F=12 (85.7%), M=2 (14.3%)	Outcome definition: Outcome 1: Decision-making discussions Outcome 2: Documentation Outcome 3: Implementation Outcome 4: Timing Outcome 5: Participation of children and adolescents Results **Outcome 1: Decision-making discussions during ACP** *Barriers identified by professionals* • Professionals thought that parents were reluctant to engage in decision-making discussions or too overburdened to make a 'right' decision. • Professionals had the impression that parents would take sudden and inexplicable decisions. *Barriers identified by parents* • Parents disapproved of insensitive communication, discussions at wrong times and places, unsuitable coping with emotions and lack of experience or knowledge on the part of professionals. *Facilitators identified by parents* • Parents found it helpful to have several paediatric advance care planning meetings with facilitators. • Parents asked that professionals take into account individual needs, place the focus on the child, discuss hypothetical scenarios and allow decision-making without pressure. **Outcome 2: Documentation during ACP** *Barriers identified by professionals and parents* • Participants did not approve for supplementary written materials to be handed out without a personal conversation. *Barriers Identified by professionals* • Professionals worried about the unclear legal status of advance care planning documents for children. *Facilitators perceived by professionals and parents* • All participants agreed that all parties involved should sign the documents. • All participants recommended keeping minutes of all discussions to ensure continuity of the process. *Facilitators perceived by professionals* • Professionals recommended the use of brief recommendations for emergencies, supplemented by larger advance directives containing a characterisation of the child, the diagnosis and the course of the disease. • Contact information should be easily retrievable and organised in accordance to priority. **Outcome 3: Implementation of ACP** *Facilitators perceived by professionals*	Strengths: • We used a participatory approach to ensure an active involvement of participants and enable them to co-determine the design of the study. • Development of the intervention followed a bottom-up strategy instead of adapting adult advance care planning to paediatrics, in order to ensure that the programme fits to the specific needs of paediatric palliative care patients, families, healthcare providers and concerned stakeholders. • The diversity of participants enabled us to cover the whole process of paediatric advance care planning including discussions, written documents and their implementation. • Parents were present and active in both the first and second workshop. Limitations: • We only recruited professionals in Bavaria and bereaved parents at the Centre for Paediatric Palliative Care in Munich. • We excluded parents of current patients in paediatric palliative care and did not include children or adolescents in the

	• Second workshop: F=11 (78.6%), M=3 (21.4%) <u>Ethnicity:</u> Not mentioned <u>Religious preference:</u> Not mentioned <u>Level of education:</u> Not mentioned <u>Other:</u> *Age of children* Range: 2-16 years	• Stakeholders wanted to receive and be informed about the documents in a personal conversation, in order to ask questions, to discuss emergency procedures and to address in advance potential conflicts between institutional policies and the family's wishes. **Outcome 4: Timing of ACP** <u>Identified barriers and facilitators for the right timing of starting ACP</u> *Barriers identified by professionals* • Professionals were concerned about the possible lack of readiness of parents to engage in paediatric advance care planning. • According to professionals, when parents are not ready, they are more likely to reject treatment limitations for their child and less likely to participate in paediatric advance care planning discussions or to complete advance directives. *Barriers identified by parents* • Most participants favoured an early start of paediatric advance care planning. Some parents questioned this approach and demanded a previous assessment of parental readiness. However, even bereaved parents were not able to give a clear definition of a 'right time' to initiate advance care planning. • Parents described in detail what they considered as wrong times: shortly after breaking bad news, shortly after overcoming a crisis or under time pressure. • 'Timing might never be right'. However, missed opportunities to engage in paediatric advance care planning may lead to regrets. *Facilitators perceived by parents* • Parents confirmed that there was a time during which they preferred to avoid thinking about end-of-life issues. However, at some point, they realised that their child was not going to get better. Parents described this moment as a turning point, after which they felt ready to engage in advance care planning. • Timing might never be right. One solution might be to offer families timely to participate in paediatric advance care planning and to repeat this offer regularly in case parents do not feel ready. <u>Identified barriers and facilitators considering the iterative process of ACP</u> *Barriers perceived by parents* • Parents may not be aware of the necessity of updating documents; thus, professionals should take the initiative and guide parents through process iteration. *Facilitators perceived by parents and health care professionals* • Participants recommended embedding paediatric advance care planning in the continuous care of families. • Care should start as soon as possible and respond to the emerging needs and increasing awareness and acceptance of the situation during the course of the disease. **Results outcome 5: Participation of children and adolescents** *Barriers identified by parents and professionals* • Professionals regarded the participation of children of all ages in paediatric advance care planning as self-evident where as parents were sceptical about involving young children. • Parents worried about healthcare providers being insensitive and scaring younger children off.	sample; thus, their perspective is missing. • We had missing attendees during both workshops. *Study funding* This work was supported by the German Federal Ministry of Education and Research. **Risk of bias** <u>Aim and appropriateness of qualitative evidence:</u> Low risk Reason: Aim is clearly described, qualitative method is appropriate. <u>Rigour in study design or validity of theoretical approach</u> Low risk Reason: Theoretical framework is based upon knowledge on paediatric Advance Care Planning discussions identified in previous studies. <u>Sample selection</u> Unclear Reason: Different groups of participant were considered eligible. However, it was not reported how these participants were selected and approached. <u>Data collection</u> Unclear Reason: Data collection was described. Place, duration and interviewer were not reported. <u>Data analysis</u> Unclear Reason: Data analysis was clearly described and done using content analysis. Saturation was not reported.

		• Some professionals complained about parents acting as gatekeepers preventing them to talk to children. They wanted to obtain support in talking with parents about their child's participation in paediatric advance care planning. • A latent conflict was identified between parents and institutional care workers, both claiming to be experts and advocates for the child. *Facilitators perceived by parents and professionals* • Parents and professionals agreed that concerned adolescents should be offered separate conversations with professionals. • Parents asked for support to be able to talk themselves about sensitive issues with their children.	<u>Results</u> Low risk Reason: Reasoning behind results is given. Results are credible.

Barriers and facilitators of shared decision-making and Advance Care Planning			
Jack et al. A qualitative study of health care professionals' views and experiences of paediatric advance care planning. BMC Palliat Care 2018;17:93.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
Study design A qualitative methodological approach which drew upon a naturalistic interpretative design, with semi-structured interviews Main study objective To explore health care professionals' views and experiences of paediatric advance care planning in hospitals, community settings and hospices Additional study characteristics UK; 2016; thematic analysis	Number and type of participants: 21 health care professionals (HCPs): • 1 hospice nurse • 1 obstetrics and gynaecology consultant • 1 hospice nurse • 1 consultant paediatrician • 1 midwife • 1 community midwife • 1 neonatal nurse • 1 consultant paediatric oncologist • 1 complimentary therapist • 1 hospice nurse • 1 paediatric palliative care nurse • 1 bereavement specialist • 1 senior hospice nurse • 1 practitioner • 1 health visitor • 1 care assistant • 1 support worker • 1 consultant neonatologist • 1 palliative care nurse specialist • 1 neonatal nurse • 1 hospice nurse Age: Not reported Sex: Not reported Ethnicity: Not reported Religious preference: Not reported	Outcome definition: Outcome 1: timing of the conversation Outcome 2: supporting effective conversations around advance care planning Results **Outcome 1: timing of the conversation** *Waiting for the relationship with the family to form:* *Barriers perceived by HCPs* There were different opinions about when the ideal time is to start to have ACP conversations. • Some professionals suggested it should be after the relationship with the family is formed and allow the family to go at their pace. • Another participant suggested the need to look for cues, e.g. when families start to ask questions that could help to open-up the conversation to approach a discussion around ACP. *Parallel planning: Facilitators* • Participants mentioned the need for parallel planning to ensure the best plan for the future care of children, so different plans were ready for potential outcomes. *Avoiding a crisis situation: Facilitators* • Some participant stated that ACP conversations should starts as soon as possible, even at point of diagnosis. Which could avoid the conversation having to take place at a critical time for the parents in the situation that when a child suddenly deteriorates. • For children with life-limiting conditions it was recognised that the timing for the conversations to start needed to be related to the health of the child, and the professional needs to be aware of any deterioration, which emphasises the ongoing need for review. • A participant pointed out that conversation should ideally not take please in crises when parents are under incredible stress. **Outcome 2: supporting effective conversations around advance care planning** *Where to have the conversation: Facilitator* Good practice was to consider the environment in which the conversation was to take place. • A professional mentioned that some families prefer to have the conversations in a quieter environment, away from the child in hospital, or another location such as home.	Strengths: • Includes staff from different clinical settings, e.g. hospitals, hospice and community teams from a large geographical area Limitations: • Only two professionals were included who had been directly involved in the end-of-life care of children during the specified timeframe *Study funding* A children's hospice and a tertiary children's hospital **Risk of bias** Aim and appropriateness of qualitative evidence: Low risk Reason: Aim is clearly described, qualitative method is appropriate. Rigour in study design or validity of theoretical approach Low risk Reason: Study approach is drawn upon a naturalistic interpretative design. Sample selection High risk Reason: Purposive sampling was used to select participants. Interviewer-participant relationship unclear. Data collection Low risk Reason: Data collection method i.e. place, duration and interviewer were clearly described. Data analysis Unclear

	Level of education: Not reported Other: Not reported	• Professionals highlighted that starting ACP conversations can be facilitated by using photographs of the child. *Flexible planning of Advance Care Planning conversations: Facilitators* • Timing was important in starting ACP conversations as soon as possible to allow for a more flexible approach to the conversation, allowing a staged approach. • The need to slowly have the conversations and building up overtime allowed the news to be absorbed.	Data analysis was described in detail and done using thematic analysis. Saturation was not reported. Results Low risk Reason: Reasoning behind results is given. Results are credible.

Barriers and facilitators of shared decision-making and Advance Care Planning			
Lord et al. Assessment of Bereaved Caregiver Experiences of Advance Care Planning for Children With Medical Complexity. JAMA Netw Open 2020;3:e2010337.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
Study design Qualitative, semi-structured interviews Main study objective To explore the experiences of bereaved family caregivers with ACP for Children with Medical Complexity (CMC) Additional study characteristics Canada; 2018; thematic analysis	Number and type of participants: 13 bereaved parents of 12 children with medical complexity: • 11 genetic or congenital • 1 acquired Age: *(mean, median, range)* Parents: not reported Child's age at death • <1 year (n=1) • 1 to <5 years (n=4) • 5-10 years (n=4) • >10 years (n=3) Sex: *(N (%))* Parents F=12 (92.3%), M=1 (7.7%) Ethnicity: Not reported Religious preference: Not reported Level of education: Not reported Other: *Home technology supports* • Feeding tube (n=10) • Respiratory support (n=10) • Wheelchair (n=9) • Long-term intravenous access (n=3) *Time since child's death* • <1 year (n=5)	Outcome definition: Outcome 1: structure of care Outcome 2: ACP process Results **Outcome 1: structure of care** *Facilitators for ACP* • Many parents mentioned that trusted health care professionals who knew their child well were an important prerequisite for ACP. • Parents found the involvement of a subspecialty palliative care team helpful for exploring goals of care. **Outcome 2: ACP process** *Family and patient context* *Facilitators* • Understanding of the child's existing medical and technological needs, given that these often informed ACP decisions. • Parents mentioned that the degree of prognostic uncertainty as aspect of their child's unique situation needs to be taken into account. • Perceptions of their child's quality of life and specific goals for their children (both short- and long-term) were key contributors to ACP (e.g. goals for being at home together as a family as much as possible or having typical family outings). • Parents appreciate when their own expertise in their child's care was acknowledged and valued. • Medical decisions regarding care escalation during an acute deterioration were influenced by the child's past experiences with escalations in care under similar clinical circumstances, which guided decisions about whether to embark on similar interventions in the future. *ACP discussions* *Pace and timing* Parents' preferences regarding pace and timing varied. *Barriers:* • Many parents felt discussions should occur early and continue regularly. Others expressed that they felt that they should be the ones indicating when they are ready to engage in such conversations or they felt the conversations were to frequent.	Strengths: • Thematic saturation was reached Limitations: • Study took place at a single centre • Available participant pool was small, due to missing contact information • Participants were recruited from Complex Care and LTV clinics, the access to the multidisciplinary professionals could have informed ACP • Participants were almost exclusively mothers *Study funding* The Norman Saunders Complex Care Initiative at the Hospital for SickChildren. **Risk of bias** Aim and appropriateness of qualitative evidence: Low risk Reason: Aim is clearly described, qualitative method is appropriate. Rigour in study design or validity of theoretical approach Low risk Reason: Theoretical framework is based upon knowledge on Advance Care Planning and CMC identified in previous studies. Sample selection High risk Reason: Purposive sampling was used to select participants. Interviewer-participant relationship unclear. Data collection Low risk Reason: Data collection method i.e. place, duration and interviewer were clearly described.

	• 1-5 years (n=6) • >5 years (n=1) *Palliative care team involvement* • Yes (n=10) • No (n=1) • Unknown (n=1)	*<u>Setting</u>* *Facilitators* • A comfortable setting, e.g. a quiet room with adequate seating. • Having appropriate people present, e.g. health care professionals who know the patient and family well and key family caregiver (ensuring both parents are present). *Communication: Facilitators* • Expressing compassion by the HCPs.	<u>Data analysis</u> Low risk Reason: Data analysis was described in detail and done according to the Braun and Clarke steps of thematic analysis. Saturation was achieved. <u>Results</u> Low risk Reason: Reasoning behind results is given. Results are credible.

Barriers and facilitators of shared decision-making and Advance Care Planning			
Lotz et al. "Hope for the best, prepare for the worst": A qualitative interview study on parents' needs and fears in paediatric advance care planning. Palliat Med 2017;31:764-71.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
Study design Qualitative, practice-informing, semi-structured interview study Main study objective Investigate parents' views and needs regarding paediatric advance care planning Additional study characteristics Germany; 2013-2015; descriptive and evaluation coding	Number and type of participants: 11 parents of 9 deceased children with following diagnoses: • 3 cancer • 1 spinal muscular atrophy type I • 1 cystic fibrosis • 1 leukodystrophy • 1 hypo plastic left heart syndrome • 1 complex malformation syndrome • 1 unknown syndrome Age: *(mean, median, range)* Parents Median: 43 years (range: 36-50) Sex: *(N (%))* Parents F=8 (72.7%), M=3 (27.3%) Children F=5 (55.6%), M=4 (44.4%) Ethnicity: Not reported Religious preference: Not reported Level of education: Not reported	Outcome definition: Outcome 1: Paediatric ACP conversations Outcome 2: Statement of preferences Results **Outcome 1: Paediatric ACP conversations** 1. Paediatric ACP conversations *Barriers mentioned by parents* • Parents identified barriers; e.g. feeling not ready, wanting to focus on the present, and suppress burdensome thoughts. • Parents mentioned the physicians' reluctance to engage in pACP conversations because of prognostic uncertainty or because they do not face up to the facts. *Facilitators mentioned by parents* • Parents indicated that early conversations and planning ahead were helpful through empowering them to make good decisions for their child and be a good parent, facilitating coping, and giving a sense of control and security by preparing for what may come. • Parents advocated for an individually adapted approach that takes into account the respective situation, needs, and concerns of the whole family. • Parents mentioned bringing in an additional, uninvolved "listener" (e.g. a friend), involving nurses for support and exchange with other parents in similar situations as helpful. • Communication trainings for physicians to improve their communication skills. • Provision of written material to introduce and inform about pACP, allows parents to determine what they are ready to address. 2. Shared decision making *Facilitators* • All parents wanted to be included in decision-making as partners, to be listened to, and taken seriously. • Parents valued open and honest information, no matter how uncertain or potentially upsetting. *3. Gradual and sensitive approach* *Facilitators* • Parents unanimously wished for a step-by-step process with repeated discussions and sensitive communication respecting their needs and reservations. • Parents mentioned that healthcare providers should gently introduce and repeatedly offer pACP conversations but should not put pressure on parents.	Strengths: • None of the parents had known the interviewer beforehand. Limitations: • The interviewees were recruited by the help of personal contacts of M.F., which may have biased the results. • Most families had been supported by a SPPHC team; therefore, our study may not match the needs and barriers relating to pACP in other care settings when families receive less support. • The experience with paediatric palliative care may also have enhanced the parents' knowledge about pACP. • The retrospective design may still underestimate barriers to pACP because in retrospect parents may be more aware of the benefits. *Study funding* The work was supported by the "Stifterverband für die Deutsche Wissenschaft". **Risk of bias** Aim and appropriateness of qualitative evidence: Low risk Reason: Aim is clearly described, qualitative method is appropriate. Rigour in study design or validity of theoretical approach Low risk

	Other: *Child age at death* Median: 7.8 years (range: 0.4-23.8) *Time since death* Median: 2.2 years (range 1.3-3.6) *Advance directive* • AD (n=2) • No AD (n=3) • Not sure (n=4)	*4. Conversations about hope and non-medical issues* *Facilitators* • All parents mentioned that discussing psychosocial and daily life issues was particularly important to them. • Several parents highlighted the importance of strengthening parents by maintaining hope, e.g. that the child lives "longer than expected," that "the days together are good," and that they "can still do a lot for their children" and be good parents. *5. Involvement of the child* *Facilitators* • All parents wanted their child to be involved in pACP (except for infants) relative to its developmental maturity. • Parents felt that their child should be heard and taken seriously even if unable to make treatment decisions. **Outcome 2: Statement of preferences** *Barriers perceived by parents* • Many parents were reluctant to make decisions in advance but wanted to decide in due course. • Parents found it hard and burdensome to imagine future scenarios and were afraid to bind themselves. *Facilitators perceived by parents* • Parents wished to be encouraged to rethink their decisions or be able to revoke advance decisions. • Parents ascribed little importance to documenting decisions in a written plan and preferred oral agreements with the care providers	Reason: Theoretical framework is based upon knowledge on Paediatric Advance Care Planning identified in previous studies. Sample selection High risk Reason: Purposive sampling was used to select participants. Interviewer-participant relationship unclear. Data collection Unclear Reason: Data collection method i.e. duration and interviewer were clearly described. Place of interviews is not described. Data analysis Unclear Data analysis was described in detail and done using descriptive and evaluation coding according to Saldaña19 and the software MAXQDA-10. Saturation was not reported. Results Low risk Reason: Reasoning behind results is given. Results are credible.

Barriers and facilitators of shared decision-making and Advance Care Planning			
Mitchell et al. Parental experiences of end of life care decision-making for children with life-limiting conditions in the paediatric intensive care unit: a qualitative interview study. BMJ Open 2019;9:e028548.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
Study design In-depth, semi-structured qualitative interview study Main study objective Provide an in-depth insight into the experience and perceptions of bereaved parents who have experienced end of life care decision-making for children with life-limiting or life-threatening conditions in the paediatric intensive care unit Additional study characteristics UK; 2016; thematic analysis of transcripts and field notes was carried out using an inductive approach	Number and type of participants: *(diagnosis)* 17 parents of 11 deceased children Child's diagnosis/Together for Short Lives category: • Category 1 (n=5) • Category 2 (n=0) • Category 3 (n=2) • Category 4 (n=4) Age: Not reported Sex: *(N (%))* Parents: F=11 (64.7%), M=6 (35.3%) Ethnicity: Not reported Religious preference: Not reported Level of education: Not reported Other: *Age of child* Mean: 62 months/Median: 2 years (range: 5 months-18 years)	Outcome definition: Outcome 1: Parents have significant knowledge and experiences that influence the decision-making process Outcome 2: Trusted relationships with HCPs are key to supporting parents making end of life decisions Outcome 3: Verbal and non-verbal communication with HCPs im-pacts on the family experience Outcome 4: Engaging with end of life care decision-making can be emotionally overwhelming, but becomes possible if parents reach a 'place of acceptance' Results **Outcome 1: Parents have significant knowledge and experiences that influence the decision-making process** *Facilitators perceived by parents* • Parental decisions related to their child receiving high-intensity treatments could also be influenced by a sense that there was 'nothing to lose'; when the alternative was that, their child would almost certainly die. *Barriers perceived by parents* • Clinical uncertainty was a common experience and was particularly confusing and difficult for parents. In this situation, parents hoped for consensus among their HCPs. **Outcome 2: Trusted relationships with HCPs are key to supporting parents making end of life decisions** *Facilitators perceived by parents* • Trusted relationships with HCPs were highly valued. Continuity of care was a key factor underpinning the development of such relationships. *Barriers perceived by parents* • Relationships with HCPs were fragile and trust was easily compromised. Trust was compromised when: o parents discovered that an aspect of their child's medical treatment was not openly discussed o Parents felt that they were not being listened to. o Parents described conflicting advice as difficult. **Outcome 3: Verbal and non-verbal communication with HCPs impacts on the family experience** *Facilitators perceived by parents*	Strengths: • The study was conducted with parents whose children had died from a diverse range of life-limiting conditions. Limitations: • The number of participants is relatively small, and they were all recruited through the same PICU, which may limit the generalisability of the findings. • While data saturation was reached around the key themes reported here, it is likely that the parents who felt unable to participate may have had views, experiences and perceptions that were different. • There were several emerging themes in our data analysis, which are not reported here, including the experience of end of life care meetings, the care of siblings, spiritual needs and bereavement care. • The study's findings are based on retrospective accounts that may have been reframed over time. • We did not capture the experiences and perceptions of families who are currently in the process of making end of life care decisions for their children, or the views of any children or young people regarding their own end of life care decision-making. *Study funding* This work was supported by Birmingham Children's Hospital Research Foundation. **Risk of bias** Aim and appropriateness of qualitative evidence: Low risk Reason: Aim is clearly described, qualitative method is appropriate.

	Time since bereavement Mean: 13 months/Median: 10 months (range: 5-23)	• Information should be presented in a clear and sometimes brutally honest fashion. It helped if this information was given by a trusted HCP. *Barriers perceived by parents* • Meetings to discuss end of life care with the clinical team were challenging experiences for parents. They were frequently outnumbered by an 'overwhelming' number of staff which they interpreted as an indication of the severity of the situation **Outcome 4: Engaging with end of life care decision-making** *Facilitators perceived by parents* • Clear guidance and the support of trusted clinicians was critical. • Parents wanted to feel that they have made a choice to 'say goodbye' rather than having to make a choice to withdraw life-sustaining treatments. • Parents described the need to be in a 'place of acceptance' in order for ACP conversations to take place. • Parents wanted to understand/observe implications of particular interventions, such as ventilation, before this was considered in an ACP. *Barriers perceived by parents* • Parents experienced wide-ranging, intense emotions towards the end of their child's life, which affected their ability to take part in end of life care decision-making. • Not all of the parents were aware of ACP, and many had not experienced this for their child. There were opposing views, with some parents feeling that ACP 'would have been very useful', and others that a plan which considered the child's death was not acceptable; 'never an option'. • Parents reported that the timing of conversations with respect to ACP was important, but could be particularly difficult where there was uncertainty about the likely outcome of a treatment or procedure, such as surgery or a new medical intervention.	Rigour in study design or validity of theoretical approach Low risk Reason: Reason: Theoretical framework is based upon knowledge on end of life care decision-making identified in previous studies. Sample selection High risk Reason: Purposive sampling was used to select participants. Interviewer-participant relationship unclear. Data collection High risk Reason: Data collection method i.e. place, duration and interviewer were not described. Data analysis Low risk Reason: Thematic analysis was carried out using an inductive approach as described by Braun and Clarke. Saturation was achieved. Results Low risk Reason: Reasoning behind results is given. Results are credible.

Barriers and facilitators of shared decision-making and Advance Care Planning			
Orkin et al. Toward an Understanding of Advance Care Planning in Children With Medical Complexity. Pediatrics 2020;145:e20192241.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
Study design Qualitative content-analysis study comprising demographic surveys and individual semi structured interviews Main study objective	Number and type of participants: 14 mothers of 14 children 11 healthcare professionals (8 physicians, 2 nurses, 1 social worker) with following specialty:	Outcome definition: Outcome 1: Holistic mind-set Outcome 2: Discussion content Outcome 3: Communication enhancers Outcome 4: ACP definition Results **Outcome 1: Holistic mind-set** This study suggests that the patient and family should be the main consideration when leading ACP discussions.	Strengths: • First qualitative study exploring how ACP is experienced by parents of CMC and their HCPs.

To develop an in-depth understanding of the ACP experiences from the perspectives of both parents and health care providers (HCPs) of children with medical complexity (CMC) <u>Additional study characteristics</u> Canada; 2016; content analysis	• 2 complex care • 3 paediatric medicine • 2 respiratory medicine • 1 paediatric haematology and oncology • 1 critical care • 1 neonatal intensive care • 1 palliative care <u>Age:</u> *(mean, median, range)* Parents • 26-35 years (n=2) • 36-40 years (n=6) • 41-50 years (n=3) • Not specified (n=3) Healthcare professionals • 36-40 years (n=1) • 41-50 years (n=6) • 50+ years (n=5) <u>Sex:</u> *(N (%))* Parents F=14 (100%), M=0 (14%) Healthcare professionals F=5 (45.5%), M=6 (54.5%) <u>Ethnicity:</u> • White (n=6) • Mixed race (n=1) • Jewish (n=1) • Filipino (n=2) • South Asian (n=1) • Not specified (n=3) <u>Religious preference:</u> Not reported <u>Level of education:</u> Parents:	*Facilitators perceived by HCPs* • HCPs noted the importance of taking time to recognize, understand, and support diversity and individuality between families. *Facilitators perceived by parents* • Parents mentioned the importance of feeling involved, respected, and accepted **Outcome 2: Discussion content** *1. <u>Quality of life</u>* *Barriers perceived by parents* • Parents mentioned that HCPs often underestimate their child's quality of life, highlighting the importance of asking the parents instead of interfering based on clinical status. *2. <u>Believes and values</u>* *Facilitators perceived by HCPs* • HCPs noted that understanding family's values and believes is a foundational aspect of ACP, allowing them to tailor care individually.' *Facilitators perceived by parents* • Several parents reinforced that understanding family's values and believes is a foundational aspect of ACP, and mentioned how their belief system and values guided their decision-making. *3. <u>Hopes and goals</u>* *Facilitators perceived by HCPs* • HCPs expressed that understanding family's hopes and goals in the context of their child's illness is an essential aspect of ACP. *Facilitators perceived by parents* • Parents indicated that ACP discussions including conversations surrounding hopes and goals for their child were beneficial for their child's life, because they provided opportunities to collaboratively work toward and/or reframe hopes and goals. **Outcome 3: Communication enhancers** 7 enhancers of ACP emerged from the data; *1. <u>Partnership in shared decision-making</u>* *Facilitators perceived by HCPs* • HCPs agreed that decisions should be made in partnership with families, respecting their unique decision-making preferences. *Barriers perceived by HCPs* • HCPs had varied perspectives regarding family-HCP partnership for SDM. Some felt parents were given too much responsibility in ACP. Others felt the decision-making process should be more collaborative. *Barriers perceived by parents* • Parents showed a large variability in how they preferred ACP decisions to be made. Some wanted to always be seen as the expert. Some wanted the HCP to make the decisions. Others wanted the HCP to provide them with all options and guidance regarding what they think is right but allow the parent to make the final decision. *2. <u>A supportive setting</u>* *Facilitators perceived by parents and HCPs*	• Sampling to select parents of children with various medical conditions, various ethnicities and economic backgrounds reflecting Ontario's diversity. <u>Limitations:</u> • Conducted in a single tertiary care institution • All parent participants were English-speaking women from predominantly well-educated, middle- to high-income families. *Study funding* The Norman Saunders Complex Care Initiative, The Hospital for Sick Children. **Risk of bias** <u>Aim and appropriateness of qualitative evidence:</u> Low risk Reason: Aim is clearly described, qualitative method is appropriate. <u>Rigour in study design or validity of theoretical approach</u> Low risk Reason: Theoretical framework is based upon knowledge on

	• Diploma or certificate from community college or nursing (n=2) • Diploma or certificate from trade, technical, vocational, or business college (n=1) • Some university experience (n=1) • Bachelor's or undergraduate degree or teacher's college (n=4) • Master's degree (n=3) • Not specified (n=3) Other: *Parents:* *Documented ACP discussion* Yes (n=14) *Health care professionals:* *Years of medical practice* • 5-10 years (n=2) • 10+ years (n=9) *Formal palliative care training* • Yes (n=2) • No (n=9)	• Ensuring a comfortable and appropriate location, budget enough time, provide the opportunity for all key team and family members to be present, and ensure that the family feels supported. *3. Early and ongoing conversations* *Facilitators perceived by parents and HCPs* • Participants emphasized that ACP should start at time of diagnosis, should occur before a medical crisis, and be an ongoing and dynamic part of the child's care. *4. Consistent language and practice* *Facilitators perceived by HCPs* • Use of constituent and unambiguous language by HCPs can enhance ACP. • HCPs were cognizant of this and advocated for better communication through use of clear, non-medicalized language. • HCPs stated the importance of delivering a consistent message between different HCPs and health care teams. *5. Family readiness* *Barriers perceived by HCPs* • Some HCPs mentioned the need to gauge family readiness and follow the family's lead. Others felt that families might never feel ready. *Barriers perceived by parents* • Parents stated that HCPs should respect their feelings and not push for conversations when they make it clear that they are not ready to engage. *6. Provider expertise in ACP discussions* *Facilitators perceived by HCPs and parents* • Some HCPs and parents stated that specific training and capacity building would be beneficial. *Facilitators perceived by HCPs* • All HCPs agreed that expertise can enhance ACP conversations. *7. Provider comfort in ACP discussions* *Barriers perceived by HCPs* • Many HPCs think that provider discomfort is a prominent barrier to ACP discussions. **Outcome 4: ACP definition** *Barriers perceived by HCPs* • Many caregivers had never heard of the term ACP. • HCP held varied perspective regarding ACP's definition; some felt it was geared towards end-of-life specifically. Others had a more general definition, like understanding the family and their goals. *Barriers perceived by parents* • Some parents viewed ACP as negative and as preparing for the worst. Others mentioned that they had positive experiences with ACP in the past and that it meant planning for the future	Advance Care Planning identified in previous studies. Sample selection High risk Reason: Purposive sampling was used to select participants. Interviewer-participant relationship unclear. Data collection Low risk Reason: Data collection method i.e. place, duration and interviewer were clearly described. Data analysis Low risk Reason: Data analysis was described in detail and done using inductive, 4-step content analysis. To achieve theoretical saturation a sample size of 25 was defined. Results Low risk Reason: Reasoning behind results is given.

3.2.2 Gezamenlijke besluitvorming

Barriers and facilitators of shared decision-making and Advance Care Planning			
Cicero-Oneto et al. Decision-making on therapeutic futility in Mexican adolescents with cancer: a qualitative study. BMC Med Ethics 2017;18:74.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**

Study design
Qualitative study with individual, face-to-face, semi-structured, and in-depth interviews
 	
Main study objective
Explore in-depth and explain the decision-making process from the perspective of Mexican oncologists, parents, and affected adolescents and to identify the ethical principles that guide such decision-making
 	
Additional study characteristics
Mexico; 2013-2015; thematic analysis
	Number and type of participants:
	
	Following population groups are interviewed:
	• 13 paediatric oncologists
	
	• 13 parents/primary cares of 13 children with following diagnosis:
	  • 2 haematological neoplasm
	  • 9 extra cranial solid tumour
	  • 2 tumour of the CNS
	7 out of 13 children had already died
	
	• 6 children (4 children of the participating parents, and 2 other children with incurable or terminal phase cancer) with following diagnoses:
	  • 1 hepatic primitive neuroectodermal tumour
	  • 1 colorectal adenocarcinoma
	  • 1 pilocytic astrocytoma
	  • 1 osteosarcoma
	  • 2 acute lymphoblastic leukaemia
	2 of these children were aware of the prognosis.
	
	Age:
	(mean, median, range)
	Oncologists:
	Median: 38 years (range: 32-52)
	
	Parents/primary cares:
	Median: 40 years (range: 21-60)
		Outcome definition:
		Outcome 1: Flow of information to inform decision-making
		Outcome 2: Decision-maker and stakeholders involved in decision-making (their values, preferences, and beliefs)
		Outcome 3: Barriers and facilitators to decision-making
		
		Results
		Outcome 1: Flow of information to inform decision-making
		Facilitators perceived by oncologists
		• Oncologists said that they preferred that the parents be the ones to determine the type and amount of information that they needed.
		Barriers perceived by oncologists
		• All oncologists thought that the announcement of therapeutic futility places the parents in a psychological state of vulnerability that reduces parents' capacity to understand the fundamental risk of deciding.
		• Oncologists revealed that they inform children only when the parents authorize it; hence, they inform the parents first. Oncologists think that the child is the one who should make choices about further treatment.
		
		Facilitators perceived by parents
		• 6/13 parents indicated that confidence in the hospital in which their children were being treated was a pivotal element in not having doubts about the treatment given to their children.
		Barriers perceived by parents
		• 2/13 parents stressed that the medical discourse, which the oncologist used in communicating the therapeutic futility to them, made the information provided incomprehensible.
		
		Facilitators perceived by children
		• The children interviewed preferred to hear the information from their parents.
		
		Outcome 2: Decision-maker and stakeholders involved in decision-making (their values, preferences, and beliefs)
		The oncologists thought that the decision about futility is strictly medical; they perceived their role as HCP as one of their role is one of "orienting" the choice of the parents toward what they thought was beneficial for the patient.
		Facilitators perceived by oncologists
		• All the oncologists said that the parents are the ones legally responsible; nonetheless, they said that they think that the children should be made aware of their impending death.
		Barriers perceived by oncologists
		• The majority of oncologists mentioned that it was difficult to specify an age at which the child should be informed the poor prognosis.
		
		Facilitators perceived by parents
			Strengths:
			• The participating oncologists were of different genders, ages, and work experience; the participating parents/carers and children were of different genders, ages, educational background; the children had distinct types of tumours; and the participating hospitals are national referral medical centres that provide medical care to patients from various parts of Mexico, provide a good foundation for developing a better understanding of how the decision-making process on therapeutic futility is carried out in Mexican children with cancer.
			
			• The methods used and the active focus of the process of research that was carried out guaranteed the representativeness of the sample.
			
			Limitations:
			• It would be expected that patients from cultural groups characterized by 'high power-distance', like those in Mexico and Latin America countries, accept authoritative and "expert" recommendations from their doctors. Different from low power-distance culture, like the U.S., in which a patient from this type of cultural background would expect to share opinions, concerns, and beliefs with their doctor.
			
			• This study relies solely on semi-structured, in-depth interviews data from the main agents of the decision-making process. This

	Age children of parents/primary carers interviewed Median: 14 years (range: 13-18) Children: Median: 15 years (range: 13-18) <u>Sex:</u> *(N (%))* Oncologists: F=8 (61.5%), M=5 (38.5%) Parents/primary carers: F=10 (77%), M=3 (23%) *Sex of children of parents/primary carers interviewed* F=2 (15.4%), M=11 (84.6%) Children: F=2 (33.3%), M=4 (66.7%) <u>Ethnicity:</u> Not reported <u>Religious preference:</u> Not reported <u>Level of education:</u> Parents: • ≤ Secondary (n=5) • Preparatory (n=5) • Bachelor's (n=2) • Master's (n=1) <u>Other:</u> *Time between disclosure of therapeutic futility and death* Median: 75 days (range: 3-365) *Time between start of non-curative treatment and death* Median: 30 days (range: 3-270)	All the parents agreed that they were the ones legally responsible for their children and that the oncologists are the true decision-makers. • Parents wanted the healthcare professionals, particularly the oncologists and the nurses, to display an interest in the patient, to explain the situation clearly, and to speak the truth. • Parents expressed the need for messages of hope, messages that "lift the spirits". *Facilitators perceived by children* • The children interviewed focused on the need for their oncologists to speak to them truthfully. *Barriers perceived by children* • When children stated that they no longer wanted to undergo more chemotherapy, they were encouraged by their parents to continue the treatment. **Outcome 3: Barriers and facilitators to decision-making** *Facilitators perceived by oncologists* • Father or mother made a firm decision concerning not to continue curative treatment. *Barriers perceived by oncologists* • Oncologists mentioned parental difficulty of understanding and accepting the prognosis. • Oncologist mentioned an emotional tie to the patient. • Oncologists mentioned their own lack of training in psychology and/or palliative care. *Facilitators perceived by parents* • Parents mentioned the prognosis given to them in terms of death, and not wanting to see their child suffer more or undergo a lot of pain. *Barriers perceived by parents* • 2/13 parents mentioned, "not acknowledging the situation, or not wanting to see..." *Facilitators perceived by children* • 1/2 children mentioned having heard of the prognosis in terms of probabilities of death in the short term and to have previously obtained information about the disease from the internet. • 1/2 children mentioned learning the prognosis in terms of null possibility of cure.	could be seen as a limitation to the full understanding of the emic perspective on the Mexican culture—as we did not include more ethnographic techniques for data generation or multiple sources of data. • This study is not generalizable in the same sense of quantitative research, because it involves non-random, purposive sample of individuals who contributed to the generation of data. *Study funding* Partially funded by the Hospital Infantil de Mexico "Federico Gomez" with Mexican National Ministry of Health's Federal Funds. **Risk of bias** <u>Aim and appropriateness of study design</u> Low risk Reason: Aim is clearly described, qualitative method is appropriate. <u>Rigour in study design or validity of theoretical approach</u> Low risk Reason: Study uses Howards descriptive theoretical decision analysis model as a theoretical approach <u>Sample selection</u> High risk Reason: Purposive sampling was used to select participants. <u>Data collection</u> Low risk Reason: Method of data collection is clearly described and adequate.

	Children informed on therapeutic futility: • Yes (n=2) (active role adopted in decision-making process) • No (n=4) (passive role adopted in decision-making process)		Data analysis Low risk Reason: Data analysis is adequately described and in accordance with the theoretical approach. To achieve theoretical saturation a sample size of 32 was defined. Results Low risk Reason: Reasoning behind results is given and described according to the theoretical framework.
Barriers and facilitators of shared decision-making and Advance Care Planning			
Day et al. "We just follow the patients' lead": Healthcare professional perspectives on the involvement of teenagers with cancer in decision making. Paediatric Blood Cancer 2018;65.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
Study design In-depth, semi-structured interviews and participant observations (during psycho-social meetings, day-care meetings and pre-ward round meeting, and informal conversations) Main study objective To investigate health care professionals' (HCP) views of teenagers' involvement in decisions about their care and treatment for leukaemia. Additional study characteristics UK; study years not reported; theoretical perspective of interactionism as framework; observations during 9 months	Number and type of participants: 58 health-care professionals specialised in haematology, haematopoietic stem cell transplantation or palliative care, working principally with patients aged 13-25 years. • 6 consultants • 19 junior doctors (foundation year, registrar/resident and specialty registrar/fellow) • 9 Clinical Nurse Specialists • 10 ward nurses • 14 allied HCP (psychologists, physiotherapists, dieticians and social workers) Age: Not reported Sex: Not reported	Outcome definition: Outcome 1: Do the 'right thing' Outcome 2: Act on the care and treatment preferences of the teenager Outcome 3: Openly disclose information about the teenager's condition, prognosis and treatment Outcome 4: Family communication style Outcome 5: Stage of the illness Outcome 6: Nature of the disease Results **Outcome 1: Do the 'right thing'** *Facilitators perceived by HCPs* • When end-of-life issues came to the fore, HCPs acknowledged that it might be beneficial to involve teenagers and parents to identify the 'right thing' from the family's perspective. *Barriers perceived by HCPs* • The 'right thing' determined by clinical assessment did not always align with what teenagers or parents wanted or deemed 'right'. **Outcome 2: Act on the care and treatment preferences of the teenager** *Facilitators perceived by HCPs* • HCP mentioned to 'follow the teenagers' lead'; this was advocated for certain decisions (e.g. place of care, minor procedures). *Barriers perceived by HCPs* • Some HCP recognised that acting of teenagers' treatment preferences might not be possible, feasible or desirable, especially for decisions governed by internationally agreed treatment protocols, or those where there was a likelihood of serious harm, death or	Strengths: - Limitations: • Limited generalizability, since HCP reports may be influenced by the unique population in this large tertiary referral hospital where the study was conducted. • Demographic data on HCP were not collected • Not all recruited HCP could be interviewed or engaged in an informal discussion, therefore some views may have been missed • This study focused specifically on decision making in haematological cancers *Study funding* Authors funded by several sources

	Ethnicity: Not reported Religious preference: Not reported Level of education: Not reported Other: *Number of whom were interviewed* • Consultant (n=5) • Clinical Nurse Specialist (n=4) • Ward nurse (n=1) • Allied HCP (n=2) *Number with whom informal conversations were held* • Consultant (n=5) • Junior doctor (n=4) • Clinical Nurse Specialist (CNS) (n=5) • Ward nurse (n=3) • Allied HCP (n=2) *Number of whom spoke at multi-disciplinary team (MDT) meetings* • Consultant (n=6) • Junior doctor (n=19) • Clinical Nurse Specialist (n=9) • Ward nurse (n=10) • Allied HCP (n=14)	suffering (e.g. refusal of curative treatment, reduction of chemotherapy dose, escalation of care to intensive care). **Outcome 3: Openly disclose information about the teenager's condition, prognosis and treatment** *Facilitators perceived by HCPs* • Open communication is paramount for involving teenagers in decision making, but this did not always mean explicit verbalisation of every outcome. • HCP recognize the importance of establishing and respecting what the teenager wanted and needed to know at different times across the illness. **Outcome 4: Family communication style** *Facilitators perceived by HCPs* • HCP felt they should take the lead on what to disclose from the teenagers themselves. They assigned responsibility to teenagers for signalling verbally and non-verbally their desired degree of involvement in decision-making. • HCPs considered the other family members' communication preferences, and acknowledged the importance of the family's role. • HCP acknowledged the importance of respecting family communication styles and allowing parents and teenagers the space to establish their roles in decision-making. *Barriers perceived by HCPs* • Common tensions between age-appropriate growing independence and the necessary dependence of a teenager diagnosed with cancer sometimes led to confusion about the influence of parents and families on teenagers' choices. **Outcome 5: Stage of the illness** *Facilitators perceived by HCPs* • HCP suggested that at the point that treatment begins to fail, families and teenagers are pulled into the decision-making, and are asked to voice their opinions and preferences. *Barriers perceived by HCPs* • Strict internationally agreed protocols, limited teenagers' involvement to listening and understanding, rather than choosing course of action. • HCP mentioned that it was difficult to respond to EOL preferences, because the final authority for such decisions making towards EOL lay with HCP and the clinical consensus. **Outcome 6: Nature of the disease** *Barriers perceived by HCPs* • During periods of uncertainty, involvement of other professionals was prioritised in reaching a decision, which limited the role for the teenager in the process.	**Risk of bias** Aim and appropriateness of qualitative evidence: Low risk Reason: Aim is clearly described, qualitative method is appropriate. Rigour in study design or validity of theoretical approach Low risk Reason: This study was part of a lager ethnographic study, theoretical perspective of interactionism was used in which the social world is recognised as a place where meaning is formed through interaction between individuals. Sample selection Unclear Reason: Data were collected from the multi-disciplinary specialist teenage and young adult haematology team. Unclear how participants were selected. Data collection Low risk Reason: Data collection method was clearly described Data analysis Unclear Reason: Analytical process was described. It is unclear whether theme saturation was achieved. Results Low risk Reason: Reasoning behind results is given. Results are credible.

Barriers and facilitators of shared decision-making and Advance Care Planning			
Henderson et al. Preparing Pediatric Healthcare Professionals for End-of-Life Care Discussions: An Exploratory Study. J Palliat Med 2017;20:662-6.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
Study design Qualitative design using a group interview Main study objective To identify what paediatric healthcare professionals consider important when preparing for an End of Life discussion Additional study characteristics Australia; 2015; descriptive content analysis	Number and type of participants: 36 healthcare professionals (including medical, nursing, and allied health professionals) Age: Not reported Sex: Not reported Ethnicity: Not reported Religious preference: Not reported Level of education: Not reported Other: Not reported	Outcome definition: Outcome 1: Communication Outcome 2: Healthcare professional perspectives Outcome 3: Interdisciplinary team role Outcome 4: Patients and carers Outcome 5: Practical issues Outcome 6: Addressing mistakes Outcome 7: Healthcare professional education Results **Outcome 1: Communication** *Facilitators perceived by Health Care Professionals* • *General communication skills* o It takes more than one discussion. o It is important to listen actively with all five senses. o Think before you speak. o Reflect on where you could go wrong with an EoL discussion. • *Language* o Use the right language. o Knowing what not to say, such as 'things happen for a reason' • *Cultural awareness* o Have cultural humility and curiosity. o Knowing the culture; be aware of cultural awareness and language, how they are used, and what is said. **Outcome 2: Healthcare professional perspectives** *Facilitators perceived by HCPs* • *Acknowledging anxiety* o Acknowledge your own anxieties to ensure you have space for listening and observing what the family is experiencing in the complex multi-layered moment. o Acknowledge the uncertainty of each case. • *Ability and expertise* Know your professional expertise, the areas you lack expertise in and when you should refer. **Outcome 3: Interdisciplinary team role** *Facilitators perceived by HCP* • *Team debriefing* o Prepare behind the scenes. o Build strong foundations for the EoL discussion. o Workout who is the most appropriate person (to lead the discussion).	Strengths: • The study sample achieved interdisciplinary representation comprising clinicians working across a range of tertiary and regional services in Queensland, Australia. Limitations: • Not all participants spoke in the interview; however, anonymous posting of comments ensured that all participants were able to have their opinions included. • Results are limited to the experiences of clinicians working in palliative care services in one Australian state. • Data saturation cannot be confirmed. *Study funding* Not reported **Risk of bias** Aim and appropriateness of qualitative evidence: Low risk Reason: Aim was clearly described, qualitative method was appropriate Rigour in study design or validity of theoretical approach Unclear Reason: Theoretical framework was not clearly described, interviews were framed using two questions.

		• *Information provision*
		  ○ When HCPS know the family from the start, it is easier to prepare and journey with the family.
		  ○ Clinical history — HCPs should be aware of expectations of family.
		  ○ HCPs know what key supports for families are in place, e.g., grandparents, close friend, elder from community, spiritual adviser?
		  ○ HCPs should have facts about families correct.
		
		Outcome 4: Patients and carers
		Facilitators perceived by HCPs
		Patients and carers
		  ○ We have our agenda of what we need to achieve.
		  ○ Be aware of the importance of needs of the child and their family, including significant others.
		  ○ Appreciate pre-existing relationship(s) with families.
		
		Outcome 5: Practical issues
		Facilitators perceived by HCPs
		• *Time of the discussion*
		  ○ The timing has to be right for the family rather than health professionals.
		• *Space for discussion*
		  ○ Find space to do EOL discussions, nothing is worse than having to do discussions in a busy ward area
		  ○ Leave practitioner distractors such as mobile phones and pagers with someone else.
		
		Outcome 6: Addressing mistakes
		Facilitators perceived by HCPs
		• *Addressing mistakes*
		  ○ Acknowledge your mistakes to family and learn from them.
		  ○ It can be helpful to acknowledge if you have said something wrong—even if not immediate.
			<u>Sample selection</u>
			Unclear
			Reason: 85 health care professionals attending a 2-day paediatric palliative care education workshop were invited to participate in the interview. Unclear whether a interviewer-participant relationship could influence results.
			
			<u>Data collection</u>
			Unclear
			Reason: Data collection method was described inadequately, unclear who conducted the interview.
			
			<u>Data analysis</u>
			Unclear
			Reason: Inadequate description of the analytic process. It is likely that the point of theoretical saturation was achieved as new themes (not found in other articles) were found.
			
			<u>Results</u>
			High risk
			Reason: Reasoning behind the results is not given. Therefore it is difficult to interpret results.

Barriers and facilitators of shared decision-making and Advance Care Planning			
Kelly et al. Identifying a conceptual shift in child and adolescent-reported treatment decision making: "Having a say, as I need at this time". Pediatr Blood Cancer 2017;64.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
Study design Descriptive qualitative research methods, with interactive interview techniques Main study objective To assess treatment decision making (TDM) preferences and experiences of children with cancer, and assess how children with cancer viewed their decisional experiences Additional study characteristics USA; study years not reported; constant comparative qualitative analysis	Number and type of participants: 29 newly diagnosed children, with following diagnoses: • 15 leukaemia and lymphoma • 7 central nervous system tumor • 7 solid tumour 30 interviews were conducted Age: *(mean, median, range)* Range: 9-17 years • <13 (n=15) • >13 (n=14) Sex: *(N (%))* F=14 (48.3%), M=15 (51.7%) Ethnicity: • Caucasian (n=13) • African American (n=11) • Hispanic (n=3) • Other (Middle Eastern, Filipino) (n=2) Religious preference: Not reported Level of education: Not reported Other: *Time since diagnosis*	Results **Illness and treatment communication preferences** *Facilitators perceived by children* • Children consistently mentioned their parents' and clinicians' central roles in meeting their communication needs. Communication preferences, desire for information and involvement in treatment discussions, were primarily influenced by what was happening to the child at a given point. • Undergoing treatment facilitated children's learning about their disease and treatment and helped them to be more involved in illness and treatment communication. **Parents and physicians acted in child's best interest** • Children mentioned how their parents and physicians were always acting with their best interests in mind. • Children stated that they trust that their parents know how much information they can handle. **Information preferences** *Facilitators perceived by children* • Children of all ages reported that they did not want to make "big" decisions. However, they might want to participate in discussions. • Children wanted more say in treatment discussions about smaller decisions because they knew how their bodies reacted to certain care procedures based on their prior experience. *Barriers perceived by children* • Information preferences varied and changed as children learned about their condition. Receiving information could either decrease anxiety or be overwhelming and cause distress; o Some children reported wanting to know "everything," including prognosis and test results. o Others described wanting to know their treatment plans and what was going to happen next. o Other children did not want to be bothered, they "just want the doctors to help them get better and to help them get out of there". • When children were very ill or in pain, they did not want to be part of treatment discussions, but just wanted to get better. **Preferences for decision-making** *Facilitators perceived by children* • Children had more control over smaller decisions, e.g. type of central venous line that would be placed or how the line was accessed. *Barriers perceived by children* • Children did not always wanted to have a say, they sometimes simply wanted to be told what to do.	Strengths: - Limitations: • Findings are based on children's retrospective accounts • Need to conduct research in varying cultures, family types, and other paediatric illnesses *Study funding* The Alex Lemonade Stand Foundation through a Discovery Award **Risk of bias** Aim and appropriateness of qualitative evidence: Low risk Reason: Aim was clearly described, qualitative method was appropriate Rigour in study design or validity of theoretical approach Low risk Reason: Theoretical framework is based upon knowledge on Treatment decision making identified in previous studies. Sample selection High risk Reason: Purposive sampling was used to select participants. None of the interviewers had clinical relationships with the research participants. Data collection Low risk Reason: Data collection method i.e. duration, place and interviewer were clearly described.

	• <6 months (n=7) • 7-12 months (n=5) • 13-24 months (n=8) • >24 months (n=10) *Relapse* • Yes (n=9) • No (n=20)	• Having no say meant not being present for treatment discussions, but when this occurred, some children spoke negatively about it. They reported feeling powerless or that nobody cared about their thoughts. **Influence of making decisions as a child** *Facilitators perceived by children* • Being part of treatment discussions provided an opportunity for children to influence their situation by learning and applying self-management skills (e.g. learning about the illness and influencing decisions to improve symptoms). • Children stated that having a say made them feel happier, less scared, more satisfied, and comfortable with decisions made. *Barriers perceived by children* • Being involved could expose the child to distressing information or pressure to make choices they were unable to make. • Children worried about making a wrong decision if they had to choose, and they were more comfortable with their parents or doctors making decisions. • Not having a say made some children feel ignored and worried that “the doctors might do something wrong because no one is telling me what is going on”. • Children acknowledged the possibility of being upset by knowing more about their condition or misinterpreting the discussion.	<u>Data analysis</u> Low risk Reason: Data analysis process was described in detail. Saturation was quite likely as after analysis of 20 interviews, 10 additional interviews were conducted to confirm results. <u>Results</u> Low risk Reason: Reasoning behind results is given. Results are credible.

Barriers and facilitators of shared decision-making and Advance Care Planning			
Mekelenkamp et al. Parental experiences in end-of-life decision-making in allogeneic pediatric stem cell transplantation: "Have I been a good parent?". Pediatr Blood Cancer 2020;67:e28229.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
Study design Qualitative descriptive study with in-depth face-to-face individual interviews and a background questionnaire Main study objective To gain insight in parental experiences in EOL decision-making in allogeneic paediatric HSCT Additional study characteristics The Netherlands; 2014-2015; thematic analysis	Number and type of participants: 14 parents of 8 children that died within a year after allogeneic HSCT, with following diagnoses: • 2 bone marrow failure • 4 malignancy • 1 hemoglobinopathy • 1 primary immune deficiency Age: Parents ≥40 (n=14) Children age at death • <12 years (n=1) • 12-16 years (n=4) • ≥16 years (n=3) Sex: Parents F=7 (50%), M=7 (50%) Children F=3 (37.5%), M=5 (62.5%) Ethnicity: Parents • Dutch (n=13) • Mixed (Dutch and other) (n=1) Religious preference: Not reported Level of education: Parent: • Low (n=1) • Middle (n=8) • High (n=5)	Outcome definition: Outcome 1: Survival-oriented decision-making Results **Outcome 1: Survival-oriented decision-making** *Facilitators perceived by parents* • Parents experiences most decisions as cure directed. Parents did not feel having made specific decision, but rather felt involved in a HCPs-guided decision-making process *Developing a frame of reference* *Facilitators perceived by parents* • Parents searched for a frame of reference to get control over the HSCT situation and to safeguard chances for survival, using different strategies; e.g. active searching for information, comparing the current situation with earlier experiences, and peer experiences. *Barriers perceived by parents* • Parents experienced the complexity of the treatment as hard to understand, and therefore felt unable to take decision-making responsibility. *Having confidence in and hope for a good outcome: Facilitators perceived by parents* • Parents felt supported by a consistent, regularly explanation of treatment decisions and the feeling they were heard in their concerns. *Preventing anticipated regret* • The parental perspective on preventing anticipated regret was focused on survival during the treatment process. As it became clear that the child would die soon, their perspective changed to avoidance of further suffering. *Barriers perceived by parents* • Parents mentioned that they would blamed themselves if their decisions would have led to a worsening scenario or even death. *Advocating getting the most out of treatment: Facilitators perceived by parents* • Many parents mentioned that their intention was to get the most out of treatment. The goals of this was to become and stay convinced	Strengths: • This study provides new in-depth insight in the meaning of parenthood in EOL decision-making in paediatric HSCT, especially in rapidly worsening situations • The opportunity to interview the parents within 2 years after the loss of their child, which provides a direct insight given the difficulty of studying this vulnerable population • Used several methods in accordance with the standards of qualitative research to strengthen the credibility and trustworthiness, including; attention to the vulnerability of the parents and a study team of experts in the field • Data saturation is achieved from a varied sample Limitations: • The parents' vulnerability has led to possible selection bias, because parents of 11 children refused to participate, because they considered the interviews too burdensome. • Of the nonparticipating families, the majority of children had malignancies and died from relapse, as compared to half of the children of participating families. *Study funding* Not reported **Risk of bias** Aim and appropriateness of qualitative evidence: Low risk Reason: Aim was clearly described, qualitative method was appropriate Rigour in study design or validity of theoretical approach

	Other: *Time of interview after child's death* Mean: 9.5 months (range 3-23 months)	that the chosen treatment would be most successful and that everything possible to help their child survive would be done. *Keep going: Facilitators perceived by parents* • Guidance from HCPs in making treatment trajectory as bearable as possible and keep the hope alive, supported parents to keep going and focus on decision-making aiming for cure. *Following the child's wishes:* *Facilitators perceived by parents* • For decision-making guidance, parents referred to their child's wish to take all opportunities for cure. • If the children died at home, their parents followed their wishes regarding EOL decisions. This was different when the children died in the hospital or when they did not have the opportunity to prepare for EOL. *Barriers perceived by parents* • Although parents appreciated age-appropriate information for their child, they reported to have the decisive role for themselves, in which they advocate for specific wishes for their child.	Low risk Reason: Study is based on a theoretical framework provided by available literature on EOL. Sample selection high risk Reason: Purposive sampling - Local staff identified eligible participants and sent a mail interview to 19 children. Data collection Low risk Reason: Data collection method i.e. duration, place and interviewer were clearly described. Data analysis Low risk Reason: Data analysis was described in detail and done according to the theoretical framework. Saturation was achieved. Results Low risk Reason: Reasoning behind results is given. Results are credible.

Barriers and facilitators of shared decision-making and Advance Care Planning			
Murrell et al. Identifying Opportunities to Provide Family-centered Care for Families With Children With Type 1 Spinal Muscular Atrophy. J Pediatr Nurs 2018;43:111-9.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
Study design Qualitative *descriptive design with individual or small group interviews guided by a semi-structured questionnaire* Main study objective To understand, from the parent perspective, the experience of the family whose child has Type 1 spinal muscular atrophy (Type 1 SMA), in the emergency centre, hospital, and clinical care settings to identify opportunities for improved family-centred care (FCC). Additional study characteristics USA; 2014-2015; framework analysis	Number and type of participants: 19 families, including 29 parents and 22 children with Type 1 SMA: • 11 children living • 11 deceased children Age parents: Mean: 27 years (range: 24-54) Age children living: Median: 60 months (range 6 months-14 years) Age children deceased: Median: 11 months (range 3-37 months) Sex: *(N (%))* Parents F=18 (62.1%), M=11 (37.9%) Ethnicity: Parents: • White non-Hispanic (n=17) • Hispanic (n=10) • African-American (n=1) • Mixed race/ethnicity (n=1) Religious preference: Not reported Level of education: Parents: • No high school or General Education Development (GED) certificate (n=4) • High school/GED (n=5) • Some college (n=8)	Outcome definition: Outcome 1: Family is the constant in a child's life Outcome 2: Different methods of coping Outcome 3: "Family culture" and cultural diversity Outcome 4: Families as families and children as children Outcome 5: Exchanging information in a supportive manner Outcome 6: Family-to-family support and networking Outcome 7: Diverse family-identified needs Results **Outcome 1: Family is the constant in a child's life** *Facilitators perceived by parents* • Families want their health care team to listen and respect their voice as the expert who has been constant in the child's life throughout diagnosis, treatment and decision-making. • Some parents described positive experiences with providers who were cognizant of the parents' sensitivity to and familiarity with their child. **Outcome 2: Different methods of coping** *Facilitators perceived by parents* • Parents appreciated the presence of a provider who understood the importance of factors influencing the family's decision-making, incl. work, school and other children. **Outcome 3: "Family culture" and cultural diversity** *Facilitators perceived by parents* • Families expressed a desire for a medical team that is culturally sensitive and anticipates how families may interpret information given their culture. *Barriers perceived by parents* • Culture was a significant indicator of how parents preferred the diagnosis to be delivered. It also differs between families and education levels. Some families preferred straightforward diagnosis delivery, while others resented receiving the news in a direct manner. • Families had a varied preference for cultural sensitivity at time of diagnosis and treatment. **Outcome 4: Families as families and children as children** *Facilitators perceived by parents*	Strengths: - Limitations: • The participant sought care in two southern U.S. states, which makes the findings maybe not generalizable to other populations in other regions • It was not possible to obtain the child's voice directly from the children with Type 1 SMA, because of the nature of their disease (either deceased, unable to speak, or concerns over psychological distress as a result of answering the questions) • The small sample of Spanish-speaking families (n=3) limits the ability to generalize across the Spanish speaking population • The interview questions were developed by the investigative team based on lack of information in the scientific literature and on the team's experiences interacting with families with children with Type 1 SMA; however these questions were not piloted prior to initiating interviews, and therefore may not have completely captured the essence of the family experience. • Recall bias could have influenced participant's accounts of care as the interval between the child's Type 1 SMA diagnosis and time of interview ranged from three months to 11 years *Study funding* Grant from Cure SMA **Risk of bias** Aim and appropriateness of qualitative evidence: Low risk Reason: Aim was clearly described, qualitative method was appropriate

	• 4 years of college (n=9) • Graduate degree (n=3) <u>Other:</u> 21 children received medical interventions: • Gastrostomy tube (n=20) • Cough assist machine (n=17) • Non-invasive ventilation via nasal mask (n=13) • Invasive ventilation via tracheostomy (n=8) • Respiratory support with sleep via a bi-level positive airway pressure (BiPAP) machine (n=6)	• Families emphasized the importance of treating their child as normally as possible to maintain a sense of childhood. **Outcome 5: Exchanging information in a supportive manner** *Facilitators perceived by parents* • Multiple families reported that they would make different decisions if they had received more complete or unbiased information on choices about ventilation. • Providers should communicate with support and empathy throughout the diagnostic and treatment process, to prepare families for significant life changes. **Outcome 6: Family-to-family support and networking** *Facilitators perceived by parents* • 18/19 families talked about the value of being connected to another family with a child with Type 1 SMA, so they could share stories and ask questions. Interactions ranged from acquiring simple information to making life-altering treatment decisions. **Outcome 7: Diverse family-identified needs** *Facilitators perceived by parents* • Families indicated a desire for providers who were flexible in their care plan, and would administer treatments based on the families wished.	<u>Rigour in study design or validity of theoretical approach</u> Low risk Reason: An Family-Centred Care approach was chosen for this study. <u>Sample selection</u> Low risk Reason: Participants were identified from SMA support groups, MDA registry lists, clinics at a large children's hospital and word of mouth. Influence of interview-participant relationship was minimal. <u>Data collection</u> Low risk Reason: Data collection method i.e. duration, place and interviewer were clearly described. <u>Data analysis</u> Unclear Data analysis was described in detail and done according to the theoretical framework. Saturation was not reported <u>Results</u> Low risk Reason: Reasoning behind results is given. Results are credible.

Barriers and facilitators of shared decision-making and Advance Care Planning			
Sasazuki et al. Decision-making dilemmas of paediatricians: a qualitative study in Japan. BMJ Open 2019;9:e026579.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
Study design Semistructured, individual face-to-face interviews Main study objective To delineate the critical decision-making processes that paediatricians apply when treating children with life-threatening conditions and the psychosocial experience of paediatricians involved in such care. Additional study characteristics Japan; 2014-2015; comprehensive qualitative analysis and second-round content analysis	Number and type of participants: 15 Medical Doctors, of following specialties: • 3 paediatric intensive care • 2 paediatric cardiology • 3 neonatology • 4 paediatric neurology • 3 paediatric oncology Age: *(mean, median, range)* • 30-34 years (n=1) • 35-39 years (n=6) • 40-44 years (n=6) • 45-49 years (n=1) • 50-54 years (n=1) Sex: *(N (%))* F=1 (6.7%), M=14 (93.3%) Ethnicity: Not reported Religious preference: Not reported Level of education: Not reported Other: Not reported	Outcome definition: Outcome 1: Paediatricians' convictions Outcome 2: Quest for the best of patients Outcome 3: Quest for medically appropriate plans Outcome 4: Confronting parents and families Outcome 5: Socioenvironmental factors Outcome 6: Interactions of the elements Results **Outcome 1: Paediatricians' convictions** *Facilitators perceived by Health Care Professionals (HCPs)* • Physicians referred to internal standards of virtue for what they considered to be right, but not to external norms. They wished to do the right things as physicians **Outcome 2: Quest for the best interests of patients** *Facilitators perceived by HCPs* Physicians tried to assess the child's best interests by carefully observing their comfort, dignity and quality of life. *Barriers perceived by HCPs* • Physicians expressed anxiety when they had difficulty identifying the children's best interests. This seemed to affect their decisions regarding life-sustaining treatment. • Each paediatrician's quest for the best interests of the patient was an essential element that caused dilemmas during and after decision-making. **Outcome 3: Quest for medically appropriate plans** *Barriers perceived by HCPs* • Participants experienced dilemmas when seeking "medically appropriate plans" and had distress concerning the planning of medication and treatments. **Outcome 4: Confronting parents and families** *Barriers perceived by HCPs* • Physicians experienced dilemmas when parents seemed unrealistic or overly optimistic about their child's condition. **Outcome 5: Socioenvironmental factors** *Barriers perceived by HCPs*	Strengths: • Constant quality of interviews by conducting all interviews by one researcher • Limited bias by changing contributors' roles in each interview Limitations: • Conducting the interviews by one interviewer could produce biased results • Only participants from different parts of Japan; cultural background of Japan is reflected by harmony as a great virtue • Only 1 female participant *Study funding* JSPS Kakenhi grant, a Health and Labour Sciences Research Grant on Evidence-based Early Diagnosis and Treatment Strategies for Neuroimmunological Diseases from the Ministry of Health, Labour and Welfare of Japan, Life Science Foundation of Japan, Takeda Science Foundation, The Mother and Child Health Foundation, The Japan Epilepsy Research Foundation and Kawano Masanori Memorial Public Interest Incorporated Foundation for Promotion of Pediatrics (YS) **Risk of bias** Aim and appropriateness of qualitative evidence: Low risk Reason: Aim was clearly described, qualitative method was appropriate Rigour in study design or validity of theoretical approach Low risk Reason: Grounded theory approach was used in this study (enables researchers to extract a new theory through the repeated process of making an inquiry) Sample selection High risk Reason: Purposive sampling was used to select participant. Interviewer-participant relationship could have influenced results.

		• Physicians experienced difficulty that was caused by lack of social consensus. They craved the availability of consensus justifying their decision-making process. Their dilemmas appeared when they struggled to reach agreement with the family, medical staff or society. **Outcome 6: Interactions of the elements** *Barriers perceived by HCPs* • Physicians indicated that their dilemma emerged when they tried to bear the parents' pain and burden in combination with the maximal efforts exerted for the child as a professional paediatrician.	<u>Data collection</u> Unclear Reason: Data collection method was described. Duration of interviews was unclear. <u>Data analysis</u> Low risk Reason: Data analysis was described in detail and done according to the grounded theory approach. Saturation was achieved. <u>Results</u> Low risk Reason: Reasoning behind results is given. Results are credible.

Barriers and facilitators of shared decision-making and Advance Care Planning			
Sisk et al. Communication in Pediatric Oncology: A Qualitative Study. Pediatrics 2020;146:e20201193.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
Study design A qualitative study using semi structured telephone interviews using an interview guide Main study objective To identify functions of communication with their children's clinicians from parental perspectives Additional study characteristics USA; 2018-2020; thematic analysis	Number and type of participants: 77 parents and 1 grandparent of 78 children, with following diagnoses: • 35 leukaemia or lymphoma • 30 solid tumour • 13 brain tumour Age: *(mean, median, range)* Parents • 20-29 years (n=4) • 30-39 years (n=25) • 40-49 years (n=30) • 50 years (n=19) Sex: *(N (%))* Parents F=66 (8.56%), M=12 (15.4%) Children F=41 (52.6%), M=37 (47.4%) Ethnicity: Parents • White (n=68) • Black (n=7) • Asian American (n=2) • Hispanic (n=2) • Other (n=1) Religious preference: Not reported	Outcome definition: Outcome 1: Building relationships Outcome 2: Exchanging information Outcome 3: Enabling family self-management Outcome 4: Providing validation Outcome 5: Managing uncertainty Outcome 6: Supporting hope Outcome 7: Making decisions Outcome 8: Central role in relationship Results **Outcome 1: Building relationships** Every transcript identified "Building relationships". *Facilitators perceived by parents* • Many parents identified the importance of open and reassuring nonverbal cues, e.g. sitting, making eye contact, smiling, and maintaining an open posture. **Outcome 2: Exchanging information** Every transcript identified "exchanging information". *Facilitators perceived by parents* • Nearly all parents mentioned the importance of consistent, accurate, and timely information that was understandable. • Parents highlighted the importance of meeting their unique information needs, especially related to the level of detail, pacing of information, and setting of the conversation. *Barriers perceived by parents* • Some parents desired transparent disclosure of difficult news. Others preferred these conversations to be tempered or delayed. **Outcome 3: Enabling family self-management** 75/78 transcripts identified "enabling family self-management" *Facilitators perceived by parents* • Many parents noted the importance of knowing what to expect. • Some parents noted the need for training in technical skills to care for their child. **Outcome 4: Providing validation** 65/78 transcripts identified "providing validation". *Facilitators perceived by parents* • Many parents noted the importance of being empowered. • Parents described the importance of having their concerns taken seriously. • Parents felt validated when clinicians reinforced their "good parent" beliefs.	Strengths: - Limitations: • Parents were predominantly well-educated, white mothers. • Children with brain tumours and older children were underrepresented. • Due to the performed telephone interviews, nonverbal cues might have been missed. • Recall and conformity bias may have occurred. • The perspectives of paediatric children have not been evaluated. *Study funding* The National Centre for Advancing Translational Sciences of the National Institutes of Health and the Conquer Cancer Foundation of the American Society of Clinical Oncology Young Investigator Award, the National Institutes of Health (NIH). **Risk of bias** Aim and appropriateness of qualitative evidence: Low risk Reason: Aim was clearly described, qualitative method was appropriate Rigour in study design or validity of theoretical approach Low risk Reason: Epstein and street's functional communication model was used as an a priori framework.

	<u>Level of education:</u> Parents • High school graduate or less (n=7) • Some college or technical school (n=15) • College or technical school graduate (n=36) • Graduate or professional school (n=20) <u>Other:</u> *Age at diagnosis* • <12 years (n=51) • >13 years (n=27) *Time point in cancer trajectory* • Treatment (n=30) • Survivorship (n=27) • Bereavement (n=21)	**Outcome 5: Managing uncertainty** 59/78 transcripts identified "managing uncertainty". *Facilitators perceived by parents* • Many parents wanted clinicians to explore uncertainties and unknowns, and develop contingency plans. *Barriers perceived by parents* • Clinicians sometimes offered guesses when facing uncertainty, which was sometimes helpful. However, at other times, guesses were frustrating. **Outcome 6: Supporting hope** 47/78 transcripts identified "supporting hope. *Facilitators perceived by parents* • Many parents expressed that hope was essential for their coping and wellbeing. *Barriers perceived by parents* • Many parents varied in their preferences for how clinicians should support hope. Some parents preferred clinicians to emphasize positives. For some parents, clinicians supported hope by expressing an intention to cure the child, even if cure was unlikely. Other parents expressed the importance of avoiding false hopes. **Outcome 7: Making decisions** 46/78 transcripts identified "making decisions". *Facilitators perceived by parents* • Many parents indicated a preference for involvement in decision-making and expressed frustration when not involved. **Outcome 8: Central role in relationship** *Facilitators perceived by parents* • Relationships influenced exchange of information, because parents believed the information if the clinician had credibility.	<u>Sample selection</u> Low risk Reason: Stratified sampling was used to select participants. Participants with any relationships to the authors were excluded. Thus, influence of interviewer-participant relationship was minimal <u>Data collection</u> Low risk Reason: Data collection method i.e. place, duration and interviewer were clearly described. <u>Data analysis</u> Low risk Reason: Data analysis was described in detail and done according to the grounded theory approach. Saturation was achieved. <u>Results</u> Low risk Reason: Reasoning behind results is given. Results are credible.

Barriers and facilitators of shared decision-making and Advance Care Planning			
Superdock et al. Exploring the vagueness of Religion & Spirituality in complex paediatric decision-making: a qualitative study. BMC Palliat Care 2018;17:107.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
Study design Longitudinal, qualitative, descriptive design, with longitudinal series of one-on-one interviews, field notes, questionnaires, and medical chart data Main study objective To illuminate the influence of R&S on parental decision-making and explore how HCPs interact with parents for whom R&S are important Additional study characteristics USA; 2008-2011; content analysis techniques described by Hsieh and Shannon *Time of follow-up* Median=380 days, mean=324 days (range=8-531, SD=174 days)	Number and type of participants: 28 parents of 17 children, with following diagnoses: • 5 complex congenital heart disease • 7 genetic/metabolic disease/HSCT • 5 extreme prematurity 108 health care professionals of following specialties: • 30 attending physicians • 5 fellow physicians • 25 nurse practitioners • 27 nurses • 22 social workers Age: *(mean, median, range)* Parents Mean: 32 years (range: 21-46, SD=6.4) Children of participating parents at study entrance • Complex congenital heart disease: mean=22 days (range: 1-61, SD=27) • Genetic/metabolic disease/HSCT: mean=11 months (range: 3-21, SD=6) • Extreme prematurity: mean=0 days (range: 0-2, SD=1) Sex: *(N (%))* Parents F=16 (57.1%), M=12 (42.9%) Health care professionals	Outcome definition: Outcome 1: value & beliefs Outcome 2: practices Outcome 3: people Results **Outcome 1: value & beliefs** • *Faith & hope* *Barriers perceived by HCPs* • HCPs had mixed feelings about parental hope and faith. Faith kept parents hopeful enough to be involved and endure stress, but became problematic when cure was no longer possible from a medical standpoint. Many HCPs began to worry that faith-based hope was allowing parents to disregard medical evidence when making decisions. *Facilitators perceived by parents* • Parents believed faith was integral to decision-making, because it gave them confidence in decisions, guarded against regret, and aided joint decision-making with their spouse. • If decisions became more complicated or consequential (e.g. new devices, goals-of-care, end-of-life), parents spoke more emphatically about the importance of maintaining hope and faith. • *God is in control* *Facilitators perceived by parents* • All mothers and most fathers emphasize the belief that God is in control. This belief empowered parents to make decisions, or at times, it motivated parents to abstain from making decisions. • Surrendering control to god-freed parents from the burden to control chaotic situations themselves, but parents admitted that it was not easy or straightforward and wanted to remain engaged in their child's care. • Parents did not expect HCPs to surrender control to God, but seemed pleased when physicians acknowledged a higher authority. *Barriers perceived by HCPs and parents* • Many HCPs believed sacrificing control should mean letting "nature take its course". • *Presence or voice of god* *Facilitators perceived by parents* Many parents said they could not have endured their circumstances or made decisions without God's presence. • *Belief in miracles/divine intervention*	Strengths: • Our research demonstrates the need for the development of clinical and educational tools to help HCPs approach situation where R&S are important to families Limitations: • Christianity was the only faith tradition represented. Future research should examine the role of R&S when parents have a different R&S background or do not identify with a particular religion. • Larger, more diverse studies may allow for analysis of differences across race, ethnicity, and geographic setting, which would be valuable given the interaction of these factors with R&S • The principal study targeted many decision-making factors, so matters pertaining to R&S were not fully explored in every interview. Research exclusively focusing on R&S could investigate several topics, including the effects of fervent belief in miracles on end-of-life decisions, how parents and HCPs communicate about R&S beliefs, and the role of hospital chaplains and other clergy in decision-making. *Study funding*

	F=77 (71.3%), M=31 (28.7%) <u>Ethnicity:</u> Parents • Caucasian (n=11) • Hispanic (n=5) • African American (n=10) • Native American (n=2) <u>Religious preference:</u> Parents • Christian (n=27) • Other (n=1) Health care professionals • Christian (n=79) • Jewish (n=7) • Hindu (n=8) • Other (n=13) <u>Level of education:</u> Parents Average years of education: 14 years (range: 7-18, SD=2.5) <u>Other:</u> *Total clinical experience* Mean: 12 years (range: 0–30, SD=9.3) *Experience in current clinical setting or specialty, i.e. NICU, BMT, etc.* Mean: 8.3 years (range: 0–30, SD=8.7) *% of children living at study exit* • Complex congenital heart disease: 40% • Genetic/metabolic disease/HSCT: 71% • Extreme prematurity: 40%	Belief in miracles was related to beliefs about God and influenced decisions in similar ways. If God is in control, then God can intervene in the world and bring about events that defy medical explanation. *Facilitators perceived by parents* • Belief in miracles sometimes pushed parents to pursue aggressive treatment, and other times allowed parents to de-escalate aggressive care. • To parents, if God miraculously brought their child into the world, he would miraculously keep them alive, and were therefore less likely to accept poor prognoses or “give up” hope. *Barriers perceived by parents* • Some parents expressed that they did not feel physicians understood their believes. *Barriers perceived by HCPs* • HCPs used the term “miracle” reluctantly. Some HCPs said their experience with medical miracles made them less confident in their ability to “predict the future”, and more cautious when communicating poor prognosis. • *<u>Meaning of suffering</u>* *Facilitators perceived by parents* • The belief that God is perfectly good affected how parents interpreted suffering. Either God predetermined a purpose for suffering, or he could bring good things from suffering *Barriers perceived by HCPs* • The issue of suffering seemed to be the greatest point of contention between HCPs and parents. HCPs believed suffering was only allowed when necessary to prolong a life of good quality. • Physicians felt that parents used R&S beliefs to “rationalize” the infant’s short-term suffering. • In one case, a physician stated that the parents “just didn’t care” that the infant was suffering. • *<u>Life & death:</u> Facilitators perceived by parents* • When parents believed they were “meant to be” their child’s parents, they were empowered to trust their instincts about what was best for the child. **Outcome 2: practices** *<u>Praying:</u> Facilitators perceived by parents* • In four cases, praying played a large role in parents’ decisions, incl. treatment initiation decisions, choice of hospital, medical procedures, relocation, resuscitation orders, withdrawal of life-sustaining therapy. • Parents did not always state the way the prayers guided the decisions, but were clear they engendered peace and confidence in their choices. **Outcome 3: people** *Barriers perceived by HCPs* • In one case, a HCP reported that a family’s pastor prohibited endotracheal tube removal, and they abided by that condition while de-escalating care in other ways.	The National Institute of Nursing Research **Risk of bias** <u>Aim and appropriateness of qualitative evidence:</u> Low risk Reason: Aim was clearly described, qualitative method was appropriate <u>Rigour in study design or validity of theoretical approach</u> Low risk Reason: Knowledge in previous literature on religion and spirituality was used in as a theoretical approach. <u>Sample selection</u> High risk Reason: Purposive sampling was used to select participant. Interviewer-participant relationship could have influenced results. <u>Data collection</u> Low risk Reason: Data collection method i.e. place, duration and interviewer were clearly described. <u>Data analysis</u> Low risk Reason: Data analysis was described in detail and done according to the content analysis techniques described by Hsieh and Shannon. Saturation was achieved. <u>Results</u> Low risk Reason: Reasoning behind results is given. Results are credible.

		Facilitators perceived by parents • Faith communities did not directly affect decision-making, but one family suggested that the support of the church community reinforced their decision to leave the hospital and care for their child at home.	

Barriers and facilitators of shared decision-making and Advance Care Planning			
Zaal-Schuller et al. How parents and physicians experience end-of-life decision-making for children with profound intellectual and multiple disabilities. Res Dev Disabil 2016;59:283-93.			
Study design & main study objective	**Patient and relevant characteristics**	**Relevant results (per outcome)**	**Additional remarks**
Study design Retrospective, qualitative study, with semi-structured interviews Main study objective To investigate the experiences of the parents and the involved physician during the end-of-life decision-making (EoLDM) process for children with PIMD. Additional study characteristics The Netherlands; study years not reported; Analysed using the qualitative data analysis software, MaxQDA	Number and type of participants: 17 parents of 14 children, with following diagnoses: • 3 post-resuscitation • 5 genetic condition • 1 neurologic condition • 2 metabolic condition • 3 unknown 11 physicians of following specialties: • 6 paediatricians • 1 rehabilitation specialists • 1 paediatric Intensive Care specialists • 3 paediatric Neurologists Age: *(mean, median, range)* Parents • 30-39 years (n=5) • 40-49 years (n=9) • 50-60 years (n=3) Children of participating parents	Outcome definition: Outcome 1: the influence of previous healthcare encounters Outcome 2: anticipation and timing of the EoLDM process Outcome 3: provision of information and advice Outcome 4: reasons for disagreement Outcome 5: contributions to decision-making Outcome 6: the final decision maker Results **Outcome 1: the influence of previous healthcare encounters** *Facilitators perceived by parents* • The majority of children had a long-lasting treatment relationship with a certain physician. Parents mentioned that they would strongly prefer to start the EoLDM process with that physician. *Barriers perceived by parents* • Negative healthcare encounters contributed to a critical attitude towards physicians. *Facilitators perceived by HCPs* • Many physicians mentioned the importance of a long-lasting treatment relationship with the parents. **Outcome 2: anticipation and timing of the EoLDM process** *Barriers perceived by parents* • Half of the 17 parents mentioned that they felt it was a missed opportunity that physicians did not take the initiative to talk about EoLDs when the child was still in a stable condition. *Facilitators perceived by HCPs* • Many physicians named acute deterioration of a child the most common reason to discuss withholding or withdrawing certain treatments. • 2/11 HCPs named improvement of physical condition as a reason to reassess the agreements and to sometimes reverse decisions. *Barriers perceived by HCPs* • Many physicians thought they knew how the parents felt about EoLD, even if they have never discussed it with the parents before. • Many physicians had an idea about how parents felt about EoLD, but found it very difficult to identify when parents were 'ready' to discuss these decisions. **Outcome 3: provision of information and advice** *Facilitators perceived by parents* • 4/17 parents emphasized that the information and advice provided by their child's regular physician was very important to them during the EoLDM process.	Strengths: • Both parents and physicians involved in the care of a particular child were interviewed, which makes it possible to directly compare their experiences during the EoLDM process Limitations: • Recall bias is possible because the participants were asked to reflect on an EoLDM process that occurred in the past • It is unknown how the fact that some children stayed alive after the EoLD was made, while others died, influenced the way parents in retrospect experienced the EoLDM process; parents can have a more positive view if their child was still alive • The fathers' perspective is almost entirely lacking, because most of the interviews were performed with the mothers, probably

	• 0-4 years (n=2) • 5-9 years (n=1) • 10-14 years (n=8) • 15-19 years (n=3) Physicians • 40-49 years (n=3) • 50-60 years (n=8) <u>Sex:</u> *(N (%))* Parents F=14 (82.4%), M=3 (17.6 %%) Children of participating parents F=10 (71.4 %%), M=4 (28.6%) Physicians F=9 (81.8%), M=2 (10.2%) <u>Ethnicity:</u> Parents: • Dutch (n=13) • Moroccan (n=4) <u>Religious preference:</u> Parents: • Protestant (n=2) • Islamic (n=4) • No affiliation (n=11) Physicians: • Catholic (n=2) • Protestant (n=1) • No affiliation (n=8)	• Many parents indicated that conversations with other parents who had been through the same would have been informative and supportive, because they would understand their feelings and complexity of their considerations. *Barriers perceived by parents* • The majority of parents expressed a lack of information during the EoLDM process, e.g. about available treatment options. • Many parents felt they lacked necessary medical background to put the received information in the right context. *Facilitators perceived by HCPs* • Some physicians thought that parents were particularly capable of understanding the information, because of their knowledge of the medical conditions and their experiences with treatments during previous critical illnesses of their child. *Barriers perceived by HCPs* • Physicians mentioned that they put lots of effort into giving clear information and advice to parents, but this is complicated by an uncertain prognosis and unforeseen complications. • Almost half of the physicians thought that parents find it hard to completely comprehend all of the information, because of a lack of sufficient medical background to put the information in the right context. • Physicians mentioned that for some parents, especially with non-Dutch backgrounds, it is difficult to fully comprehend medical concepts. **Outcome 4: reasons for disagreement** 8/17 parents recalled one or more disagreements with a physician during the EoLDM process. *Facilitators perceived by parents* • Not all of the parents believed that disagreements were disturbing. They made them reconsider their opinion about which choice to make. *Barriers perceived by parents* • Parents mentioned that disturbing disagreements arose especially after an acute deterioration of their child's condition, because decisions had to be made under time pressure and often without their regular physician. • Parents felt not heard and felt that physicians regarded their child's life as less valuable than a typically developed child. • One couple of parents with a Moroccan background reported that the cultural and legislative differences between The Netherlands and Morocco were a complicating factor, which caused disagreement with physicians. *Facilitators perceived by HCPs* • Physicians emphasized that not all disagreements were disturbing. Disagreements could also challenge them to think about alternatives that would be more suitable for the specific situation of the child. *Barriers perceived by HCPs* • EoLDM could be complicated by differences in ethnic, religious and/or linguistic backgrounds. *Barriers perceived by HCPs and parents* • 2/11 HCPs and 3/17 parents expressed that disturbing disagreements had arisen when parents still wanted 'everything to be done', also treatments physicians considered to be futile at that point. • HCPs and 2/17 parents mentioned disagreement when parents wanted a treatment to be forgone, while the physician still anticipated a realistic chance of improvement.	because they are the primary caregiver • Physicians were reluctant to speak about their disagreements with individual parents, which led to broad answers that made making comparisons between parents' and physicians' experiences more difficult • This study only describes experiences of EoLDM in Dutch hospitals, which may limit generalizability *Study funding* Rehabilitation Fund (het Revalidatiefonds); the Fund for Intellectual Disabilities (het Fonds Verstandelijk Gehandicapten); and the Erasmus Medical Centre, Department of Intellectual Disability Medicine **Risk of bias** <u>Aim and appropriateness of qualitative evidence:</u> Low risk Reason: Aim was clearly described, qualitative method was appropriate <u>Rigour in study design or validity of theoretical approach</u> Low risk Reason: Knowledge in previous literature on EoLD

	Level of education: Parents: • Primary education (n=2) • Secondary education (n=6) • Higher education (n=9) Other: *Treatment decision* • Forgo resuscitation (n=5) • Forgo life-saving surgical procedure (n=2) • Forego life support (n=1) • Forego artificial nutrition (n=2) • Administrating medication to alleviate pain (n=3) • Palliative sedation (n=1) *Deceased* • No (n=12) • Yes (n=2)	**Outcome 5: contributions to decision-making** *Facilitators perceived by parents* • Nearly all parents emphasized that they felt that they were the experts on their child, meaning that they know a lot about the medical conditions of their child, and that they needed to be the 'translator' for their child's physician (e.g. explaining how their child was feeling and whether their child was in pain). Parents felt that their role as expert was recognized by the regular physician, although it could take some time to gain the physician's trust. *Facilitators perceived by HCPs* • Half of 11 physicians emphasized that they regarded the parents as the expert of their child, because they needed the parents to be a 'translator' that told them how their child was doing. **Outcome 6: the final decision maker** *Facilitators perceived by parents* • Almost all parents felt that they were the right people to make the final decision, because it were decisions concerning their *own* child. • Many parents expressed that they were glad that they were able to make the EoLD with their involved physician. *Barriers perceived by parents* • Some parents mentioned it was difficult for them to make certain decisions, e.g. resuscitation orders or decisions about medical ventilation. *Facilitators perceived by HCPs* • Physicians stressed that making decisions together is very important, because this could facilitate the grieving process of the parents. *Barriers perceived by HCPs* • Making decisions together with parents meant different things to different physicians; ○ 3/11 HCPs agreed that the parents' opinions should weight the heaviest. ○ 4/11 HCPs explained that in their opinion, shared decision-making implied that they supported the decisions made by the parents. ○ 3/11 HCPs expressed their role was solely give objective information to the parents that would enable them to make the best decisions. • Some physicians mentioned that in some situations they had chosen to make the final decision alone. This happened especially in cases of disagreement in which they wished to protect the child from further suffering.	was used in as a theoretical approach. Sample selection Unclear Reason: Participants were selected in different ways, via participant organizations, via specialized day care centres, via an annual national meeting and via physicians. Influence of interviewer-participant relationship was unclear/not reported. Data collection Low risk Reason: Data collection method i.e. place, duration and interviewer were clearly described. Data analysis Low risk Reason: Data analysis was described in detail. Saturation was achieved. Results Low risk Reason: Reasoning behind results is given. Results are credible

4 Samenvatting en gradering van bewijs

4.1 Effectiviteit van ACP interventies

4.1.1 Geïncludeerde uitkomstmaten

Included outcomes
Completion of legal statement of treatment preferences
Congruence in end of life treatment preferences among dyads
Agreement to limit treatment among dyads
Agreement to give family leeway among dyads
Anxiety in adolescents
Anxiety in adult surrogates
Depression in adolescents
Depression in adult surrogates
Quality of life in adolescents
Spirituality in adolescents

4.1.2 *Advance Care Planning*

Family-centred Advance Care planning				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Completion of legal statement of treatment preferences, percentage of dyads who completed legal statement of treatment preferences				
Lyon, 2010 (is it safe?)	Adolescents with HIV-infection aged 14 to 20 years and their adult surrogates	Total of 38 dyads Intervention: 20 dyads • Adolescents: 20 • Adult surrogates: 20 Control: 18 dyads • Adolescents: 18 • Adult surrogates: 18	Family-centred Advance Care planning Three weekly 60-90 minute family interview sessions. Session 1 – Lyon Advance Care Planning Adolescent and Surrogate Versions Session 2 – The Respecting Choices Interview, a facilitated ACP conversation Session 3 – Completion of the Five wishes, a legal statement of treatment preferences Control Three weekly 60-90 minute family interview sessions: Session 1 – Developmental History Session 2 – Safety Tips Session 3 – School and Career Planning interview	**Completion legal statement of preferences at 3-month follow-up (intervention vs. control)** 90% vs. 11%, p<0.001 completed legal statement of treatment preferences
Lyon, 2014 (a longitudinal, randomized, controlled trial)	Adolescents with cancer aged 14 to 21 and their adult surrogates	Total of 30 dyads Intervention: 17 dyads • Adolescents: 17 • Adult surrogates: 17 Control: 13 dyads • Adolescents: 13 Adult surrogates: 13	Family-centred Advance Care planning Three sixty minute sessions scheduled one week apart. Session 1 – Lyon Family Centered ACP Survey: Session 2 – Respecting Choices, a facilitated ACP conversation Session 3 – Completion of the Five wishes, a legal statement of treatment preferences Usual care Usual care, provision of a brochure with information	**Completion of legal statement of treatment preferences at 3 month follow-up (intervention vs. control):** 100% vs 0%, *When asked, "When do you think is the best time to bring up end-of-life decisions?" intervention adolescents responded, "Before getting sick" (19%; n = 3), "At diagnoses" (19%; n= 3), "When first hospitalized" (0%); "When dying" (25%; n = 4), or all of the above (38%; n = 6). Only one adolescent reported ever talking to anyone about wishes for care at EOL before the study*
Grade assessment				
Study design:	+4	2 Randomized Controlled Trial		
Study limitations	-2	Serious limitations - Selection bias: low 1/2, unclear in 1/2; Attrition bias: low in 2/2; Performance bias: high in 2/2; Detection bias: unclear in 2/2		
Consistency:	0	No important inconsistency.		
Directness:	0	Results are direct		
Precision:	-1	Some imprecision due to small sample size (n=68).		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence that Family-centred Advance Care planning increases the completion of a legal statement of treatment preferences at 3 month follow-up in adolescents with HIV-infection or cancer and their adult surrogates as compared to control or usual care.**		

Family-centred Advance Care planning				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Congruence in End of Life treatment preferences, the Prevalence Adjusted Bias Adjusted Kappa (PABAK), higher PABAK scores indicating more congruence in agreement. PABAK scores: 0 = no agreement; 0 to 0.19 = slight agreement; 0.2 to 0.39 = fair agreement; 0.4 to 0.59 = moderate agreement; 0.6 to 0.79 = substantial agreement; and 0.8 to 1 = almost perfect agreement.				
Lyon, 2017	Adolescents with HIV-infection aged 14 to 20 years and their adult surrogates	Total of 105 dyads Intervention: 54 dyads • Adolescents: 54 • Adult surrogates: 54 Control: 51 dyads • Adolescents: 51 • Adult surrogates: 51	Family-centred Advance Care planning Three sixty minute sessions scheduled one week apart. Session 1 – Lyon Family Centered ACP Survey: Session 2 – Respecting Choices, a facilitated ACP conversation Session 3 – Completion of the Five wishes, a legal statement of treatment preferences Control Three sixty minute sessions scheduled one week apart. Session 1 – Developmental History. Session 2 – Safety Tips Session 3 – Nutrition and exercise	**Congruence in treatment preferences post-session 2 (intervention vs control)** • Situation 1 – Long hospitalization PABAK = 0.688 (substantial agreement) vs PABAK = 0.335 (fair agreement) • Situation 2 – functional impairment PABAK = 0.687 (substantial agreement) vs PABAK = 0.029 (slight agreement) • Situation 3 – mental impairment PABAK = 0.717 (substantial agreement) vs PABAK = 0.341 (fair agreement) **Congruence in treatment preferences at 3 month follow-up (intervention vs control)** • Situation 1 – Long hospitalization PABAK = 0.599 (moderate agreement) vs PABAK = 0.34 (fair agreement) • Situation 2 – functional impairment: PABAK = 0.318 (fair agreement) vs PABAK = 0.031 (slight agreement) • Situation 3 – mental impairment PABAK = 0.419 (moderate agreement) vs PABAK = 0.328 (fair agreement)
Grade assessment				
Study design:	+4	1 Randomized Controlled Trial		
Study limitations	-2	Serious limitations - Selection bias: unclear; Attrition: bias high; Performance bias: high; Detection bias: unclear		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Results are direct		
Precision:	-1	Some imprecision (sample size =105) Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		**⊕⊖⊖⊖ VERY LOW**		
Conclusion:		**There is very low quality of evidence that Family-centred Advance Care planning increases congruence in treatment preferences post-session-2 and at 3 month follow-up among adolescents with HIV-infection and their adult surrogates in the situations long hospitalization, functional impairment and mental impairment, as compared to control. It was unclear whether this effect was significant.**		

Family-centred Advance Care planning				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Congruence in End of Life treatment preferences, chance-adjusted agreement between surrogate and adolescent responses was assessed using the k-coefficient				
Lyon, 2013	Adolescents with cancer aged 14 to 21 and their adult surrogates	Total of 30 dyads Intervention: 17 dyads • Adolescents: 17 • Adult surrogates: 17 Control: 13 dyads • Adolescents: 13 Adult surrogates: 13	Family-centred Advance Care planning Three sixty minute sessions scheduled one week apart. Session 1 – Lyon Family Centered ACP Survey: Session 2 – Respecting Choices, a facilitated ACP conversation Session 3 – Completion of the Five wishes, a legal statement of treatment preferences Usual care Usual care, provision of a brochure with information	**Treatment preference congruence post-session 3 (Intervention vs control):** K coefficients assessed chance-adjusted agreement between surrogate and adolescent responses, and difference in K coefficients between conditions was tested. • Situation 1 – long hospitalization K = 0.59 vs K = -0.13; p = 0.001 • Situation 2 – treatments would extend my life K = 0.6 vs K = -0.06; p < 0.001 • Situation 3 – functional impairment K = 0.89 vs K = 0.11; p < 0.001 • Situation 4 – mental impairment K = 0.63 vs K = 0.19; p < 0.001 • Situation 5 – attempting cardiopulmonary resuscitation K = 0.34 vs K = -0.03; p = 0.12; • Situation 6 – mechanical ventilation K = 1.00 vs K = -0.00; p < 0.001

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-1	Some limitations - Selection bias: low; Attrition bias: low ; Performance bias: high; Detection bias: unclear
Consistency:	0	No important inconsistency. Only 1 study performed
Directness:	0	Results are direct
Precision:	-2	Some imprecision due to small sample size (n=30). Only 1 study performed
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence that Family-centred Advance Care planning increases congruence in treatment preferences post-session-3 among adolescents with cancer and their adult surrogates in the situations long hospitalization, treatment would extend my life, functional impairment, mental impairment, attempting cardiopulmonary resuscitation and mechanical ventilation, as compared to usual care. This effect was not significant for the situation attempting cardiopulmonary resuscitation.**

Family-centred Advance Care planning				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Agreement to limit treatment post-session 2, percentage of dyads that decided to limit treatment				
Lyon, 2017	Adolescents with HIV-infection aged 14 to 20 years and their adult surrogates	Total of 105 dyads Intervention: 54 dyads • Adolescents: 54 • Adult surrogates: 54 Control: 51 dyads • Adolescents: 51 • Adult surrogates: 51	Family-centred Advance Care planning Three sixty minute sessions scheduled one week apart. Session 1 – Lyon Family Centered ACP Survey: Session 2 – Respecting Choices, a facilitated ACP conversation Session 3 – Completion of the Five wishes, a legal statement of treatment preferences Control Three sixty minute sessions scheduled one week apart. Session 1 – Developmental History. Session 2 – Safety Tips Session 3 – Nutrition and exercise	**Agreement to limit treatment post-session 2 (intervention vs control)** Percentage of dyads that decided to limit treatment 'stop all efforts to keep me alive, quality of life is more important than length of life' • Situation 1 – Long hospitalization 14.6% vs 0%, p = 0.013 • Situation 2 – Functional impairment 12.5% vs 4.4%, p = 0.269 • Situation 3 – Mental impairment 22.9% vs 4.4%, p = 0.015
Grade assessment				
Study design:	+4	1 Randomized Controlled Trial		
Study limitations	-2	Serious limitations - Selection bias: unclear; Attrition bias: high; Performance bias: high; Detection bias: unclear		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Results are direct		
Precision:	-1	Some imprecision (sample size =105). Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence that Family-centred Advance Care planning increases agreement to limit treatment post-session-2 among adolescents with HIV-infection and their adult surrogates in the situations long hospitalization and mental impairment, as compared to control. This effect was not significant in the situation of functional impairment.**		

Family-centred Advance Care planning				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Agreement to limit treatment at 3 month follow-up, percentage of dyads that decided to limit treatment				
Lyon, 2010	Adolescents with HIV-infection aged 14 to 20 years and their adult surrogates	Total of 38 dyads Intervention: 20 dyads • Adolescents: 20 • Adult surrogates: 20 Control: 18 dyads • Adolescents: 18 • Adult surrogates: 18	Family-centred Advance Care planning Three weekly 60-90 minute family interview sessions. Session 1 – Lyon Advance Care Planning Adolescent and Surrogate Versions Session 2 – The Respecting Choices Interview, a facilitated ACP conversation Session 3 – Completion of the Five wishes, a legal statement of treatment preferences Control Three weekly 60-90 minute family interview sessions: Session 1 – Developmental History Session 2 – Safety Tips Session 3 – School and Career Planning interview	**Agreement of dyads to limit extraordinary treatment at 3 month follow-up (intervention vs control)** Percentage of dyads (adolescents and adult surrogates) that decided to stop treatment 'stop all efforts to keep me alive'. • Situation 1 - Long hospitalization 15% (n = 3) vs 6% (n = 1), p = 0.187 • Situation 2 - Functional impairment 25% (n = 5) vs 28 % (n = 5), p = 1.000 • Situation 3 - Mental impairment 30% (n = 6) vs 17% (n- = 3), p = 0.528.
Lyon, 2017	Adolescents with HIV-infection aged 14 to 20 years and their adult surrogates	Total of 105 dyads Intervention: 54 dyads • Adolescents: 54 • Adult surrogates: 54 Control: 51 dyads • Adolescents: 51 • Adult surrogates: 51	Family-centred Advance Care planning Three sixty minute sessions scheduled one week apart. Session 1 – Lyon Family Centered ACP Survey: Session 2 – Respecting Choices, a facilitated ACP conversation Session 3 – Completion of the Five wishes, a legal statement of treatment preferences Control Three sixty minute sessions scheduled one week apart. Session 1 – Developmental History. Session 2 – Safety Tips Session 3 – Nutrition and exercise	**Agreement of dyads to limit extraordinary treatment at 3 month follow-up (intervention vs control)** Percentage of dyads that decided to limit treatment 'stop all efforts to keep me alive, quality of life is more important than length of life' • Situation 1 – Long hospitalization 9.8% vs 0%, p = unknown • Situation 2 – Functional impairment 20% vs 4.9%, p = 0.048 • Situation 3 – Mental impairment 19.5% vs 7.3%, p = unknown

Grade assessment		
Study design:	+4	2 Randomized Controlled Trial
Study limitations	-2	Serious limitations - Selection bias: unclear in 2/2; Attrition bias: low in 1/2, high in 1/2; Performance bias: high in 2/2; Detection bias: unclear in 2/2
Consistency:	0	No important inconsistency
Directness:	0	Results are direct
Precision:	0	No important imprecision (sample size = 143)
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ **LOW**
Conclusion:		**There is low quality of evidence that Family-centred Advance Care planning increases agreement to limit treatment at 3 month follow-up among adolescents with HIV-infection and their adult surrogates in the situation of functional impairment, as compared to control. This effect was not significant in the situation of long hospitalization or mental impairment.**

Family-centred Advance Care planning				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Agreement to give family leeway, extent to which adolescent wished to grand their family leeway 'do what the family thinks is best at the time.				
Lyon, 2017	Adolescents with HIV-infection aged 14 to 20 years and their adult surrogates	Total of 105 dyads Intervention: 54 dyads • Adolescents: 54 • Adult surrogates: 54 Control: 54 dyads • Adolescents: 51 • Adult surrogates: 51	Family-centred Advance Care planning Three sixty minute sessions scheduled one week apart. Session 1 – Lyon Family Centred ACP Survey: Session 2 – Respecting Choices, a facilitated ACP conversation Session 3 – Completion of the Five wishes, a legal statement of treatment preferences Control Three sixty minute sessions scheduled one week apart. Session 1 – Developmental History. Session 2 – Safety Tips Session 3 – Nutrition and exercise	**Agreement to give family leeway post-session 2 (intervention vs control)** 62.5% vs. 45.7%, p= 0.1012
Lyon, 2013	Adolescents with cancer aged 14 to 21 and their adult surrogates	Total of 30 dyads Intervention: 17 dyads • Adolescents: 17 • Adult surrogates: 17 Control: 13 dyads • Adolescents: 13 • Adult surrogates: 13	Family-centred Advance Care planning Three sixty minute sessions scheduled one week apart. Session 1 – Lyon Family Centred ACP Survey: Session 2 – Respecting Choices, a facilitated ACP conversation Session 3 – Completion of the Five wishes, a legal statement of treatment preferences Usual care Usual care, provision of a brochure with information	**Agreement to give family leeway post-session 3 (intervention vs control)** 100% vs 62%, p=0.009
Grade assessment				
Study design:	+4	2 Randomized Controlled Trial		
Study limitations	-2	Serious limitations - Selection bias: low in 1/2, unclear in 1/2; Attrition bias: low in 1/2, high in 1/2; Performance bias: high in 2/2; Detection bias: unclear in 2/2		
Consistency:	0	No important inconsistency.		
Directness:	0	Results are direct		
Precision:	0	No important imprecision (sample size = 135)		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		**⊕⊕⊖⊖ LOW**		
Conclusion:		**There is low quality of evidence that Family-centred Advance Care planning increases agreement to give family leeway post-session-2/3 among adolescents with cancer and their adult surrogates, as compared to controls. This effect was not signicant among adolescents with HIV-infection and their adult surrogates.**		

Family-centred Advance Care planning				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Agreement to give family leeway at 3 month follow-up, extent to which adolescent wished to grand their family leeway 'do what the family thinks is best at the time.				
Lyon, 2017	Adolescents with HIV-infection aged 14 to 20 years and their adult surrogates	Total of 105 dyads Intervention: 54 dyads • Adolescents: 54 • Adult surrogates: 54 Control: 51 dyads • Adolescents: 51 • Adult surrogates: 51	Family-centred Advance Care planning Three sixty minute sessions scheduled one week apart. Session 1 – Lyon Family Centred ACP Survey: Session 2 – Respecting Choices, a facilitated ACP conversation Session 3 – Completion of the Five wishes, a legal statement of treatment preferences Control Three sixty minute sessions scheduled one week apart. Session 1 – Developmental History. Session 2 – Safety Tips Session 3 – Nutrition and exercise	**Agreement to give family leeway at 3 month follow-up (intervention vs control)** 68% vs 51%, p=0.13
Grade assessment				
Study design:	+4	1 Randomized Controlled Trial		
Study limitations	-2	Serious limitations - Selection bias: unclear; Attrition: bias high; Performance bias: high; Detection bias: unclear		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Results are direct		
Precision:	-1	Some imprecision (n=105). Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence that there is no significant effect of Family-centred Advance Care planning on agreement to give family leeway at 3 month follow-up among adolescents with HIV-infection and their adult surrogates, as compared to controls.**		

Family-centred Advance Care planning				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Anxiety in adolescents, Beck Anxiety Index (BAI), score ranging from 0 to 63, higher scores represent presence of more anxiety related symptoms Scores: 0 to 7 = minimal anxiety; 8 to 15 = mild anxiety; 16 to 25 = moderate anxiety; 26 – 63 = severe anxiety				
Lyon, 2010	Adolescents with HIV-infection aged 14 to 20 years and their adult surrogates	Total of 38 dyads Intervention: 20 dyads • Adolescents: 20 • Adult surrogates: 20 Control: 18 dyads • Adolescents: 18 • Adult surrogates: 18	Family-centred Advance Care planning Three weekly 60-90 minute family interview sessions. Session 1 – Lyon Advance Care Planning Adolescent and Surrogate Versions Session 2 – The Respecting Choices Interview, a facilitated ACP conversation Session 3 – Completion of the Five wishes, a legal statement of treatment preferences Control Three weekly 60-90 minute family interview sessions: Session 1 – Developmental History Session 2 – Safety Tips Session 3 – School and Career Planning interview	**Mean anxiety scores (intervention vs control)** Baseline 2.76 (95%CI 1.38–4.60) vs 1.38 (95%CI 0.44–2.84), p = 0.170 3 month follow-up 2.48 (95%CI 1.14–4.34) vs 1.06 (95%CI 0.24–2.45), p =0.149
Lyon, 2014	Adolescents with cancer aged 14 to 21 and their adult surrogates	Total of 30 dyads Intervention: 17 dyads • Adolescents: 17 • Adult surrogates: 17 Control: 13 dyads • Adolescents: 13 Adult surrogates: 13	Family-centred Advance Care planning Three sixty minute sessions scheduled one week apart. Session 1 – Lyon Family Centred ACP Survey: Session 2 – Respecting Choices, a facilitated ACP conversation Session 3 – Completion of the Five wishes, a legal statement of treatment preferences Usual care Usual care, provision of a brochure with information	**Mean (SD) anxiety scores (intervention vs control)** *(according to generalized estimating equation model)* Baseline *6.8 (8.2) vs 9.8 (10.0)* 3 month follow-up *2.6 (2.2) vs 4.0 (3.20)* There was no significant difference in anxiety scores of adolescents between intervention and control group, β = - *3.1, p = 0.3542)* **Mean (SD) anxiety scores (baseline vs 3-month follow-up)** *(according to generalized estimating equation model)* *Adolescents* Intervention: 6.8 (8.2) vs 2.6 (2.2), β = -5.6; p = 0.0212 Control: 9.8 (10.0) vs 4.0 (3.2), β = -5.6; p = 0.0212 Anxiety scores of adolescents significantly decreased in both intervention and control group over time.
Grade assessment				
Study design:	+4	2 Randomized Controlled Trial		
Study limitations	-2	Serious limitations - Selection bias: low 1/2, unclear in 1/2; Attrition bias: low in 2/2; Performance bias: high in 2/2; Detection bias: unclear in 2/2		
Consistency:	0	No important inconsistency.		
Directness:	0	Results are direct		
Precision:	-1	Some imprecision due to small sample size (n=68).		
Publication bias:	0	Unlikely		

Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence that there is no significant effect of Family-centred Advance Care planning on anxiety at 3 month follow-up in adolescents with HIV-infection or cancer, as compared to control or usual care.**

Family-centred Advance Care planning				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Anxiety in adult surrogates, Beck Anxiety Index (BAI), score ranging from 0 to 63, higher scores represent presence of more anxiety related symptoms Scores: 0 to 7 = minimal anxiety; 8 to 15 = mild anxiety; 16 to 25 = moderate anxiety; 26 – 63 = severe anxiety				
Lyon, 2010	Adolescents with HIV-infection aged 14 to 20 years and their adult surrogates	Total of 38 dyads Intervention: 20 dyads • Adolescents: 20 • Adult surrogates: 20 Control: 18 dyads • Adolescents: 18 • Adult surrogates: 18	Family-centred Advance Care planning Three weekly 60-90 minute family interview sessions. Session 1 – Lyon Advance Care Planning Adolescent and Surrogate Versions Session 2 – The Respecting Choices Interview, a facilitated ACP conversation Session 3 – Completion of the Five wishes, a legal statement of treatment preferences Control Three weekly 60-90 minute family interview sessions: Session 1 – Developmental History Session 2 – Safety Tips Session 3 – School and Career Planning interview	**Mean anxiety scores in adult surrogates(intervention vs control)** Baseline 1.64 (95%CI 0.62–3.14) vs 2.51 (95%CI 1.14–4.41), p = 0.*394* 3 month follow-up 2.48 (95%CI 1.20–4.22) 2.35 (95%CI 1.06–4.15), p = 0.901
Lyon, 2014	Adolescents with cancer aged 14 to 21 and their adult surrogates	Total of 30 dyads Intervention: 17 dyads • Adolescents: 17 • Adult surrogates: 17 Control: 13 dyads • Adolescents: 13 Adult surrogates: 13	Family-centred Advance Care planning Three sixty minute sessions scheduled one week apart. Session 1 – Lyon Family Centred ACP Survey: Session 2 – Respecting Choices, a facilitated ACP conversation Session 3 – Completion of the Five wishes, a legal statement of treatment preferences Usual care Usual care, provision of a brochure with information	**Mean (SD) anxiety scores (intervention vs control)** *(according to generalized estimating equation model)* Baseline *3.4 (3.4) vs 4.3 (8.6)* 3 month follow-up *4.0 (5.1) vs 3.5 (8.7),* There was no significant difference in anxiety scores of adult surrogates over time between intervention and control group β = - *0.9, p = 6973* **Mean (SD) anxiety scores (Baseline vs 3-month follow-up)** *(according to generalized estimating equation model)*. Intervention: 3.4 (3.4) vs 4.0 (5.1), p = NS Control: 4.3 (8.6) vs 3.5 (8.6), β = -1.2, P = 0.0314 The anxiety of surrogates score dropped significantly in the control group but increased in families in the intervention group
Grade assessment				
Study design:	+4	2 Randomized Controlled Trial		
Study limitations	-2	Serious limitations - Selection bias: low 1/2, unclear in 1/2; Attrition bias: low in 2/2; Performance bias: high in 2/2; Detection bias: unclear in 2/2		
Consistency:	0	No important inconsistency.		
Directness:	0	Results are direct		
Precision:	-1	Some imprecision due to small sample size (n=68).		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		

Quality of evidence:	**⊕⊖⊖⊖ VERY LOW**
Conclusion:	**There is very low quality of evidence that there is no significant effect of Family-centred Advance Care planning on anxiety at 3 month follow-up in adult surrogates of adolescents with HIV-infection or cancer, as compared to control or usual care.**

Family-centred Advance Care planning				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Depression in adolescents, Beck depression Inventory-II (BDI-II). , score ranging from 0 to 63, higher scores represent presence of more depression related symptoms Scores: 0 to 13 = minimal depression; 14 to 19 = mild depression; 20 to 28 = moderate depression; 19 to 63 = severe depression				
Lyon, 2010	Adolescents with HIV-infection aged 14 to 20 years and their adult surrogates	Total of 38 dyads Intervention: 20 dyads • Adolescents: 20 • Adult surrogates: 20 Control: 18 dyads • Adolescents: 18 • Adult surrogates: 18	<u>Family-centred Advance Care planning</u> Three weekly 60-90 minute family interview sessions. Session 1 – Lyon Advance Care Planning Adolescent and Surrogate Versions Session 2 – The Respecting Choices Interview, a facilitated ACP conversation Session 3 – Completion of the Five wishes, a legal statement of treatment preferences <u>Control</u> Three weekly 60-90 minute family interview sessions: Session 1 – Developmental History Session 2 – Safety Tips Session 3 – School and Career Planning interview	**Mean depression scores (intervention vs control)** <u>Baseline</u> 7.8 (95%CI 4.73–11.69) vs 1.27 (95%CI 0.22–3.17), p = 0.001 <u>3 month follow-up</u> 5.06 (95%CI 2.57–8.39) vs 3.43 (95%CI 1.35–6.45), p = 0.432
Lyon, 2014	Adolescents with cancer aged 14 to 21 and their adult surrogates	Total of 30 dyads Intervention: 17 dyads • Adolescents: 17 • Adult surrogates: 17 Control: 13 dyads • Adolescents: 13 Adult surrogates: 13	<u>Family-centred Advance Care planning</u> Three sixty minute sessions scheduled one week apart. Session 1 – Lyon Family Centred ACP Survey: Session 2 – Respecting Choices, a facilitated ACP conversation Session 3 – Completion of the Five wishes, a legal statement of treatment preferences <u>Usual care</u> Usual care, provision of a brochure with information	**Mean (SD) depression scores (intervention vs control)** *(according to generalized estimating equation model)* <u>Baseline</u> *5.5 (4.8)vs 10.9 (8.1)* <u>3 month follow-up</u> *Adolescents: 6.3 (5.3) vs 4 7.4 (4.3),* β = *- 5.4, p = 0.0268* Intervention group had a significantly lower depression score at baseline and 3 month follow-up as compared with controls. **Mean (SD) depression scores (baseline vs 3 month follow-up)** *(according to generalized estimating equation model)* Intervention: 5.5 (4.8) vs 6.3 (5.3), Control: 10.9 (8.1) vs 7.4 (4.3) There was no significant difference in depression scores over time between intervention and control group β = -3.0, p = 0.1007
Grade assessment				
<u>Study design:</u>	+4	2 Randomized Controlled Trial		
<u>Study limitations</u>	-2	Serious limitations - Selection bias: low 1/2, unclear in 1/2; Attrition bias: low in 2/2; Performance bias: high in 2/2; Detection bias: unclear in 2/2		

Consistency:	0	No important inconsistency.
Directness:	0	Results are direct
Precision:	-1	Some imprecision due to small sample size (n=68).
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		**⊕⊖⊖⊖ VERY LOW**
Conclusion:		**There is very low quality of evidence that Family-centred Advance Care planning decreases depression at 3 month follow-up in adolescents with cancer, as compared to usual care. There is no significant effect among adolescents with HIV-infection.**

Family-centred Advance Care planning				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Depression in adult surrogates, Beck depression Inventory-II (BDI-II). , score ranging from 0 to 63, higher scores represent presence of more depression related symptoms Scores: 0 to 13 = minimal depression; 14 to 19 = mild depression; 20 to 28 = moderate depression; 19 to 63 = severe depression				
Lyon, 2010	Adolescents with HIV-infection aged 14 to 20 years and their adult surrogates	Total of 38 dyads Intervention: 20 dyads • Adolescents: 20 • Adult surrogates: 20 Control: 18 dyads • Adolescents: 18 • Adult surrogates: 18	<u>Family-centred Advance Care planning</u> Three weekly 60-90 minute family interview sessions. Session 1 – Lyon Advance Care Planning Adolescent and Surrogate Versions Session 2 – The Respecting Choices Interview, a facilitated ACP conversation Session 3 – Completion of the Five wishes, a legal statement of treatment preferences <u>Control</u> Three weekly 60-90 minute family interview sessions: Session 1 – Developmental History Session 2 – Safety Tips Session 3 – School and Career Planning interview	**Mean depression scores (intervention vs control)** <u>Baseline</u> 2.0 (95%CI 0.66–4.09) vs 3.65 (95%CI 1.62–6.50), p = 0.261 <u>3 month follow-up</u> 2.73 (95%CI 1.26–4.77) vs 3.29 (95%CI 1.57–5.65), p = 0.676
Lyon, 2014	Adolescents with cancer aged 14 to 21 and their adult surrogates	Total of 30 dyads Intervention: 17 dyads • Adolescents: 17 • Adult surrogates: 17 Control: 13 dyads • Adolescents: 13 Adult surrogates: 13	<u>Family-centred Advance Care planning</u> Three sixty minute sessions scheduled one week apart. Session 1 – Lyon Family Centred ACP Survey: Session 2 – Respecting Choices, a facilitated ACP conversation Session 3 – Completion of the Five wishes, a legal statement of treatment preferences <u>Usual care</u> Usual care, provision of a brochure with information	**Mean (SD) depression scores (intervention vs control)** *(according to generalized estimating equation model)* <u>Baseline</u> *5.4 (6.6) vs 5.8 (5.8)* <u>3 month follow-up</u> *5.3 (7.7) vs 5.3 (8.0)*, β = *- 0.4, p = 0.8424* There was no significant difference in depression scores of adult surrogates between intervention and control group. **Mean (SD) depression scores (baseline vs 3 month follow-up)** *(according to generalized estimating equation model)* Intervention 5.4 (4.8 vs 5.3 (7.7), p = NS Control: 5.8 (5.8) vs 5.3 (8.0), P = NS There was no significant difference in depression scores over time between intervention and control group β = -0.9 p = 0.5357
Grade assessment				
<u>Study design:</u>	+4	2 Randomized Controlled Trial		
<u>Study limitations</u>	-2	Serious limitations - Selection bias: low 1/2, unclear in 1/2; Attrition bias: low in 2/2; Performance bias: high in 2/2; Detection bias: unclear in 2/2		
<u>Consistency:</u>	0	No important inconsistency.		
<u>Directness:</u>	0	Results are direct		

Precision:	-1	Some imprecision due to small sample size (n=68).
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence that there is no significant effect of Family-centred Advance Care planning on depression at 3 month follow-up in adult surrogates of adolescents with HIV-infection or cancer, as compared to control or usual care.**

Family-centred Advance Care planning				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Health-related Quality of Life, Paediatric Quality of life inventory (Peds QL 4.0), higher score representing higher quality of life				
Lyon, 2010	Adolescents with HIV-infection aged 14 to 20 years and their adult surrogates	Total of 38 dyads Intervention: 20 dyads • Adolescents: 20 • Adult surrogates: 20 Control: 18 dyads • Adolescents: 18 • Adult surrogates: 18	<u>Family-centred Advance Care planning</u> Three weekly 60-90 minute family interview sessions. Session 1 – Lyon Advance Care Planning Adolescent and Surrogate Versions Session 2 – The Respecting Choices Interview, a facilitated ACP conversation Session 3 – Completion of the Five wishes, a legal statement of treatment preferences <u>Control</u> Three weekly 60-90 minute family interview sessions: Session 1 – Developmental History Session 2 – Safety Tips Session 3 – School and Career Planning interview	**Generic health-related Quality of Life at 3-month follow-up (Intervention vs. control)** *Adolescents:* 338.5 (95%CI 321-355) vs. 345.6 (95%CI 327.3-363.1), p = 0.568
Lyon, 2014	Adolescents with cancer aged 14 to 21 and their adult surrogates	Total of 30 dyads Intervention: 17 dyads • Adolescents: 17 • Adult surrogates: 17 Control: 13 dyads • Adolescents: 13 Adult surrogates: 13	<u>Family-centred Advance Care planning</u> Three sixty minute sessions scheduled one week apart. Session 1 – Lyon Family Centred ACP Survey: Session 2 – Respecting Choices, a facilitated ACP conversation Session 3 – Completion of the Five wishes, a legal statement of treatment preferences <u>Usual care</u> Usual care, provision of a brochure with information	**Mean (SD) Quality of life scores (intervention vs control)** *(according to generalized estimating equation model)* <u>Baseline</u> *Adolescents: 71.9 (17.4) vs 68.7 (17.4)* <u>3 month follow-up</u> *Adolescents: 77.2 (13.4) vs 4 76.2 (10.4)),* β = 3.1, *p = 0.6123* There was no significant difference in Quality of life scores of adolescents at baseline and 3 month follow-up between intervention and control. **Mean (SD) Quality of Life scores (baseline vs 3 month follow-up)** *(according to generalized estimating equation model)* *Adolescents* Intervention: 71.9 (17.4) vs 77.2 (13.4), P = NS Control: 68.7 (17.4) 76.2 (10.4), p = NS Intervention vs control (over time): β = 5.9, p = 0.1123 There was no significant difference in Quality of Life in adolescents scores over time between intervention and control group
Grade assessment				
<u>Study design:</u>	+4	2 Randomized Controlled Trial		
<u>Study limitations</u>	-2	Serious limitations - Selection bias: low 1/2, unclear in 1/2; Attrition bias: low in 2/2; Performance bias: high in 2/2; Detection bias: unclear in 2/2		
<u>Consistency:</u>	0	No important inconsistency.		

Directness:	0	Results are direct
Precision:	-1	Some imprecision due to small sample size (n=68).
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence that there is no significant effect of Family-centred Advance Care planning on Quality of Life at 3 month follow-up in adolescents with HIV-infection or cancer, as compared to control or usual care.**

Family-centred Advance Care planning				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Spiritual well-being,	Spiritual Well-Being Scale of the Functional Assessment of Chronic Illness Therapy Version 4, higher score indicating better spiritual well-being			
Lyon, 2014 (a longitudinal, randomized, controlled trial)	Adolescents with cancer aged 14 to 21 and their adult surrogates	Total of 30 dyads Intervention: 17 dyads • Adolescents: 17 • Adult surrogates: 17 Control: 13 dyads • Adolescents: 13 Adult surrogates: 13	Family-centred Advance Care planning Three sixty minute sessions scheduled one week apart. Session 1 – Lyon Family Centred ACP Survey: Session 2 – Respecting Choices, a facilitated ACP conversation Session 3 – Completion of the Five wishes, a legal statement of treatment preferences Usual care Usual care, provision of a brochure with information	**Mean (SD) spirituality scores (intervention vs control)** Baseline: *Total: 78.9 (13.1) vs 70.8 (7.8)* *Peace: 28.2 (3.8) vs 24.4 (5.5)* *Faith: 13.2 (4.0) vs 11.8 (3.7)* 3 month follow-up *Total: 78.2 (8.1) vs 67.2 (14.3)* Intervention group was higher at baseline and 3 month follow-up, compared to control. β = 8.1, p =.0296. *Peace: 27.6 (3.6) vs 25.4 (4.0)* Intervention group was higher at baseline and 3 month follow-up, compared to control, β = 3.9, p =.0239 *Faith: 12.2 (4.4) vs 9.9 (4.9)* No significant difference between intervention and control group. β = 3.1, p = 0.3286 **Mean (SD) spirituality scores (baseline vs 3-month follow-up)** *Total* Intervention: 78.9 (13.1) vs 78.2 (8.1), Control: 70.8 (7.8) vs 67.2 (14.3) *Peace:* Intervention: 28.2 (3.8) vs 27.6 (3.6), Control: 24.4 (5.5) vs 25.4 (4.0), *Faith:* Intervention: 13.2 (4.0) vs 12.2 (4.4), p = 0.466 Control: 11.8 (3.7) vs 9.9 (4.9), p = 0.446 Faith subscale scores dropped significantly from baseline to 3 month follow-up
Grade assessment				
Study design:	+4	1 Randomized Controlled Trial		
Study limitations	-1	Some limitations - Selection bias: low; Attrition bias: low ; Performance bias: high; Detection bias: unclear		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Results are direct		
Precision:	-2	Some imprecision due to small sample size (n=30). Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		

Conclusion:	**There is very low quality of evidence that Family-centred Advance Care planning increases spiritual well-being at 3 month follow-up in adolescents with cancer, as compared to usual care.**

4.2 Belemmerende en bevorderende factoren van ACP en gezamenlijke besluitvorming

4.2.1 Geïncludeerde thema;s

Included themes
Information provision
Involvement
Interpersonal relations and communication
Holistic approach to care
Timing
Preparation
Documentation
Setting
Support
Education

4.2.2 Informatie voorziening

4.2.2.1 Geïncludeerde subthema's

Included subthemes
Information on treatment and prognosis
Uncertainty about diagnosis, prognosis

4.2.2.2 Informatievoorziening over behandeling en prognose

4.2.2.2.1 Ouderperspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Information provision on treatment and prognosis			
Beecham, 2017 – Qualitative study	18 parents • 9 parents whose child was currently receiving palliative care • 9 bereaved parents whose child had received palliative care Children had following type of conditions: ○ 10 neurologic ○ 2 metabolic ○ 2 oncologic ○ 1 gastroenterological ○ 1 immunologic ○ 1 respiratory ○ 1 chromosomal abnormality	Open-ended, semi-structured interviews.	*Facilitators perceived by parents* • Parents mentioned it would be helpful to have more information about treatment options and likely outcomes.
Edwards, 2020 – Qualitative study	44 parents of 43 children: • 18 contemporaneous invasive long-term ventilation decision-makers • 10 contemporaneous non-invasive long-term ventilation decision-makers • 8 former invasive long-term ventilation decision-makers • 8 former non-invasive long-term ventilation decision-makers 1 young woman using invasive long-term ventilation 1 adolescent girl being initiated on non-invasive long-term ventilation	Semi-structured interviews using an open-ended interview guide. Interviews were conducted in person or over the phone	*Facilitators perceived by parents* • 40/44 emphasized the importance of knowing everything about their child's condition(s) and long-term ventilation, regardless if the information was upsetting or not. As they needed this to make a well-informed decision for their child and to be prepared for the future. • Majority of the parents felt devastated by their child's condition and/or tremendously stressed about their decision on long-term ventilation because they felt like they did not receive the desired information. • All families should be offered the full range of options, also to not initiate long-term ventilation. 1/16 former decision-makers. • 4/44 parents wanted HCPs' opinions and suggestions about everything, including what would be the best option for their child • Information concerning child's diagnosis or prognosis was insufficient, lacked detail on long-term ventilation or was not provided timely. 14/28 *Barriers perceived by parents* • 4/44 parents acknowledged that they preferred to receive only positive messages (e.g., the benefits of long-term ventilation) or did not want to hear negative information (e.g., the risks of long-term ventilation) unless it was specifically relevant to a decision at hand.
Lord, 2020 – Qualitative study	13 bereaved parents of 12 children with medical complexity: • 11 genetic or congenital • 1 acquired	Qualitative, semi-structured interviews.	*Facilitators perceived by parents* • Understanding of the child's existing medical and technological needs, given that these often informed ACP decisions.
Lotz, 2017 – Qualitative study	11 parents of 9 deceased children with following diagnoses: • 3 cancer • 1 spinal muscular atrophy type I	Qualitative, practice-informing, semi-structured interview study.	*Facilitators perceived by parents* • Provision of written materials to introduce and inform about ACP, allows parents to determine what they are ready to address in ACP discussions.

	• 1 cystic fibrosis • 1 leukodystrophy • 1 hypo plastic left heart syndrome • 1 complex malformation syndrome • 1 unknown syndrome		
Mitchell, 2019 – Qualitative study	17 parents of 11 deceased children Child's diagnosis/Together for Short Lives category: • Category 1 (n=5) • Category 2 (n=0) • Category 3 (n=2) • Category 4 (n=4)	In-depth, semi-structured qualitative interview study.	*Facilitators perceived by parents* • Parents wanted to understand/observe implications of particular interventions, such as ventilation, before this was considered in an ACP.

Cicero-Oneto 2017 – Qualitative study	• 13 parents/primary cares of 13 children with following diagnosis:
	  • 2 haematological neoplasm
	  • 9 extracranial solid tumour
	  • 2 tumour of the CNS
	7 out of 13 children had already died
		Qualitative study with individual, face-to-face, semi-structured, and in-depth interviews.	*Barriers perceived by parents*
			• 2/13 parents stressed that the medical discourse, that the oncologist used in communicating the therapeutic futility to them, made the information provided incomprehensible.

Mekelenkamp 2020 – Qualitative study	14 parents of 8 children that died within a year after allogeneic HSCT, with following diagnoses: • 2 bone marrow failure • 4 malignancy • 1 hemoglobinopathy • 1 primary immune deficiency	Qualitative descriptive study with in-depth face-to-face individual interviews and a background questionnaire.	*Barriers perceived by parents* • Parents experienced the complexity of the treatment as hard to understand, and therefore felt unable to take decision-making responsibility. *Facilitators perceived by parents* • Parents felt supported by a consistent, regularly explanation of treatment decisions and the feeling they were heard in their concerns.
Murrell 2018 – Qualitative study	19 families, including 29 parents and 22 children with Type 1 SMA: • 11 children living • 11 deceased children	Qualitative descriptive design with individual or small group interviews guided by a semi-structured questionnaire.	*Barriers perceived by parents* • Multiple families reported that they would make different decisions if they had received more complete or unbiased information on choices about ventilation.
Sisk 2020 – Qualitative study	77 parents and 1 grandparent of 78 children with following diagnoses: • 35 leukaemia or lymphoma • 30 solid tumor • 13 brain tumor	A qualitative study using semistructured telephone interviews using an interview guide.	*Facilitators perceived by parents* • Nearly all parents mentioned the importance of consistent, accurate, and timely information that was understandable. • Many parents noted the importance of knowing what to expect. • Parents highlighted the importance of meeting their unique information needs, especially related to the level of detail, and pacing of information. • Some parents noted the need for training in technical skills to care for their child. *Barriers perceived by parents* • Some parents desired transparent disclosure of difficult news.
Zaal-Schuller 2016 – Qualitative study	17 parents of 14 children with following diagnoses: • 3 post-resuscitation • 5 genetic condition • 1 neurologic condition	Retrospective, qualitative study, with semi-structured interviews.	*Barriers perceived by parents* • The majority of parents expressed a lack of information during the EOL decision-making process, e.g. about available treatment options. • Many parents felt they lacked necessary medical background to put the received information in the right context.

• 2 metabolic condition • 3 unknown		
GRADE CERQual assessment (for conclusions reported in more than one study)		
Study design:	+4	9 qualitative studies
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 9/9; Study design and theoretical approach: low in 9/9; Sample selection: low in 2/9, unclear in 2/9, high in 5/9; Data collection: low in 8/9, high in 1/9; Data analysis: low in 7/9, unclear in 2/9; Results: low in 9/9
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	0	No concerns on sufficiency of saturation
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**
Conclusion:		• **Parents expressed the need to know what to expect and wished complete and unbiased information about the child's condition, likely outcomes and treatment options (including the option to stop or not initiate treatment) (6 studies).** • **Parents needed consistent, accurate and understandable information that is timely and regularly explained, and in accordance with the unique situation of the child (4 studies). When parents lacked medical background or did not understand the complexity of treatment, they felt unable to take decision-making responsibility (3 studies).**
GRADE CERQual assessment (for conclusions reported in only one study)		
Study design:	+4	2 qualitative studies
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 2/2; Study design and theoretical approach: low in 2/2; Sample selection: unclear in 1/2, high in 1/2; Data collection: low in 1/2, unclear in 1/2; Data analysis: low in 1/2, unclear in 1/2; Results: low in 2/2
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	-1	Some concerns on sufficiency of saturation due to small sample size (N=11). Only 1 study performed.
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**
Conclusion:		• **A minority of parents only wanted to receive negative information when it was relevant for a specific decision (1 study).** • **Written materials about ACP help parents to determine what they are ready to address (1 study).**

4.2.2.2.2 Kindperspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Information on treatment and prognosis			

Cicero-Oneto 2017 – Qualitative study	• 6 children (4 children of the participating parents, and 2 other children with incurable or terminal phase cancer) with following diagnoses:
	  • 1 hepatic primitive neuroectodermal tumour
	  • 1 colorectal adenocarcinoma
	  • 1 pilocytic astrocytoma
	  • 1 osteosarcoma
	  • 2 acute lymphoblastic leukaemia
	2 of these children were aware of the prognosis.
		Qualitative study with individual, face-to-face, semi-structured, and in-depth interviews.	*Facilitators perceived by children*
			• The children interviewed preferred to hear the information from their parents.
			• The children interviewed focused on the need for their oncologists to speak to them truthfully.
			• 1/2 children mentioned having heard of the prognosis in terms of probabilities of death in the short term and to have previously obtained information about the disease from the internet.
			• 1/2 children mentioned learning the prognosis in terms of null possibility of cure.

Kelly 2017 – Qualitative study	29 newly diagnosed children with following diagnoses:
	• 15 leukaemia and lymphoma
	• 7 central nervous system tumor
	• 7 solid tumor
		Descriptive qualitative research methods, with interactive interview techniques.	*Facilitators perceived by children*
			• Children consistently mentioned their parents' and clinicians' central roles in meeting their communication needs. Communication preferences and desire for information, were primarily influenced by what was happening to the child at a given point.
			• Children stated that they trust that their parents know how much information they can handle.
			Barriers perceived by children
			• Information preferences varied and changed as children learned about their condition;
			  ○ Some children reported wanting to know "everything," including prognosis and test results.
			  ○ Some children described wanting to know their treatment plans and what was going to happen next.
			  ○ Some children did not want to be bothered, they "just want the doctors to help them get better and to help them get out of there".

GRADE CERQual assessment			
Study design:	+4	2 qualitative studies	
Methodological limitations:	-1	Aim and appropriateness of qualitative evidence: low in 2/2; Study design and theoretical approach: low in 2/2; Sample selection: high in 2/2; Data collection: low in 2/2; Data analysis: low in 2/2; Results: low in 2/2	
Coherence:	-1	Some concerns on coherence, information preferences vary among children	
Relevance:	0	No concerns on relevance	
Sufficiency of saturation:	0	No concerns on sufficiency of saturation	
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**	

Conclusion:	• **Some children preferred to hear information from their parents, and mentioned their parents' and clinicians' central roles in meeting their communication needs (2 studies).**
	• **Children's information preferences varied and tended to change as children learned about their condition (2 studies);**
	  ○ **Some children wanted to know everything including prognosis and test results, and needed their HCPs to speak truthfully to them (2 studies).**
	  ○ **Some children did not want to receive information (1 study).**

4.2.2.2.3 Zorgprofessional perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Information on treatment and prognosis			
Edwards, 2017 – Qualitative study	15 directors/codirectors of paediatric home ventilation programs at children's hospital of following expertise: • 11 paediatric pulmonologists • 2 paediatric intensivists • 2 specialized in both paediatric pulmonology and critical care Children treated in children's hospital: Children with Chronic Respiratory Failure (CRF)	In-depth, semi-structured interviews over the phone, using an open-ended interview guide.	*Barriers perceived by HCPs* • Not fully informing families (14/15) • Inability to provide prognosis (and sometimes diagnosis) (4/15) • 13/15 directors conceded that using the internet was inevitable, and that it was a helpful source of information/support. However, they added that it could be obstructive, recommending caution, and that families talk to them about what they find. • Mixed or inconsistent messages (3/15) • Inability to really grasp the information provided or the "big picture" (7/15) • Influence from outside sources/people (6/15) • Misinformation from outside sources/people (5/15) *Facilitators perceived by HCPs* • Beyond explaining the child's condition and (when possible) prognosis with and without long-term ventilation, all directors highlighted the need to inform families of potential benefits, risks, and burdens, and financial impact of long-term ventilation for the child and family. • Directors stressed that HCPs should be transparent, candid and consistent when conveying information to families and addressing barriers and worries.
Odeniyi, 2017 – Qualitative study	10 Health Care Professionals of following expertise: • 2 intensivist attendings • 1 intensive care fellow • 4 oncologist attendings • 3 oncologist fellows	Qualitative study using semi-structured interviews.	*Barriers perceived by HCPs* • Intensivist felt responsible for parents understanding the child's prognosis and treatment choices, but struggled with making recommendations about what was best for the child.
Orkin, 2020 – Qualitative study	11 Health Care Professionals (8 physicians, 2 nurses, 1 social worker) of following expertise: • 2 complex care • 3 paediatric medicine • 2 respiratory medicine • 1 paediatric haematology and oncology	Qualitative content-analysis study comprising demographic surveys and individual semi-structured interviews.	*Facilitators perceived by HCPs* • HCPs stated the importance of delivering a consistent message between different HCPs and health care teams.

	• 1 critical care • 1 neonatal intensive care • 1 palliative care		
Cicero-Oneto 2017 – Qualitative study	• 13 paediatric oncologists	Qualitative study with individual, face-to-face, semi-structured, and in-depth interviews.	*Facilitators perceived by HCPs* • Oncologists said that they preferred that the parents be the ones to determine the type and amount of information that they needed. *Barriers perceived by HCPs* • Oncologists mentioned parental difficulty of understanding and accepting the prognosis.
Day 2018 – Qualitative study	58 Health Care Professionals specialised in haematology, haematopoietic stem cell transplantation or palliative care, working principally with patients aged 13-25 years. • 6 consultants • 19 junior doctors (foundation year, registrar/resident and specialty registrar/fellow) • 9 Clinical Nurse Specialists • 10 ward nurses • 14 allied HCP (psychologists, physiotherapists, dieticians and social workers)	In-depth, semi-structured interviews and participant observations (during psycho-social meetings, day-care meetings and pre-ward round meeting, and informal conversations).	*Barriers perceived by HCPs* • HCPs recognize the importance of establishing and respecting what the teenager wanted and needed to know at different times across the illness.
Henderson 2017 – Qualitative study	36 Health Care Professionals (including medical, nursing, and allied health professionals)	Qualitative design using a group interview.	*Facilitators perceived by HCPs* • Acknowledge the uncertainty of each and every case
Zaal-Schuller 2016 – Qualitative study	11 Health Care Professionals of following expertise: • 6 paediatricians • 1 rehabilitation specialists • 1 paediatric Intensive Care specialists • 3 paediatric Neurologists	Retrospective, qualitative study, with semi-structured interviews.	*Barriers perceived by HCPs* • Physicians mentioned that they put lots of effort into giving clear information and advice to parents, but this is complicated by an uncertain prognosis and unforeseen complications. • Almost half of the physicians thought that parents find it hard to completely comprehend all of the information, because of a lack of sufficient medical background to put the information in the right context. • Physicians mentioned that for some parents, especially with non-Dutch backgrounds, it is difficult to fully comprehend medical concepts. • Some physicians thought that parents were particularly capable of understanding the information, because of their knowledge of the medical conditions and their experiences with treatments during previous critical illnesses of their child.
GRADE CERQual assessment (for conclusions reported in more than one study)			
Study design:	+4	7 qualitative studies	
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 7/7; Study design and theoretical approach: low in 6/7, unclear in 1/7; Sample selection: unclear in 4/7, high in 3/7; Data collection: low in 4/7, unclear in 3/7; Data analysis: low in 5/7, unclear in 2/7; Results: low in 6/7, high in 1/7	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	
Sufficiency of saturation:	0	No concerns on sufficiency of saturation	

Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**
Conclusion:		• **Although HCPs mentioned it is complicated to give clear and consistent information due to prognostic uncertainty (3 studies), they acknowledge the need to deliver transparent, candid and consistent information to parents (3 studies).** • **Although HCPs prefer parents and teenagers to determine the type and amount of information they want and need at different times (2 studies), not fully informing families was perceived as a barrier in ACP discussions (1 study).** • **Some HCPs mentioned that understanding medical information and prognosis is difficult for parents (3 studies), especially parents with non-Dutch backgrounds, other HCPs did consider parents capable of understanding medical information, because of their knowledge and experience with their child's medical condition (1 study).**
GRADE CERQual assessment (for conclusions reported in only one study)		
Study design:	+4	1 qualitative study
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 1/1; Study design and theoretical approach: low in 1/1; Sample selection: unclear in 1/1; Data collection: low in 1/1; Data analysis: low in 1/1; Results: low in 1/1
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	-1	Some concerns on sufficiency of saturation due to small sample size (N=15). Only 1 study performed.
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**
Conclusion:		**Misinformation or influence from outside sources and people were mentioned as barriers (1 study).**

4.2.2.3 Onzekerheid over diagnose en prognose

4.2.2.3.1 Ouder perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Uncertainty about diagnosis and prognosis			
Hein, 2020 – Qualitative study	9 bereaved parents of children aged 2 to 16 years with following type of conditions: • 3 metabolic • 2 oncological • 2 perinatal • 1 cardiological • 2 neuromuscular	2 transdisciplinary workshops: • First workshop – discussion groups to explore experiences with paediatric advance care planning (6 parents, 14 HCPs). • Second workshop – dialogue groups to discuss topics such as, participation of children and adolescents; paediatric advance care planning documentation; supplementary written materials (5 parents, 14 HCPs).	*Facilitators perceived by parents* • Parents asked that professional discuss hypothetical scenarios.
Lord, 2020 – Qualitative study	13 bereaved parents of 12 children with medical complexity: • 11 genetic or congenital • 1 acquired	Qualitative, semi-structured interviews.	*Facilitators perceived by parents* • Parents mentioned that the degree of prognostic uncertainty as aspect of their child's unique situation needs to be taken into account.
Lotz, 2017 – Qualitative study	11 parents of 9 deceased children with following diagnoses: • 3 cancer • 1 spinal muscular atrophy type I • 1 cystic fibrosis • 1 leukodystrophy • 1 hypo plastic left heart syndrome • 1 complex malformation syndrome • 1 unknown syndrome	Qualitative, practice-informing, semi-structured interview study.	*Barriers perceived by parents* • Parents mentioned the physicians' reluctance to engage in ACP conversations because of prognostic uncertainty or because they do not face up to the facts.
Mitchell, 2019 – Qualitative study	17 parents of 11 deceased children Child's diagnosis/Together for Short Lives category: • Category 1 (n=5) • Category 2 (n=0) • Category 3 (n=2) • Category 4 (n=4)	In-depth, semi-structured qualitative interview study.	*Barriers perceived by parents* • Clinical uncertainty was a common experience and was particularly confusing and difficult for parents. In this situation, parents hoped for consensus among their HCPs.

Cicero-Oneto 2017 – Qualitative study	• 13 parents/primary cares of 13 children with following diagnosis:
	  • 2 haematological neoplasm
	  • 9 extracranial solid tumour
	  • 2 tumour of the CNS
	7 out of 13 children had already died
		Qualitative study with individual, face-to-face, semi-structured, and in-depth interviews.	*Facilitators perceived by parents*
			• Parents mentioned the prognosis given to them in terms of death as facilitator, and not wanting to see their child suffer more or undergo a lot of pain.

Sisk 2020 – Qualitative study	77 parents and 1 grandparent of 78 children with following diagnoses: • 35 leukaemia or lymphoma • 30 solid tumor • 13 brain tumor	A qualitative study using semistructured telephone interviews using an interview guide.	*Facilitators perceived by parents* • Many parents wanted clinicians to explore uncertainties and unknowns, and develop contingency plans. *Barriers perceived by parents* • Clinicians sometimes offered guesses when facing uncertainty, which was sometimes helpful. But at other times, guesses were frustrating.

GRADE CERQual assessment (for conclusions reported in more than one study)		
Study design:	+4	5 qualitative studies
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 5/5; Study design and theoretical approach: low in 5/5; Sample selection: low in 1/5, unclear in 1/5, high in 3/5; Data collection: low in 2/5, unclear in 2/5, high in 1/5; Data analysis: low in 3/5, unclear in 2/5; Results: low in 5/5
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	0	No concerns on sufficiency of saturation
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**
Conclusion:		• **Parents mentioned that uncertainty on the child's prognosis can be frustrating and confusing during ACP and EOL discussions, as it often led to guesses or disagreement among HCPs (3 studies).** • **Parents mentioned that uncertainties on diagnosis and prognosis need to be taken into account as an aspect of the child's unique situation and need to be explored by HCPs to develop contingent plans (3 studies).**
GRADE CERQual assessment (for conclusions reported in only one study)		
Study design:	+4	1 qualitative study
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 1/1; Study design and theoretical approach: low in 1/1; Sample selection: high in 1/1; Data collection: low in 1/1; Data analysis: low in 1/1; Results: low in 1/1
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	-1	Some concerns on sufficiency of saturation due to small sample size (N=13). Only 1 study performed.
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**
Conclusion:		**Parents mentioned that a prognosis given in terms of death and not wanting to see their child suffer anymore are helpful for making decisions (1 study).**

4.2.3 Betrokkenheid

4.2.3.1 Geïncludeerde subthema's

Included subthemes
Involvement of parents
Involvement of children and young people
Involvement of HCPs
Personal preferences for involvement

4.2.3.2 Betrokkenheid van ouders

4.2.3.2.1 Ouder perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Involvement of parents			
Beecham, 2017 – Qualitative study	18 parents • 9 parents whose child was currently receiving palliative care • 9 bereaved parents whose child had received palliative care Children had following type of conditions: ○ 10 neurologic ○ 2 metabolic ○ 2 oncologic ○ 1 gastroenterological ○ 1 immunologic ○ 1 respiratory ○ 1 chromosomal abnormality	Open-ended, semi-structured interviews.	*Barriers perceived by parents* • Parents mentioned that sometimes HCPs asked them to make a particular decision, but parents did not always want the HCP to involve them in decision making. • Sometimes parents were happy to go along with the recommendation given by the HCP(s), or the HCP(s) went along with the parents' preference. Other times, parents and HCPs jointly weighed the benefits and risks of different options. • 8/18 parents feel like they did not had much choice with regard to feeding options (e.g. because their child had a nasogastric tube fitted directly after birth). *Facilitators perceived by parents* • Parents stated the importance of clinicians understanding the need for them to take professional control at certain times and provide practical help. • 8/18 parents reported accepting clinicians advice after receiving a strong advice from them regarding limiting treatment, despite misgivings.
Edwards, 2020 – Qualitative study	44 parents of 43 children: • 18 contemporaneous invasive long-term ventilation decision-makers • 10 contemporaneous non-invasive long-term ventilation decision-makers • 8 former invasive long-term ventilation decision-makers • 8 former non-invasive long-term ventilation decision-makers 1 young woman using invasive long-term ventilation 1 adolescent girl being initiated on non-invasive long-term ventilation	Semi-structured interviews using an open-ended interview guide. Interviews were conducted in person or over the phone	*Facilitators perceived by parents* Parents had various approaches to manage stress in decision-making • 4/44 parents recommended that other parents trust their own intuition and experience regarding their child, even sometimes over those of medical professionals. • Being supportive was considered helpful by contemporaneous decision makers. 5/29
Fahner, 2021 – Qualitative study	18 Health Care Professionals (1 nurse, 17 physicians) of following expertise: • 1 cardiology • 1 gastroenterology • 1 general paediatrics • 1 haematology • 2 hereditary and congenital disorders • 2 intensive care • 3 metabolic diseases • 1 nephrology • 1 neurology • 2 oncology	Qualitative interviews; focus group interviews and individual interviews.	*Facilitators perceived by parents* • Parents stated that their paediatrician's acknowledgement of their child as an individual, and their tasks and expertise as parents, would be a precondition for sharing their deepest thoughts regarding their child's future. *Facilitators perceived by parents and HCPs* • Paediatricians and parents expressed the need for a caring attitude and attention when sharing future perspectives. *Barriers perceived by parents* • Parents saw themselves as the best advocates for their child, yet they struggled to define their child's best interests.

	• 3 pulmonology 20 parents of 17 children with life-limiting conditions (10 bereaved parents of 6 children who died) with following diagnoses: • 7 chromosomal anomaly • 4 congenital heart disease • 2 CNS tumour • 1 cystic Fibrosis • 1 neuromuscular disease • 1 epilepsy syndrome • 1 perinatal asphyxia		
Fahner, 2020 – Qualitative study	20 parents of 17 seriously ill children with following diagnoses: • 7 chromosomal anomaly • 4 congenital heart disease • 2 CNS tumour • 1 cystic fibrosis • 1 neuromuscular disease • 1 epilepsy syndrome • 1 perinatal asphyxia 6 children are deceased. 10 parents participated in a focus group interview.	Interpretive qualitative study, with individual face-to-face interviews and two focus group interviews.	*Facilitators perceived by parents* • Parents want their growing expertise to be acknowledged and taken into account when it comes to medical decision making, and felt a struggle to be treated as the expert of their child.
Hein, 2020 – Qualitative study	9 bereaved parents of children aged 2 to 16 years with following type of conditions: • 3 metabolic • 2 oncological • 2 perinatal • 1 cardiological • 2 neuromuscular	2 transdisciplinary workshops: • First workshop - discussion groups to explore experiences with paediatric advance care planning (6 parents, 14 HCPs). • Second workshop - dialogue groups to discuss topics such as, participation of children and adolescents; paediatric advance care planning documentation; supplementary written materials (5 parents, 14 HCPs).	*Barriers perceived by parents* • Parents disapproved of insensitive communication, discussions at wrong times and places and unsuitable coping with emotions.
Lord, 2020 – Qualitative study	13 bereaved parents of 12 children with medical complexity: • 11 genetic or congenital • 1 acquired	Qualitative, semi-structured interviews.	*Facilitators perceived by parents* • Parents appreciate when their own expertise in their child's care was acknowledged and valued. • Expressing compassion by the HCPs
Lotz, 2017 – Qualitative study	11 parents of 9 deceased children with following diagnoses: • 3 cancer • 1 spinal muscular atrophy type I	Qualitative, practice-informing, semi-structured interview study.	*Facilitators perceived by parents* • All parents wanted to be included in decision-making as partners, to be listened to, and taken seriously.

	• 1 cystic fibrosis • 1 leukodystrophy • 1 hypo plastic left heart syndrome • 1 complex malformation syndrome • 1 unknown syndrome		
Mitchell, 2019 – Qualitative study	17 parents of 11 deceased children Child's diagnosis/Together for Short Lives category: • Category 1 (n=5) • Category 2 (n=0) • Category 3 (n=2) • Category 4 (n=4)	In-depth, semi-structured qualitative interview study.	*Facilitators perceived by parents* • Clear guidance and the support of trusted clinicians was critical.
Orkin, 2020 – Qualitative study	14 mothers of 14 children 11 Health Care Professionals (8 physicians, 2 nurses, 1 social worker) of following expertise: • 2 complex care • 3 paediatric medicine • 2 respiratory medicine • 1 paediatric haematology and oncology • 1 critical care • 1 neonatal intensive care • 1 palliative care	Qualitative content-analysis study comprising demographic surveys and individual semi-structured interviews.	*Facilitators perceived by parents* • Parents mentioned the importance of feeling involved, respected, and accepted. *Barriers perceived by parents* • Parents showed a large variability in how they preferred ACP decisions to be made. Some wanted to always be seen as the expert. Some wanted the HCP to make the decisions. Others wanted the HCP to provide them with all options and guidance regarding what they think is right but allow the parent to make the final decision.

Cicero-Oneto 2017 – Qualitative study	• 13 parents/primary cares of 13 children with following diagnosis:
	  • 2 haematological neoplasm
	  • 9 extracranial solid tumour
	  • 2 tumour of the CNS
	7 out of 13 children had already died
		Qualitative study with individual, face-to-face, semi-structured, and in-depth interviews.	*Facilitators perceived by parents*
			• All the parents agreed that they were the ones legally responsible for their children and that the oncologists are the true decision-makers.

Mekelenkamp 2020 – Qualitative study	14 parents of 8 children that died within a year after allogeneic HSCT, with following diagnoses: • 2 bone marrow failure • 4 malignancy • 1 hemoglobinopathy • 1 primary immune deficiency	Qualitative descriptive study with in-depth face-to-face individual interviews and a background questionnaire.	*Facilitators perceived by parents* • Parents experiences most decisions as cure directed. Parents did not feel having made specific decision, but rather felt involved in a HCPs-guided decision-making process
Murrell 2018 – Qualitative study	19 families, including 29 parents and 22 children with Type 1 SMA: • 11 children living • 11 deceased children	Qualitative descriptive design with individual or small group interviews guided by a semi-structured questionnaire.	*Facilitators perceived by parents* • Families want their health care team to listen and respect their voice as the expert who has been constant in the child's life throughout diagnosis, treatment and decision-making.

			• HCPs should communicate with support and empathy throughout the diagnostic and treatment process, to prepare families for significant life changes.
Sisk 2020 – Qualitative study	77 parents and 1 grandparent of 78 children with following diagnoses: • 35 leukaemia or lymphoma • 30 solid tumor • 13 brain tumor	A qualitative study using semistructured telephone interviews using an interview guide.	*Facilitators perceived by parents* • Many parents noted the importance of being empowered. • Parents described the importance of having their concerns taken seriously. • Parents felt validated when clinicians reinforced their "good parent" beliefs. *Barriers perceived by parents* • Many parents indicated a preference for involvement in decision-making and expressed frustration when not involved.
Zaal-Schuller 2016 – Qualitative study	17 parents of 14 children with following diagnoses: • 3 post-resuscitation • 5 genetic condition • 1 neurologic condition • 2 metabolic condition • 3 unknown	Retrospective, qualitative study, with semi-structured interviews.	*Facilitators perceived by parents* • Nearly all parents emphasized that they felt that they were the experts on their child, meaning that they know a lot about the medical conditions of their child, and that they needed to be the 'translator' for their child's physician (e.g. explaining how their child was feeling and whether their child was in pain). • Parents felt that their role as expert was recognized by the regular physician, although it could take some time to gain the physician's trust. • Almost all parents felt that they were the right people to make the final decision, because it were decisions concerning their *own* child. • Many parents expressed that they were glad that they were able to make the EOL discussions with their involved physician.
GRADE CERQual assessment (for conclusions reported in more than one study)			
Study design:	+4	14 qualitative studies	
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 14/14; Study design and theoretical approach: low in 14/14; Sample selection: low in 2/14, unclear in 3/14, high in 9/14; Data collection: low in 10/14, unclear in 3/14, high in 1/14; Data analysis: low in 9/14, unclear in 5/14; Results: low in 14/14	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	
Sufficiency of saturation:	0	No concerns on sufficiency of saturation	
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**	

Conclusion:		• **Parents wanted to be acknowledged as the expert of their child, and mentioned the importance of feeling respected, accepted and supported during decision-making in ACP and EOL discussions (12 studies).**
		• **Parents had different perspectives regarding their level of involvement in ACP and EOL decision-making (7 studies):**
		  ○ **Some parents wanted to make decisions in collaboration with HCPs (6 studies).**
		  ○ **Some parents wanted to be the final decision-maker (2 studies).**
		  ○ **Some parents did not want to be involved and wanted HCPs to make the decisions (2 studies).**
		  ○ **Some parents felt like they did not have a choice, as there was only one option due to the treatment process (2 studies).**	

GRADE CERQual assessment (for conclusions reported in only one study)			
Study design:	+4	1 qualitative study	
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 1/1; Study design and theoretical approach: low in 1/1; Sample selection: high in 1/1; Data collection: unclear in 1/1; Data analysis: unclear in 1/1; Results: low in 1/1	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	

Sufficiency of saturation:	-1	Some concerns on sufficiency of saturation, due to small sample size (N=20). Only 1 study performed.
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**
Conclusion:		**Parents saw themselves as the best advocates for their child, but struggled to define their child's best interest (1 study).**

4.2.3.2.2 Zorgprofessional perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Involvement of parents			
Edwards, 2017 – Qualitative study	15 directors/co-directors of paediatric home ventilation programs at children's hospital of following expertise: • 11 paediatric pulmonologists • 2 paediatric intensivists • 2 specialized in both paediatric pulmonology and critical care Children treated in children's hospital: Children with Chronic Respiratory Failure (CRF)	In-depth, semi-structured interviews over the phone, using an open-ended interview guide.	*Facilitators perceived by HCPs* • All directors felt that families should be the final decision-makers.
Fahner, 2021 – Qualitative study	18 Health Care Professionals (1 nurse, 17 physicians) of following expertise: • 1 cardiology • 1 gastroenterology • 1 general paediatrics • 1 haematology • 2 hereditary and congenital disorders • 2 intensive care • 3 metabolic diseases • 1 nephrology • 1 neurology • 2 oncology • 3 pulmonology 20 parents of 17 children with life-limiting conditions (10 bereaved parents of 6 children who died) with following diagnoses: • 7 chromosomal anomaly • 4 congenital heart disease	Qualitative interviews; focus group interviews and individual interviews.	*Facilitators perceived by HCPs and parents* • Paediatricians and parents expressed the need for a caring attitude and attention when sharing future perspectives.

	• 2 CNS tumour • 1 cystic Fibrosis • 1 neuromuscular disease • 1 epilepsy syndrome • 1 perinatal asphyxia		
Odeniyi, 2017 – Qualitative study	10 Health Care Professionals of following expertise: • 2 intensivist attendings • 1 intensive care fellow • 4 oncologist attendings • 3 oncologist fellows	Qualitative study using semi-structured interviews.	*Barriers perceived by HCPs* • Intensivists and oncologist struggled with placing the burden of major decisions on parents, because parents have to live with the consequences of their decisions, and because they might not have the medical knowledge to understand the implications of certain conditions. • Oncologist acknowledged that attempts to place decisions solely in parents' hands were unfair and place an undue burden on them, especially when the child was likely to die. *Facilitators perceived by HCPs* • Intensivists described the central importance of listening to parents and respecting their wishes. • Both specialties expressed the sentiment that 'parents are always right' in terms of their ultimate decision for their child's care, and acknowledged the need to respect parental beliefs and decisions because they felt that parents knew their child best.
Hein, 2020 – Qualitative study	14 Health Care Professionals of following expertise: • 4 paediatricians • 1 emergency physician • 1 psychologist • 1 chaplain • 3 nurses (intensive care, out-patient) • 2 social workers • 2 special education teachers	2 transdisciplinary workshops: • First workshop - discussion groups to explore experiences with paediatric advance care planning (6 parents, 14 HCPs). • Second workshop - dialogue groups to discuss topics such as, participation of children and adolescents; paediatric advance care planning documentation; supplementary written materials (5 parents, 14 HCPs).	*Barriers perceived by HCPs* • Professionals thought that parents were reluctant to engage in decision-making discussions or too overburdened to make a 'right' decision. • Professionals had the impression that parents would take sudden and inexplicable decisions.
Orkin, 2020 – Qualitative study	14 mothers of 14 children 11 Health Care Professionals (8 physicians, 2 nurses, 1 social worker) of following expertise: • 2 complex care • 3 paediatric medicine • 2 respiratory medicine • 1 paediatric haematology and oncology • 1 critical care • 1 neonatal intensive care • 1 palliative care	Qualitative content-analysis study comprising demographic surveys and individual semi-structured interviews.	*Barriers perceived by HCPs* • HCPs had varied perspectives regarding family-HCP partnership for SDM. Some felt parents were given too much responsibility in ACP. Some felt the decision-making process should be more collaborative. *Facilitators perceived by HCPs* • HCPs agreed that decisions should be made in partnership with families, respecting their unique decision-making preferences.

Day 2018 – Qualitative study	58 Health Care Professionals specialised in haematology, haematopoietic stem cell transplantation or palliative care, working principally with patients aged 13-25 years. • 6 consultants • 19 junior doctors (foundation year, registrar/resident and specialty registrar/fellow) • 9 Clinical Nurse Specialists • 10 ward nurses • 14 allied HCP (psychologists, physiotherapists, dieticians and social workers)	In-depth, semi-structured interviews and participant observations (during psycho-social meetings, day-care meetings and pre-ward round meeting, and informal conversations).	*Facilitators perceived by HCPs* • When end-of-life issues came to the fore, HCPs acknowledged that it might be beneficial to involve teenagers and parents to identify the 'right thing' from the family's perspective.
Zaal-Schuller 2016 – Qualitative study	11 Health Care Professionals of following expertise: • 6 paediatricians • 1 rehabilitation specialists • 1 paediatric Intensive Care specialists • 3 paediatric Neurologists	Retrospective, qualitative study, with semi-structured interviews.	*Facilitators perceived by HCPs* • Half of 11 physicians emphasized that they regarded the parents as the expert of their child, because they needed the parents to be a 'translator' that told them how their child was doing. • Physicians stressed that making decisions together is very important, because this could facilitate the grieving process of the parents. *Barriers perceived by HCPs* • Many physicians thought they knew how the parents felt about EOL discussions, even if they have never discussed it with the parents before. • Making decisions together with parents meant different things to different physicians; o 3/11 HCPs agreed that the parents' opinions should weight the heaviest. o 4/11 HCPs explained that in their opinion, shared decision-making implied that they supported the decisions made by the parents.

GRADE CERQual assessment

Study design:	+4	7 qualitative studies
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 7/7; Study design and theoretical approach: low in 7/7; Sample selection: unclear in 4/7, high in 3/7; Data collection: low in 3/7, unclear in 4/7; Data analysis: low in 4/7, unclear in 3/7; Results: low in 7/7
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	0	No concerns on sufficiency of saturation
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**
Conclusion:		• **HCPs had different perspectives regarding the level of involvement of parents in ACP and EOL decision-making (7 studies):** o **Some HCPs felt that parents should be the final decision-makers (3 studies).** o **Some HCPs felt the decision-making process should be more collaborative with parents and children, and parents should be acknowledging as their child's expert and translator (5 studies).** o **Some HCPs were reluctant to engage parents in ACP or EOL decision-making because they felt it would burden parents giving them too much responsibility (3 studies), or because they thought they already knew how parents felt about these discussions (1 study).**

4.2.3.3 Betrokkenheid van kinderen

4.2.3.3.1 Ouder perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Involvement of children and young people			
Edwards, 2020 – Qualitative study	44 parents of 43 children: • 18 contemporaneous invasive long-term ventilation decision-makers • 10 contemporaneous non-invasive long-term ventilation decision-makers • 8 former invasive long-term ventilation decision-makers • 8 former non-invasive long-term ventilation decision-makers 1 young woman using invasive long-term ventilation 1 adolescent girl being initiated on non-invasive long-term ventilation	Semi-structured interviews using an open-ended interview guide. Interviews were conducted in person or over the phone	*Facilitators perceived by parents* • 3/16 former decision-makers wanted their child to be informed as much as possible.
Fahner, 2021 – Qualitative study	18 Health Care Professionals (1 nurse, 17 physicians) of following expertise: • 1 cardiology • 1 gastroenterology • 1 general paediatrics • 1 haematology • 2 hereditary and congenital disorders • 2 intensive care • 3 metabolic diseases • 1 nephrology • 1 neurology • 2 oncology • 3 pulmonology 20 parents of 17 children with life-limiting conditions (10 bereaved parents of 6 children who died) with following diagnoses: • 7 chromosomal anomaly • 4 congenital heart disease • 2 CNS tumour • 1 cystic Fibrosis • 1 neuromuscular disease • 1 epilepsy syndrome • 1 perinatal asphyxia	Qualitative interviews; focus group interviews and individual interviews.	*Facilitators perceived by parents, children and HCPs* • Paediatricians, parents and children all emphasised the importance of the child's perspective. *Barriers perceived by parents and HCPs* • Strategies to elicit the voice of the child are needed, either through direct communication with the child or by trying to understand the child's perspective.

	13 children with following type of conditions: • 1 auto-immune disorder • 1 congenital heart disease • 2 hematologic disease • 1 metabolic disease • 3 neuroendocrine disease • 2 pulmonary disease • 1 renal disease • 2 siblings of a child with life-limiting condition		
Fahner, 2020 – Qualitative study	20 parents of 17 seriously ill children with following diagnoses: • 7 chromosomal anomaly • 4 congenital heart disease • 2 CNS tumour • 1 cystic fibrosis • 1 neuromuscular disease • 1 epilepsy syndrome • 1 perinatal asphyxia 6 children are deceased. 10 parents participated in a focus group interview.	Interpretive qualitative study, with individual face-to-face interviews and two focus group interviews.	*Facilitators perceived by parents* • Some parents mentioned taking their child's perspective helped them define goals of care and treatment; "what would my child value most?"
Hein, 2020 – Qualitative study	9 bereaved parents of children aged 2 to 16 years with following type of conditions: • 3 metabolic • 2 oncological • 2 perinatal • 1 cardiological • 2 neuromuscular 14 Health Care Professionals of following expertise: • 4 paediatricians • 1 emergency physician • 1 psychologist • 1 chaplain • 3 nurses (intensive care, out-patient) • 2 social workers • 2 special education teachers	2 transdisciplinary workshops: • First workshop – discussion groups to explore experiences with paediatric advance care planning (6 parents, 14 HCPs). • Second workshop – dialogue groups to discuss topics such as, participation of children and adolescents; paediatric advance care planning documentation; supplementary written materials (5 parents, 14 HCPs).	*Barriers perceived by parents* • Parents were sceptical about involving young children. • Parents worried about HCPs being insensitive and scaring younger children off. *Facilitators perceived by parents and HCPs* • Parents and professionals agreed that concerned adolescents should be offered separate conversations with professionals. *Facilitators perceived by parents* • Parents asked for support to be able to talk themselves about sensitive issues with their children. • Parents asked that professionals take into account individual needs of their child.
Lotz, 2017 – Qualitative study	11 parents of 9 deceased children with following diagnoses: • 3 cancer • 1 spinal muscular atrophy type I • 1 cystic fibrosis	Qualitative, practice-informing, semi-structured interview study.	*Facilitators perceived by parents* • All parents wanted their child to be involved in ACP (except for infants) relative to its developmental maturity. • Parents felt that their child should be heard and taken seriously even if unable to make treatment decisions.

	• 1 leukodystrophy • 1 hypo plastic left heart syndrome • 1 complex malformation syndrome • 1 unknown syndrome		
Mekelenkamp 2020 – Qualitative study	14 parents of 8 children that died within a year after allogeneic HSCT, with following diagnoses: • 2 bone marrow failure • 4 malignancy • 1 hemoglobinopathy • 1 primary immune deficiency	Qualitative descriptive study with in-depth face-to-face individual interviews and a background questionnaire.	*Barriers perceived by parents* • Although parents appreciated age-appropriate information for their child, they reported to have the decisive role for themselves, in which they advocate for specific wishes for their child.
Murrell 2018 – Qualitative study	19 families, including 29 parents and 22 children with Type 1 SMA: • 11 children living • 11 deceased children	Qualitative descriptive design with individual or small group interviews guided by a semi-structured questionnaire.	*Facilitators perceived by parents* • Families emphasized the importance of treating their child as normally as possible to maintain a sense of childhood.
GRADE CERQual assessment			
Study design:	+4	7 qualitative studies	
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 7/7; Study design and theoretical approach: low in 7/7; Sample selection: low in 1/7, unclear in 2/7, high in 4/7; Data collection: low in 4/7, unclear in 3/7; Data analysis: low in 3/7, unclear in 4/7; Results: low in 7/7	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	
Sufficiency of saturation:	0	No concerns on sufficiency of saturation	
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**	

Conclusion:		• **Parents felt that their child's perspective should be taken into account when making ACP and EOL decisions (3 studies).**
		• **Parents felt that their child could be involved in decision-making, but had different perspectives regarding their level of involvement in ACP and EOL discussions (5 studies):**
		  ○ **Some parents felt children should be involved in decision making (2 studies).**
		  ○ **Some parents felt the level of involvement is dependent on the child's age. They appreciate age-appropriate information, but were sceptical about involving young children, while they thought teenagers should be involved (3 studies).**
		  ○ **Some parents wanted to talk themselves with their children about sensitive issues (1 study).**
		  ○ **Some parents wanted their child to be treated as normally as possible (1 study).**	

4.2.3.3.2 Kind perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Involvement of children and young people perceived by children			
Kelly 2017 – Qualitative study	29 newly diagnosed children with following diagnoses: • 15 leukaemia and lymphoma • 7 central nervous system tumor • 7 solid tumor	Descriptive qualitative research methods, with interactive interview techniques.	*Facilitators perceived by children* • Children consistently mentioned their parents' and clinicians' central roles in meeting their communication needs. Communication preferences and desire for involvement in treatment discussions, were primarily influenced by what was happening to the child at a given point. • Undergoing treatment facilitated children's learning about their disease and treatment and helped them to be more involved in illness and treatment communication. • Children mentioned how their parents and physicians were always acting with their best interests in mind. • Children wanted more say in treatment discussions about smaller decisions because they knew how their bodies reacted to certain care procedures based on their prior experience. • Children had more control over smaller decisions, e.g. type of central venous line that would be placed or how the line was accessed. • Children of all ages reported that they did not want to make "big" decisions. But they might want to participate in discussions. • Being part of treatment discussions provided an opportunity for children to influence their situation by learning and applying self-management skills (e.g. learning about the illness and influencing decisions to improve symptoms). • Children stated that having a say made them feel happier, less scared, more satisfied, and comfortable with decisions made. • Receiving information could decrease anxiety. *Barriers perceived by children* • When children were very ill or in pain, they did not want to be part of treatment discussions, but just wanted to get better. • Children did not always wanted to have a say, they sometimes simply wanted to be told what to do. • Not having a say made some children feel ignored and worried that "the doctors might do something wrong because no one is telling me what is going on". • Having no say meant not being present for treatment discussions, but when this occurred, some children spoke negatively about it. They reported feeling powerless or that nobody cared about their thoughts. • Being involved could expose the child to distressing information or pressure to make choices they were unable to make. • Children worried about making a wrong decision if they had to choose, and they were more comfortable with their parents or doctors making decisions. • Children acknowledged the possibility of being upset by knowing more about their condition or misinterpreting the discussion. • Receiving information could be overwhelming and cause distress.

GRADE CERQual assessment		
Study design:	+4	1 qualitative study
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 1/1; Study design and theoretical approach: low in 1/1; Sample selection: high in 1/1; Data collection: low in 1/1; Data analysis: low in 1/1; Results: low in 1/1
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	-1	Some concerns on sufficiency of saturation. Only 1 study performed.
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**

Conclusion:		• **Children had different perspectives on their own level of involvement in ACP and EOL decision-making (1 study):**
		  ○ **Some children wanted to be involved in making smaller decisions, and not in making "big" decisions (1 study).**
		  ○ **Some children did not want to make decisions when they were too ill or in pain (1 study).**
		  ○ **Some children felt ignored, worried and powerless when not involved in EOL discussions (1 study).**
		  ○ **Some children were more comfortable with their parents or HCPs making decisions, since they always act in their best interest (1 study).**
		• **Although some children perceived being involved in EOL discussions as satisfying and comforting, others felt this could be overwhelming and upsetting (1 study).**

4.2.3.3.3 Zorgprofessional perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Involvement of children and young people			
Edwards, 2017 – Qualitative study	15 directors/co-directors of paediatric home ventilation programs at children's hospital of following expertise: • 11 paediatric pulmonologists • 2 paediatric intensivists • 2 specialized in both paediatric pulmonology and critical care Children treated in children's hospital: Children with Chronic Respiratory Failure (CRF)	In-depth, semi-structured interviews over the phone, using an open-ended interview guide.	*Facilitators perceived by HCPs* • All directors insist that cognitively capable older children be involved in discussions and even decision-making around long-term ventilation.
Fahner, 2021 – Qualitative study	18 Health Care Professionals (1 nurse, 17 physicians) of following expertise: • 1 cardiology • 1 gastroenterology • 1 general paediatrics • 1 haematology • 2 hereditary and congenital disorders • 2 intensive care • 3 metabolic diseases • 1 nephrology • 1 neurology • 2 oncology • 3 pulmonology 20 parents of 17 children with life-limiting conditions (10 bereaved parents of 6 children who died) with following diagnoses: • 7 chromosomal anomaly • 4 congenital heart disease • 2 CNS tumour • 1 cystic Fibrosis • 1 neuromuscular disease • 1 epilepsy syndrome • 1 perinatal asphyxia 13 children with following type of conditions: • 1 auto-immune disorder • 1 congenital heart disease • 2 hematologic disease	Qualitative interviews; focus group interviews and individual interviews.	*Facilitators perceived by HCPs, parents and children* • Paediatricians, parents and children all emphasised the importance of the child's perspective. *Barriers perceived by HCPs* • Paediatricians reported challenging experiences when trying to approach children and communicate adequately with them. *Barriers perceived by HCPs and parents* • Strategies to elicit the voice of the child are needed, either through direct communication with the child or by trying to understand the child's perspective.

	• 1 metabolic disease • 3 neuroendocrine disease • 2 pulmonary disease • 1 renal disease • 2 siblings of a child with life-limiting condition		
Hein, 2020 – Qualitative study	9 bereaved parents of children aged 2 to 16 years with following type of conditions: • 3 metabolic • 2 oncological • 2 perinatal • 1 cardiological • 2 neuromuscular 14 Health Care Professionals of following expertise: • 4 paediatricians • 1 emergency physician • 1 psychologist • 1 chaplain • 3 nurses (intensive care, out-patient) • 2 social workers • 2 special education teachers	2 transdisciplinary workshops: • First workshop - discussion groups to explore experiences with paediatric advance care planning (6 parents, 14 HCPs). • Second workshop - dialogue groups to discuss topics such as, participation of children and adolescents; paediatric advance care planning documentation; supplementary written materials (5 parents, 14 HCPs).	*Barriers perceived by HCPs and parents* • Professionals regarded the participation of children of all ages in paediatric advance care planning as self-evident. *Barriers perceived by HCPs* • Some professionals complained about parents acting as gatekeepers preventing them to talk to children. They wanted to obtain support in talking with parents about their child's participation in paediatric advance care planning. *Facilitators perceived by HCPs and parents* • Parents and professionals agreed that concerned adolescents should be offered separate conversations with professionals.
Cicero-Oneto 2017 – Qualitative study	• 13 paediatric oncologists	Qualitative study with individual, face-to-face, semi-structured, and in-depth interviews.	*Barriers perceived by HCPs* • Oncologists revealed that they inform children only when the parents authorize it; hence they inform the parents first. • All the oncologists said that the parents are the ones legally responsible; nonetheless, they said that they think that the children should be made aware of their impending death. • The majority of oncologists mentioned that it was difficult to specify an age at which the child should be informed the poor prognosis. *Facilitators perceived by HCPs* • Oncologists think that the child is the one who should make choices about further treatment.
Day 2018 – Qualitative study	58 Health Care Professionals specialised in haematology, haematopoietic stem cell transplantation or palliative care, working principally with patients aged 13-25 years. • 6 consultants • 19 junior doctors (foundation year, registrar/resident and specialty registrar/fellow) • 9 Clinical Nurse Specialists • 10 ward nurses	In-depth, semi-structured interviews and participant observations (during psycho-social meetings, day-care meetings and pre-ward round meeting, and informal conversations).	*Barriers perceived by HCPs* • Some HCPs recognised that acting of teenagers' treatment preferences might not be possible, feasible or desirable, especially for decisions governed by internationally agreed treatment protocols, or those where there was a likelihood of serious harm, death or suffering (e.g. refusal of curative treatment, reduction of chemotherapy dose, escalation of care to intensive care). • During periods of uncertainty involvement of other professionals was prioritised in reaching a decision, which limited the role for the teenager in the process. • Common tensions between age-appropriate growing independence and the necessary dependence of a teenager diagnosed with cancer sometimes led to confusion about the influence of parents and families on teenagers' choices.

• 14 allied HCP (psychologists, physiotherapists, dieticians and social workers)		• Strict internationally agreed protocols, limited teenagers' involvement to listening and understanding, rather than choosing course of action. • HCPs mentioned that it was difficult to respond to EOL preferences, because the final authority for such decisions making towards EOL lay with HCPs and the clinical consensus. *Facilitators perceived by HCPs* • HCPs mentioned to 'follow the teenagers' lead', this was advocated for certain decisions (e.g. place of care, minor procedures).
GRADE CERQual assessment		
Study design:	+4	5 qualitative studies
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 5/5; Study design and theoretical approach: low in 5/5; Sample selection: unclear in 2/5, high in 3/5; Data collection: low in 2/5, unclear in 3/5; Data analysis: low in 2/5, unclear in 3/5; Results: low in 5/5
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	0	No concerns on sufficiency of saturation
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**

Conclusion:		• **HCPs had different perspectives regarding the level of involvement of children in ACP and EOL decision-making (5 studies):**
		  ○ **Some HCPs felt that children of all ages should participate in discussions (4 studies), other felt cognitively capable older children should be involved, but found it difficult to specify an age at which the child should be informed about their prognosis (2 studies).**
		  ○ **Some HCPs felt that involving teenagers might not be always possible, feasible or desirable, like when internationally agreed protocols are in place, when it could impose harm, death or suffering, or when involvement from other professionals was prioritised (1 study).**
		• **HCPs mentioned challenges when communicating with children, including understanding their perspectives and the role of parents as gatekeepers and influencing their child's choices (4 studies).**

4.2.3.4 Betrokkenheid van zorgprofessionals

4.2.3.4.1 Zorgprofessional perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Involvement of HCPs			
Cicero-Oneto 2017 – Qualitative study	• 13 paediatric oncologists	Qualitative study with individual, face-to-face, semi-structured, and in-depth interviews.	*Barriers perceived by HCPs* • The oncologists thought that the decision about futility is strictly medical; they perceived their role as HCP as one of their role is one of "orienting" the choice of the parents toward what they thought was beneficial for the patient.
Zaal-Schuller 2016 – Qualitative study	11 Health Care Professionals of following expertise: • 6 paediatricians • 1 rehabilitation specialists • 1 paediatric Intensive Care specialists • 3 paediatric Neurologists	Retrospective, qualitative study, with semi-structured interviews.	*Facilitators perceived by HCPs* • 3/11 HCPs expressed their role was solely give objective information to the parents that would enable them to make the best decisions. • Some physicians mentioned that in some situations they had chosen to make the final decision alone. This happened especially in cases of disagreement in which they wished to protect the child from further suffering.
Day 2018 – Qualitative study	58 Health Care Professionals specialised in haematology, haematopoietic stem cell transplantation or palliative care, working principally with patients aged 13-25 years. • 6 consultants • 19 junior doctors (foundation year, registrar/resident and specialty registrar/fellow) • 9 Clinical Nurse Specialists • 10 ward nurses • 14 allied HCP (psychologists, physiotherapists, dieticians and social workers)	In-depth, semi-structured interviews and participant observations (during psycho-social meetings, day-care meetings and pre-ward round meeting, and informal conversations).	*Facilitators perceived by HCPs* • HCPs felt they should take the lead on what to disclose from the teenager themselves. They assigned responsibility to teenagers for signalling verbally and non-verbally their desired degree of involvement in decision-making.
GRADE CERQual assessment (for conclusions reported in more than one study)			
Study design:	+4	2 qualitative studies	
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 2/2; Study design and theoretical approach: low in 2/2; Sample selection: unclear in 1/2, high in 1/2; Data collection: low in 2/2; Data analysis: low in 2/2; Results: low in 2/2	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	
Sufficiency of saturation:	0	No concerns on sufficiency of saturation	
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**	
Conclusion:		• **HCPs had different perspectives regarding their level of involvement in ACP and EOL decision-making (2 studies):** ○ **Some HCPs felt their role was solely providing information, enabling parents to make the best decisions (1 study).**	

		○ **Some HCPs felt they had an "orienting" role, directing parents towards what they thought is beneficial for the child (1 study).** ○ **Some HCPs mentioned making the final decision alone in certain situations when they wanted to protect the child from further suffering (1 study).**
GRADE CERQual assessment (for conclusions reported in only one study)		
Study design:	+4	1 qualitative study
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 1/1; Study design and theoretical approach: low in 1/1; Sample selection: unclear in 1/1; Data collection: low in 1/1; Data analysis: unclear in 1/1; Results: low in 1/1
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	-1	Some concerns on sufficiency of saturation. Only 1 study performed.
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**
Conclusion:		**HCPs felt they should take the lead about what to disclose from teenagers, and assigned responsibility to the teenager for signalling their desired degree of involvement in decision-making (1 study).**

4.2.3.5 Persoonlijke voorkeuren voor betrokkenheid

4.2.3.5.1 Ouderperspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Personal preferences for involvement			
Beecham, 2017 – Qualitative study	18 parents • 9 parents whose child was currently receiving palliative care • 9 bereaved parents whose child had received palliative care Children had following type of conditions: ○ 10 neurologic ○ 2 metabolic ○ 2 oncologic ○ 1 gastroenterological ○ 1 immunologic ○ 1 respiratory ○ 1 chromosomal abnormality	Open-ended, semi-structured interviews.	*Barriers perceived by parents* • Parents reported that it was difficult to visualize the likely consequences of limiting treatment. • Parents reported conflicted feeling about decisions about limitation of treatment, since they did not want their child to suffer, but also wanted to do everything possible to try to increase the length of their child's life. • Parent mentioned that making decisions about future treatment was difficult because their way of thinking care or treatment were hypothetical, and their preferences might change in the future as circumstances altered. *Facilitators perceived by parents* • Many parents' narratives indicated a desire to keep options open. Stating they would decide at the time or by agreeing to limit treatment with the knowledge they could change their mind later.
Edwards, 2020 – Qualitative study	44 parents of 43 children: • 18 contemporaneous invasive long-term ventilation decision-makers • 10 contemporaneous non-invasive long-term ventilation decision-makers • 8 former invasive long-term ventilation decision-makers • 8 former non-invasive long-term ventilation decision-makers 1 young woman using invasive long-term ventilation 1 adolescent girl being initiated on non-invasive long-term ventilation	Semi-structured interviews using an open-ended interview guide. Interviews were conducted in person or over the phone	*Barriers perceived by parents* • 7/44 *parents* felt that there was no decision to be made because supporting their child's breathing or preserving their life was the "only" option to them, and not doing so was unimaginable. • 15/44 parents describe as difficult, as if there were no great options and they had to choose between substantial downsides. • 3 parents said that their first response was to reject long-term ventilation and/or deny their child's situation. • Majority of the parents felt devastated by their child's condition and/or tremendously stressed about their decision on long-term ventilation because they worried about downsides of long-term ventilation for their child
Fahner, 2020 – Qualitative study	20 parents of 17 seriously ill children with following diagnoses: • 7 chromosomal anomaly • 4 congenital heart disease • 2 CNS tumour • 1 cystic fibrosis • 1 neuromuscular disease • 1 epilepsy syndrome • 1 perinatal asphyxia 6 children are deceased.	Interpretive qualitative study, with individual face-to-face interviews and two focus group interviews.	*Barriers perceived by parents* • Struggling and suffering parents saw the future as a black box. • Parents who had broader, all-encompassing, value based aims; e.g. being happy or try to live an ordinary life, had more difficulty to demonstrate how these aims could guide them to formulate goals of future care. *Facilitators perceived by parents* • Parents with consistent and balanced views could more easily look forward. • Perspectives did not seem to be related to better or worse prognosis. In case of more prognostic certainty, parents showed more ability to elaborate on the future. • Parents were more tempted to reflect on future scenario's if they seemed realistic, even when it confronted them with unfavourable outcomes.

	10 parents participated in a focus group interview.		• Some parents mentioned that feeling at peace with the past made them more open-minded towards thinking and discussing about the future, where similar scenarios could happen. • Few parents envisioned the future in relations to decisions made in the past. To see if they had made different choices in the past. These elaborations were followed by thoughts about the good things being a parent of a seriously ill child had brought and these positive thoughts supported them to face the future. • Parents who clear short-term disease-related aims; e.g. correction of tracheostomy, could more easily formulate goals of future care.
Lord, 2020 – Qualitative study	13 bereaved parents of 12 children with medical complexity: • 11 genetic or congenital • 1 acquired	Qualitative, semi-structured interviews.	*Facilitators perceived by parents* • Medical decisions regarding care escalation during an acute deterioration were influenced by the child's past experiences with escalations in care under similar clinical circumstances, which guided decisions about whether to embark on similar interventions in the future.
Lotz, 2017 – Qualitative study	11 parents of 9 deceased children with following diagnoses: • 3 cancer • 1 spinal muscular atrophy type I • 1 cystic fibrosis • 1 leukodystrophy • 1 hypo plastic left heart syndrome • 1 complex malformation syndrome • 1 unknown syndrome	Qualitative, practice-informing, semi-structured interview study.	*Barriers perceived by parents* • Parents identified barriers; e.g. feeling not ready, wanting to focus on the present, and suppress burdensome thoughts. • Many parents were reluctant to make decisions in advance but wanted to decide in due course. • Parents found it hard and burdensome to imagine future scenarios and were afraid to bind themselves. Facilitators perceived by parents • Parents wished to be encouraged to rethink their decisions or be able to revoke advance decisions.
Mitchell, 2019 – Qualitative study	17 parents of 11 deceased children Child's diagnosis/Together for Short Lives category: • Category 1 (n=5) • Category 2 (n=0) • Category 3 (n=2) • Category 4 (n=4)	In-depth, semi-structured qualitative interview study.	*Facilitators perceived by parents* • Parental decisions related to their child receiving high-intensity treatments could also be influenced by a sense that there was 'nothing to lose'; when the alternative was that, their child would almost certainly die. • Parents wanted to feel that they have made a choice to 'say goodbye' rather than having to make a choice to withdraw life-sustaining treatments. *Barriers perceived by parents* • Parents experienced wide-ranging, intense emotions towards the end of their child's life, which affected their ability to take part in end of life care decision-making.

Cicero-Oneto 2017 – Qualitative study	• 13 parents/primary cares of 13 children with following diagnosis:
	  • 2 haematological neoplasm
	  • 9 extracranial solid tumour
	  • 2 tumour of the CNS
	7 out of 13 children had already died
		Qualitative study with individual, face-to-face, semi-structured, and in-depth interviews.	*Barrier perceived by parents*
			• 2/13 parents mentioned "not acknowledging the situation, or not wanting to see...".

Mekelenkamp 2020 – Qualitative study	14 parents of 8 children that died within a year after allogeneic HSCT, with following diagnoses: • 2 bone marrow failure • 4 malignancy • 1 hemoglobinopathy	Qualitative descriptive study with in-depth face-to-face individual interviews and a background questionnaire.	*Facilitators perceived by parents* • The parental perspective on preventing anticipated regret was focused on survival during the treatment process. As it became clear that the child would die soon, their perspective changed to avoidance of further suffering. *Barriers perceived by parents*

	• 1 primary immune deficiency		• Parents mentioned that they would blame themselves if their decisions would have led to a worsening scenario or even death.
Zaal-Schuller 2016 – Qualitative study	17 parents of 14 children with following diagnoses: • 3 post-resuscitation • 5 genetic condition • 1 neurologic condition • 2 metabolic condition • 3 unknown	Retrospective, qualitative study, with semi-structured interviews.	*Barriers perceived by parents* • Some parents mentioned it was difficult for them to make certain decisions, e.g. resuscitation orders or decisions about medical ventilation.
GRADE CERQual assessment			
Study design:	+4	9 qualitative studies	
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 9/9; Study design and theoretical approach: low in 9/9; Sample selection: unclear in 2/9, high in 7/9; Data collection: low in 7/9, unclear in 1/9, high in 1/9; Data analysis: low in 7/9, unclear in 2/9; Results: low in 9/9	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	
Sufficiency of saturation:	0	No concerns on sufficiency of saturation	
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**	

Conclusion:		• **Parents experienced difficulty in EOL and ACP decision-making because (7 studies):**
		  ○ **Parents did not feel ready to make decision because they could not acknowledge the child's situation, wanted to focus on the present, suppressed burdensome thoughts and had intense emotions (4 studies).**
		  ○ **Parents did not want their child to suffer but also wanted to do everything possible to try to increase the length of their child's life (3 studies).**
		  ○ **Parents could not foresee consequences of some decisions and would feel regret (2 studies).**
		  ○ **Parents wanted to keep options open, because they were afraid to bind themselves when their preferences might change (2 studies).**
		• **Parents' decisions about future care were influenced by past experiences with the child's care. Parents mentioned decision-making was easier when these experiences were good and when they had clear short-term disease related goals (2 studies).**	

4.2.3.5.2 Zorgprofessional perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Personal preferences for involvement			
Edwards, 2017 – Qualitative study	15 directors/codirectors of paediatric home ventilation programs at children's hospital of following expertise: • 11 paediatric pulmonologists • 2 paediatric intensivists • 2 specialized in both paediatric pulmonology and critical care Children treated in children's hospital: Children with Chronic Respiratory Failure (CRF)	In-depth, semi-structured interviews over the phone, using an open-ended interview guide.	*Barriers perceived by HCPs* • Not willing to broach difficult topics (2/15) • Unrealistic expectations (6/15) • Focusing on the here and now to the detriment of the long term (3/15) • Stress/fear of making any decision (3/15) • Denial or lack of readiness/willingness to hear information (3/15)
Fahner, 2021 – Qualitative study	18 Health Care Professionals (1 nurse, 17 physicians) of following expertise: • 1 cardiology • 1 gastroenterology • 1 general paediatrics • 1 haematology • 2 hereditary and congenital disorders • 2 intensive care • 3 metabolic diseases • 1 nephrology • 1 neurology • 2 oncology • 3 pulmonology	Qualitative interviews; focus group interviews and individual interviews.	*Barriers perceived by HCPs* • Paediatricians need to feel confident to ask families about sensitive themes.
Odeniyi, 2017 – Qualitative study	10 Health Care Professionals of following expertise: • 2 intensivist attendings • 1 intensive care fellow • 4 oncologist attendings • 3 oncologist fellows	Qualitative study using semi-structured interviews.	*Barriers perceived by HCPs* • Intensivists and oncologists experienced personal conflicts about addressing goals of care and shared decision-making.
Orkin, 2020 – Qualitative study	11 Health Care Professionals (8 physicians, 2 nurses, 1 social worker) of following expertise: • 2 complex care • 3 paediatric medicine • 2 respiratory medicine • 1 paediatric haematology and oncology • 1 critical care • 1 neonatal intensive care	Qualitative content-analysis study comprising demographic surveys and individual semi-structured interviews.	*Barriers perceived by HCPs* • Many HCPs think that provider discomfort is a prominent barrier to ACP discussions.

	• 1 palliative care		
Cicero-Oneto 2017 – Qualitative study	• 13 paediatric oncologists	Qualitative study with individual, face-to-face, semi-structured, and in-depth interviews.	*Barriers percieved by HCPs* • Oncologist mentioned an emotional tie to the patient. • All oncologists thought that the announcement of therapeutic futility places the parents in a psychological state of vulnerability that reduces parents' capacity to understand the fundamental risk of deciding.
Henderson 2017 – Qualitative study	36 Health Care Professionals (including medical, nursing, and allied health professionals)	Qualitative design using a group interview.	*Facilitators perceived by HCPs* • Acknowledge your own anxieties to ensure you have space for listening and observing what the family is experiencing in the complex multi-layered moment. • Know your professional expertise, the areas you lack expertise in and when you should refer. • Reflect on where you could go wrong with an EOL discussion.
Sasazuki 2019 – Qualitative study	15 Health Care Professionals of following specialties: • 3 paediatric intensive care • 2 paediatric cardiology • 3 neonatology • 4 paediatric neurology • 3 paediatric oncology	Semi-structured, individual face-to-face interviews.	*Facilitators perceived by HCPs* • Physicians tried to assess the child's best interests by carefully observing their comfort, dignity and quality of life. *Barriers perceived by HCPs* • Physicians expressed anxiety when they had difficulty identifying the children's best interests. This seemed to affect their decisions regarding life-sustaining treatment. • Each paediatrician's quest for the best interests of the patient was an essential element that caused dilemmas during and after decision-making. • Participants experienced dilemmas when seeking "medically appropriate plans" and had distress concerning the planning of medication and treatments.
GRADE CERQual assessment (for conclusions reported in more than one study)			
Study design:	+4	7 qualitative studies	
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 7/7; Study design and theoretical approach: low in 6/7, unclear in 1/7; Sample selection: unclear in 2/7, high in 5/7; Data collection: low in 2/7, unclear in 5/7; Data analysis: low in 5/7, unclear in 2/7; Results: low in 6/7, high in 1/7	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	
Sufficiency of saturation:	0	No concerns on sufficiency of saturation	
Overall assessment of confidence in findings		⊕⊕⊕⊖ **MODERATE confidence in the evidence**	
Conclusion:		• **HCPs experienced discomfort and distress with addressing sensitive themes and assessing the child's best interest during and after ACP and EOL decision-making (6 studies).** • **HCPs mentioned that parents had difficulty with making EOL and ACP decisions because parents experienced stress or fear for making decisions (2 studies).**	
GRADE CERQual assessment (for conclusions reported in only one study)			
Study design:	+4	2 qualitative studies	
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 2/2; Study design and theoretical approach: low in 2/2; Sample selection: high in 2/2; Data collection: low in 1/2, unclear in 1/2; Data analysis: low in 2/2; Results: low in 2/2	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	
Sufficiency of saturation:	-1	Some concerns on sufficiency of saturation due to small sample size (N=13/N=15). Only 1 study performed.	

Overall assessment of confidence in findings	**⊕⊕⊖⊖ LOW confidence in the evidence**
Conclusion:	• **HCPs mentioned an emotional tie to patients as a barrier for EOL discussions (1 study).** • **HCPs mentioned that parents had difficulty with making EOL and ACP decisions because parents did not feel ready to make decisions because they could not acknowledge their child's situation, wanted to focus on the present or had unrealistic expectations (1 study).**

4.2.4 Interpersoonlijke relaties en communicatie

4.2.4.1 Geïncludeerde thema's

Included subthemes
Communication
Interpersonal relations

4.2.4.2 Communicatie

4.2.4.2.1 Ouderperspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Staff behaviour and communication style			
Edwards, 2020 – Qualitative study	44 parents of 43 children: • 18 contemporaneous invasive long-term ventilation decision-makers • 10 contemporaneous non-invasive long-term ventilation decision-makers • 8 former invasive long-term ventilation decision-makers • 8 former non-invasive long-term ventilation decision-makers 1 young woman using invasive long-term ventilation 1 adolescent girl being initiated on non-invasive long-term ventilation	Semi-structured interviews using an open-ended interview guide. Interviews were conducted in person or over the phone	*Facilitators perceived by parents* Following provider practices/qualities regarding communication were considered helpful by contemporaneous decision makers (n=28) • Being honest. 9/28 • Being tactful and using sensitive language. 9/28 • Using lay language 4/28 • Using interpreters for non-English speakers 3/28 *Barriers perceived by parents* Following communication practices were considered unhelpful by contemporaneous decision makers. • Frequent changing of medical professionals hindered communication or decision-making. 4/28
Lotz, 2017 – Qualitative study	11 parents of 9 deceased children with following diagnoses: • 3 cancer • 1 spinal muscular atrophy type I • 1 cystic fibrosis • 1 leukodystrophy • 1 hypo plastic left heart syndrome • 1 complex malformation syndrome • 1 unknown syndrome	Qualitative, practice-informing, semi-structured interview study.	*Facilitators perceived by parents* • Parents valued open and honest information, no matter how uncertain or potentially upsetting.
Mitchell, 2019 – Qualitative study	17 parents of 11 deceased children Child's diagnosis/Together for Short Lives category: • Category 1 (n=5) • Category 2 (n=0) • Category 3 (n=2)	In-depth, semi-structured qualitative interview study.	*Facilitators perceived by parents* • Information should be presented in a clear and sometimes brutally honest fashion. It helped if this information was given by a trusted HCP.

	• Category 4 (n=4)		

Cicero-Oneto 2017 – Qualitative study	• 13 parents/primary cares of 13 children with following diagnosis:
	  • 2 haematological neoplasm
	  • 9 extracranial solid tumour
	  • 2 tumour of the CNS
	7 out of 13 children had already died
		Qualitative study with individual, face-to-face, semi-structured, and in-depth interviews.	*Facilitators perceived by parents*
			• Parents wanted the HCPs, particularly the oncologists and the nurses, to display an interest in the patient, to explain the situation clearly, and to speak the truth.

Sisk 2020 – Qualitative study	77 parents and 1 grandparent of 78 children with following diagnoses: • 35 leukaemia or lymphoma • 30 solid tumor • 13 brain tumor	A qualitative study using semistructured telephone interviews using an interview guide.	*Facilitators perceived by parents* • Many parents identified the importance of open and reassuring nonverbal cues, e.g. sitting, making eye contact, smiling, and maintaining an open posture.
GRADE CERQual assessment (for conclusions reported in more than one study)			
Study design:	+4	4 qualitative studies	
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 4/4; Study design and theoretical approach: low in 4/4; Sample selection: unclear in 1/4, high in 3/4; Data collection: low in 2/4, unclear in 1/4, high in 1/4; Data analysis: low in 3/4, unclear in 1/4; Results: low in 4/4	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	
Sufficiency of saturation:	0	No concerns on sufficiency of saturation	
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**	
Conclusion:		• **Parents valued open, honest and clear lay language and information, even if it was uncertain or potentially upsetting (4 studies).** • **Parents found it helpful when information was provided by a trusted HCP, and mentioned frequent changes in HCPs as a barrier for communication (2 studies).**	
GRADE CERQual assessment (for conclusions reported in only one study)			
Study design:	+4	2 qualitative studies	
Methodological limitations:	0	No methodological limitations. Aim and appropriateness of qualitative evidence: low in 2/2; Study design and theoretical approach: low in 2/2; Sample selection: low in 1/2, unclear in 1/2; Data collection: low in 2/2; Data analysis: low in 2/2; Results: low in 2/2	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	
Sufficiency of saturation:	-1	Some concerns on sufficiency of saturation. Only 1 study performed for each conclusion below.	
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**	
Conclusion:		• **Parents considered using interpreters for non-English speakers helpful (1 study).** • **Parents mentioned the importance of open and reassuring nonverbal cues including sitting, making eye contact, smiling, and maintaining an open posture (1 study).**	

4.2.4.2.2 Zorgprofessional perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Staff behaviour and communication style			
Edwards, 2017 - Qualitative study	15 directors/codirectors of paediatric home ventilation programs at children's hospital of following expertise: • 11 paediatric pulmonologists • 2 paediatric intensivists • 2 specialized in both paediatric pulmonology and critical care Children treated in children's hospital: Children with Chronic Respiratory Failure (CRF)	In-depth, semi-structured interviews over the phone, using an open-ended interview guide.	*Facilitators perceived by HCPs* • Directors encourage lay appropriate language without euphemisms. • HCPs should be compassionate and supportive which means being receptive to what families are saying/not saying. • HCPs not engendering a sense of trust in families (1/15)
Orkin, 2020 – Qualitative study	11 Health Care Professionals (8 physicians, 2 nurses, 1 social worker) of following expertise: • 2 complex care • 3 paediatric medicine • 2 respiratory medicine • 1 paediatric haematology and oncology • 1 critical care • 1 neonatal intensive care • 1 palliative care	Qualitative content-analysis study comprising demographic surveys and individual semi-structured interviews.	*Facilitators perceived by HCPs* • Use of constituent and unambiguous language by HCPs can enhance ACP. • HCPs were cognizant of this and advocated for better communication through use of clear, non-medicalized language.
Day 2018 – Qualitative study	58 Health Care Professionals specialised in haematology, haematopoietic stem cell transplantation or palliative care, working principally with patients aged 13-25 years. • 6 consultants • 19 junior doctors (foundation year, registrar/resident and specialty registrar/fellow) • 9 Clinical Nurse Specialists • 10 ward nurses • 14 allied HCP (psychologists, physiotherapists, dieticians and social workers)	In-depth, semi-structured interviews and participant observations (during psycho-social meetings, day-care meetings and pre-ward round meeting, and informal conversations).	*Facilitators perceived by HCPs* • Open communication is paramount for involving teenagers in decision making, but this did not always mean explicit verbalisation of every outcome. • HCPs considered the other family members' communication preferences, and acknowledged the importance of the family's role. • HCP acknowledged the importance of respecting family communication styles and allowing parents and teenagers the space to establish their roles in decision-making.
Henderson 2017 – Qualitative study	36 Health Care Professionals (including medical, nursing, and allied health professionals)	Qualitative design using a group interview.	*Facilitators perceived by HCPs* • Think before you speak. • Knowing what not to say, such as 'things happen for a reason' • Use the right language. • It is important to listen actively with all five senses.

GRADE CERQual assessment (for conclusions reported in more than one study)		
Study design:	+4	3 qualitative studies
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 3/3; Study design and theoretical approach: low in 2/3, unclear in 1/3; Sample selection: unclear in 1/3, high in 2/3; Data collection: low in 1/3, unclear in 2/3; Data analysis: low in 2/3, unclear in 1/3; Results: low in 2/3, high in 1/3
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	0	No concerns on sufficiency of saturation (0)/ Some concerns on sufficiency of saturation (-1) / Important concerns on sufficiency of saturation (-2)/
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**
Conclusion:		• **HCPs mentioned the importance of using clear, lay language that is consistent and unambiguous (3 studies).** • **HCPs mentioned the importance of being compassionate and supportive, listen actively to families, thinking before you speak and knowing what not to say, such as 'things happen for a reason' (2 studies).**
GRADE CERQual assessment (for conclusions reported in only one study)		
Study design:	+4	1 qualitative study
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 1/1; Study design and theoretical approach: low in 1/1; Sample selection: unclear in 1/1; Data collection: low in 1/1; Data analysis: unclear in 1/1; Results: low in 1/1
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	-1	Some concerns on sufficiency of saturation. Only 1 study performed.
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**
Conclusion:		• **HCPs mentioned the importance of respecting the individual family's communication preferences and styles (1 study).** • **HCPs stated that open communication is important for involving children in decision-making, but mentioned that not every outcome has to be explicitly mentioned (1 study).**

4.2.4.3 Interpersoonlijke relaties

4.2.4.3.1 Ouder perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Interpersonal relations			
Edwards, 2020 – Qualitative study	44 parents of 43 children: • 18 contemporaneous invasive long-term ventilation decision-makers • 10 contemporaneous non-invasive long-term ventilation decision-makers • 8 former invasive long-term ventilation decision-makers • 8 former non-invasive long-term ventilation decision-makers 1 young woman using invasive long-term ventilation 1 adolescent girl being initiated on non-invasive long-term ventilation	Semi-structured interviews using an open-ended interview guide. Interviews were conducted in person or over the phone	*Barriers perceived by parents* • Some parents perceived overly negative attitudes or statements about their child, depersonalization of their child and conversations about their child that excluded them.
Fahner, 2020 – Qualitative study	20 parents of 17 seriously ill children with following diagnoses: • 7 chromosomal anomaly • 4 congenital heart disease • 2 CNS tumour • 1 cystic fibrosis • 1 neuromuscular disease • 1 epilepsy syndrome • 1 perinatal asphyxia 6 children are deceased. 10 parents participated in a focus group interview.	Interpretive qualitative study, with individual face-to-face interviews and two focus group interviews.	*Facilitators perceived by parents* • Parents expressed a need for a consistent approach of clinicians regarding future care and treatment over time and among different disciplines. They reported to struggle to get all clinicians on the same page. If parents felt a shared goal within the team and felt part of the team, this positively influenced their openness to share perspectives.
Lord, 2020 – Qualitative study	13 bereaved parents of 12 children with medical complexity: • 11 genetic or congenital • 1 acquired	Qualitative, semi-structured interviews.	*Facilitators perceived by parents* • Many parents mentioned that trusted HCPs who knew their child well were an important prerequisite for ACP. • Parents found the involvement of a subspecialty palliative care team helpful for exploring goals of care.
Mitchell, 2019 – Qualitative study	*4.2.4.4 17 parents of 11 deceased children* Child's diagnosis/Together for Short Lives category: • Category 1 (n=5) • Category 2 (n=0) • Category 3 (n=2)	In-depth, semi-structured qualitative interview study.	*Facilitators perceived by parents* • Trusted relationships with HCPs were highly valued. Continuity of care was a key factor underpinning the development of such relationships. *Barriers perceived by parents* • Relationships with HCPs were fragile and trust was easily compromised. Trust was compromised when: ○ parents discovered that an aspect of their child's medical treatment was not openly discussed

	• Category 4 (n=4)		○ Parents felt that they were not being listened to. ○ Parents described conflicting advice as difficult.
Orkin, 2020 – Qualitative study	14 mothers of 14 children	Qualitative content-analysis study comprising demographic surveys and individual semi-structured interviews.	*Barriers perceived by parents* • Parents mentioned that HCPs often underestimate their child's quality of life, highlighting the importance of asking the parents instead of interfering based on clinical status.

Cicero-Oneto 2017 – Qualitative study	• 13 parents/primary cares of 13 children with following diagnosis:
	  • 2 haematological neoplasm
	  • 9 extracranial solid tumour
	  • 2 tumour of the CNS
	7 out of 13 children had already died
		Qualitative study with individual, face-to-face, semi-structured, and in-depth interviews.	*Facilitators perceived by parents*
			• 6/13 parents indicated that confidence in the hospital in which their children were being treated was a pivotal element in not having doubts about the treatment given to their children.

Murrell 2018 – Qualitative study	19 families, including 29 parents and 22 children with Type 1 SMA: • 11 children living • 11 deceased children	Qualitative descriptive design with individual or small group interviews guided by a semi-structured questionnaire.	*Facilitators perceived by parents* • Some parents described positive experiences with HCPs who were cognizant of the parents' sensitivity to and familiarity with their child. • Families indicated a desire for HCPs who were flexible in their care plan, and would administer treatments based on the family's wishes.
Sisk 2020 – Qualitative study	77 parents and 1 grandparent of 78 children with following diagnoses: • 35 leukaemia or lymphoma • 30 solid tumor • 13 brain tumor	A qualitative study using semistructured telephone interviews using an interview guide.	*Facilitators perceived by parents* • Relationships influenced exchange of information, because parents believed the information if the clinician had credibility.
Zaal-Schuller 2016 – Qualitative study	17 parents of 14 children with following diagnoses: • 3 post-resuscitation • 5 genetic condition • 1 neurologic condition • 2 metabolic condition • 3 unknown 11 Health Care Professionals of following expertise: • 6 paediatricians • 1 rehabilitation specialists • 1 paediatric Intensive Care specialists • 3 paediatric Neurologists	Retrospective, qualitative study, with semi-structured interviews.	*Facilitators perceived by parents* • The majority of children had a long-lasting treatment relationship with a certain physician. Parents mentioned that they would strongly prefer to start the EOL decision-making process with that physician. • 4/17 parents emphasized that the information and advice provided by their child's regular physician was very important to them during the EOL decision-making process. • Not all of the parents believed that disagreements were disturbing. They made them reconsider their opinion about which choice to make. • Parents mentioned that disturbing disagreements arose especially after an acute deterioration of their child's condition, because decisions had to be made under time pressure and often without their regular physician. *Barriers perceived by parents* • Negative healthcare encounters contributed to a critical attitude towards physicians. • 8/17 parents recalled one or more disagreements with a physician during the EOL decision-making process. • In cases of disagreement, some parents felt not heard and felt that physicians regarded their child's life as less valuable than a typically developed child. *Barriers perceived by HCPs and parents* • 2/11 HCPs and 3/17 parents expressed that disturbing disagreements had arisen when parents still wanted 'everything to be done', also treatments physicians considered to be futile at that point.

		• HCPs and 2/17 parents mentioned disagreement when parents wanted a treatment to be forgone, while the physician still anticipated a realistic chance of improvement.
GRADE CERQual assessment (for conclusions reported in more than one study)		
Study design:	+4	7 qualitative studies
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 7/7; Study design and theoretical approach: low in 7/7; Sample selection: low in 1/7, unclear in 2/7, high in 4/7; Data collection: low in 6/7, unclear in 1/7; Data analysis: low in 7/7; Results: low in 7/7
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	0	No concerns on sufficiency of saturation
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**
Conclusion:		• **Parents mentioned the importance of long-lasting, trusted relationships with HCPs (5 studies).** • **Relationships were considered fragile and were easily compromised when parents felt not heard by HCPs. This included situations in which parents felt that their child's quality of life was underestimated or felt that they were excluded from conversations about the child (4 studies).**
GRADE CERQual assessment (for conclusions reported in only one study)		
Study design:	+4	4 qualitative studies
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 4/4; Study design and theoretical approach: low in 4/4; Sample selection: low in 1/4, unclear in 1/4, high in 2/4; Data collection: low in 3/4, unclear in 1/4; Data analysis: low in 2/4, unclear in 2/4; Results: low in 4/4
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	-1	Some concerns on sufficiency of saturation. Only 1 study performed for each conclusion below.
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**
Conclusion:		• **Parents sometimes experienced disagreements with HCPs. Not all disagreements were considered disturbing, it could also make parents reconsider options. Disturbing disagreements arose when: parents still wanted 'everything to be done' but HCPs thought it was futile; when decisions had to be made under time pressure because of acute deterioration of the child's condition and when parents wanted a treatment to be forgone when there was still a realistic chance of improvement (1 study).** • **When parents felt part of the multidisciplinary team when discussing care goals, this positively influenced their openness to share perspectives (1 study). Involvement of a subspecialty palliative care team was considered helpful (1 study).** • **Parents preferred HCPs who are conscious of the family's sensitivity and familiarity with the child, and desired HCPs who are flexible in their care plans based on the family's wishes (1 study).**

4.2.4.4.1 Zorgprofessional perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Interpersonal relations			
Edwards, 2017 – Qualitative study	15 directors/codirectors of paediatric home ventilation programs at children's hospital of following expertise: • 11 paediatric pulmonologists • 2 paediatric intensivists • 2 specialized in both paediatric pulmonology and critical care Children treated in children's hospital: Children with Chronic Respiratory Failure (CRF)	In-depth, semi-structured interviews over the phone, using an open-ended interview guide.	*Barriers perceived by HCPs* • Changing inpatient HCPs (2/15) • Disagreement/discord between family and HCPs (1/15)
Odeniyi, 2017 – Qualitative study	10 Health Care Professionals of following expertise: • 2 intensivist attendings • 1 intensive care fellow • 4 oncologist attendings • 3 oncologist fellows	Qualitative study using semi-structured interviews.	*Barriers perceived by HCPs* • Intensivist and oncologists were unsure whether increased intimacy with patients made them more or less successful at engaging in challenging conversations. • Intensivist and oncologists agreed that oncologist had longer relations and stronger ties with the patients; however, they were concerned that the parents would feel that they were 'giving up' if they initiated goals of care discussions. • Intensivist felt at times uncomfortable broaching sensitive discussions when they had a less intimate relationship with the family.
Hein, 2020 – Qualitative study	14 Health Care Professionals of following expertise: • 4 paediatricians • 1 emergency physician • 1 psychologist • 1 chaplain • 3 nurses (intensive care, out-patient) • 2 social workers • 2 special education teachers 9 bereaved parents of children aged 2 to 16 years with following type of conditions: • 3 metabolic • 2 oncological • 2 perinatal • 1 cardiological • 2 neuromuscular	2 transdisciplinary workshops: • First workshop – discussion groups to explore experiences with paediatric advance care planning (6 parents, 14 HCPs). • Second workshop – dialogue groups to discuss topics such as, participation of children and adolescents; paediatric advance care planning documentation; supplementary written materials (5 parents, 14 HCPs).	*Barriers perceived by HCPs and parents* • A latent conflict was identified between parents and institutional care workers, both claiming to be experts and advocates for the child.
Day 2018 – Qualitative study	58 Health Care Professionals specialised in haematology, haematopoietic stem cell transplantation or palliative care, working principally with patients aged 13-25 years.	In-depth, semi-structured interviews and participant observations (during psycho-social meetings, day-care meetings and pre-ward round meeting, and informal conversations).	*Barriers perceived by HCPs* • The 'right thing' determined by clinical assessment did not always align with what teenagers or parents wanted or deemed 'right'.

	• 6 consultants • 19 junior doctors (foundation year, registrar/resident and specialty registrar/fellow) • 9 Clinical Nurse Specialists • 10 ward nurses • 14 allied HCP (psychologists, physiotherapists, dieticians and social workers)		
Henderson 2017 – Qualitative study	36 Health Care Professionals (including medical, nursing, and allied health professionals)	Qualitative design using a group interview.	*Facilitators perceived by HCPs* • Acknowledge your mistakes to family and also learn from them. • It can be helpful to acknowledge if you have said something wrong—even if not immediate. • Appreciate pre-existing relationship(s) with families. • When HCPs know the family from the start, it is easier to prepare and journey with the family.
Sasazuki 2019 – Qualitative study	15 Health Care Professionals of following specialties: • 3 paediatric intensive care • 2 paediatric cardiology • 3 neonatology • 4 paediatric neurology • 3 paediatric oncology	Semi-structured, individual face-to-face interviews.	*Barriers perceived by HCPs* • Physicians experienced dilemmas when parents seemed unrealistic or overly optimistic about their child's condition. • Physicians experienced difficulty that was caused by lack of social consensus. They craved the availability of consensus justifying their decision-making process. Their dilemmas appeared when they struggled to reach agreement with the family, medical staff or society. • Physicians indicated that their dilemma emerged when they tried to bear the parents' pain and burden in combination with the maximal efforts exerted for the child as a professional paediatrician. *Facilitators perceived by HCPs* • Physicians referred to internal standards of virtue for what they considered to be right, but not to external norms. They wished to do the right things as physicians.
Zaal-Schuller 2016 – Qualitative study	17 parents of 14 children with following diagnoses: • 3 post-resuscitation • 5 genetic condition • 1 neurologic condition • 2 metabolic condition • 3 unknown 11 Health Care Professionals of following expertise: • 6 paediatricians • 1 rehabilitation specialists • 1 paediatric Intensive Care specialists • 3 paediatric Neurologists	Retrospective, qualitative study, with semi-structured interviews.	*Facilitators perceived by HCPs* • Many physicians mentioned the importance of a long-lasting treatment relationship with the parents. *Facilitators perceived by HCPs* • Physicians emphasized that not all disagreements were disturbing. Disagreements could also challenge them to think about alternatives that would be more suitable for the specific situation of the child. *Barriers perceived by HCPs and parents* • 2/11 HCPs and 3/17 parents expressed that disturbing disagreements had arisen when parents still wanted 'everything to be done', also treatments physicians considered to be futile at that point. • HCPs and 2/17 parents mentioned disagreement when parents wanted a treatment to be forgone, while the physician still anticipated a realistic chance of improvement.
GRADE CERQual assessment (for conclusions reported in more than one study)			

Study design:	+4	7 qualitative studies
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 7/7; Study design and theoretical approach: low in 6/7, unclear in 1/7; Sample selection: unclear in 5/7, high in 2/7; Data collection: low in 2/7, unclear in 5/7; Data analysis: low in 4/7, unclear in 3/7; Results: low in 6/7, high in 1/7
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	0	No concerns on sufficiency of saturation
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**
Conclusion:		• **HCPs mentioned a long-lasting treatment relationship with parents as a facilitator for decision-making (4 studies).** • **HCPs mentioned that it can be difficult to reach agreement with parents and/or children when opinions about ACP or EOL decisions differed (3 studies).** • **HCPs experienced disagreements with families (3 studies). Not all disagreements were considered disturbing, it could also challenge HCPs to think of more suitable alternatives. Disturbing disagreements arose when: parents were unrealistic or overly optimistic and when parents wanted a treatment to be forgone when there was still a realistic chance of improvement (1 study).**
GRADE CERQual assessment (for conclusions reported in only one study)		
Study design:	+4	1 qualitative study
Methodological limitations:	-1	Serious methodological limitations. Aim and appropriateness of qualitative evidence: low in 1/1; Study design and theoretical approach: unclear in 1/1; Sample selection: unclear in 1/1; Data collection: unclear in 1/1; Data analysis: unclear in 1/1; Results: high in 1/1
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	-1	Some concerns on sufficiency of saturation. Only 1 study performed.
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**
Conclusion:		**Acknowledging mistakes and learning from it is considered helpful by HCPs (1 study).**

4.2.5 Holistische benadering van zorg

4.2.5.1 Geincludeerde subthema's

Included subthemes
Attention for the families' situation
Provision of hope
Attention for differentcultures
Attention for faith and religion

4.2.5.2 Aandacht voor de situatievan de familie

4.2.5.2.1 Ouderperspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Attention for the families' situation			
Beecham, 2017 – Qualitative study	18 parents • 9 parents whose child was currently receiving palliative care • 9 bereaved parents whose child had received palliative care Children had following type of conditions: ○ 10 neurologic ○ 2 metabolic ○ 2 oncologic ○ 1 gastroenterological ○ 1 immunologic ○ 1 respiratory ○ 1 chromosomal abnormality	Open-ended, semi-structured interviews.	*Facilitators perceived by parents* • All parents prominently mentioned the interaction between clinicians and parents, including the need for clinicians to understand the bigger picture of the life of the child and the wider family, rather than simply focusing on treating a particular symptom.
Fahner, 2021 – Qualitative study	20 parents of 17 children with life-limiting conditions (10 bereaved parents of 6 children who died) with following diagnoses: • 7 chromosomal anomaly • 4 congenital heart disease • 2 CNS tumour • 1 cystic Fibrosis • 1 neuromuscular disease • 1 epilepsy syndrome • 1 perinatal asphyxia	Qualitative interviews; focus group interviews and individual interviews.	*Facilitators perceived by parents* • Patients wanted paediatricians to explore what their lives were like from a psychological, social and spiritual point of view.
Fahner, 2020 – Qualitative study	20 parents of 17 seriously ill children with following diagnoses: • 7 chromosomal anomaly • 4 congenital heart disease • 2 CNS tumour • 1 cystic fibrosis • 1 neuromuscular disease • 1 epilepsy syndrome • 1 perinatal asphyxia 6 children are deceased. 10 parents participated in a focus group interview.	Interpretive qualitative study, with individual face-to-face interviews and two focus group interviews.	*Barriers perceived by parents* • Parents mentioned the need for acknowledgment for their challenging context, and expressed they felt that clinicians have no idea how caring for a seriously ill child impacts their daily life. • Parents reported little room to share perspectives outside the medical domain, but would appreciate it. And expressed to value clinician's awareness of the child's identity apart from their disease. • Paediatricians rather talk about medical themes relating to ACP than exploring individual family values. *Facilitators perceived by parents* • Most parents did not spontaneously talk about underlying views, values, hopes, fears, and worries. Recognizing or discussing parent's fears confronted them with worst-case scenarios as a reality. It enabled them to prevent or prepare themselves for a feared situation and left them with greater peace of mind in the present.

			• Some parents mentioned that they would have valued more attention to their fears, because it made them feel overwhelmed and unprepared when a worst-case scenario occurred
Hein, 2020 – Qualitative study	9 bereaved parents of children aged 2 to 16 years with following type of conditions: • 3 metabolic • 2 oncological • 2 perinatal • 1 cardiological • 2 neuromuscular	2 transdisciplinary workshops: • First workshop – discussion groups to explore experiences with paediatric advance care planning (6 parents, 14 HCPs). • Second workshop – dialogue groups to discuss topics such as, participation of children and adolescents; paediatric advance care planning documentation; supplementary written materials (5 parents, 14 HCPs).	*Facilitators perceived by parents* • Parents asked that professionals place the focus on the child.
Lord, 2020 – Qualitative study	13 bereaved parents of 12 children with medical complexity: • 11 genetic or congenital • 1 acquired	Qualitative, semi-structured interviews.	*Facilitators perceived by parents* • Perceptions of their child's quality of life and specific goals for their children (both short- and long-term) were key contributors to ACP (e.g. goals for being at home together as a family as much as possible or having typical family outings).
Lotz, 2017 – Qualitative study	11 parents of 9 deceased children with following diagnoses: • 3 cancer • 1 spinal muscular atrophy type I • 1 cystic fibrosis • 1 leukodystrophy • 1 hypo plastic left heart syndrome • 1 complex malformation syndrome • 1 unknown syndrome	Qualitative, practice-informing, semi-structured interview study.	*Facilitators perceived by parents* • All parents mentioned that discussing psychosocial and daily life issues was particularly important to them. • Parents advocated for an individually adapted approach that takes into account the respective situation, needs, and concerns of the whole family.
Orkin, 2020 – Qualitative study	14 mothers of 14 children	Qualitative content-analysis study comprising demographic surveys and individual semi-structured interviews.	*Facilitators perceived by parents* • Several parents reinforced that understanding family's values and believes is a foundational aspect of ACP, and mentioned how their belief system and values guided their decision-making. • Parents indicated that ACP discussions including conversations surrounding hopes and goals for their child were beneficial for their child's life, because they provided opportunities to collaboratively work toward and/or reframe hopes and goals.
Murrell 2018 – Qualitative study	19 families, including 29 parents and 22 children with Type 1 SMA: • 11 children living • 11 deceased children	Qualitative descriptive design with individual or small group interviews guided by a semi-structured questionnaire.	*Facilitators perceived by parents* • Parents appreciated the presence of a HCP who understood the importance of factors influencing the family's decision-making, incl. work, school and other children.
GRADE CERQual assessment			
Study design:	+4	8 qualitative studies	
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 8/8; Study design and theoretical approach: low in 8/8; Sample selection: low in 1/8, unclear in 1/8, high in 6/8; Data collection: low in 4/8, unclear in 4/8; Data analysis: low in 3/8, unclear in 5/8; Results: low in 8/8	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	

Sufficiency of saturation:	0	No concerns on sufficiency of saturation
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**
Conclusion:		• **Parents mentioned the need for HCPs to understand and acknowledge the impact on daily life of the child and family including psychological and social issues, such as work, school and other children, rather than simply focusing on medical problems only (7 studies).** • **Parents mentioned the importance of HCPs understanding family's individual values, believes, hopes, goals and fears for making ACP and EOL decisions and preparing parents for worst-case scenarios (2 studies).**

4.2.5.2.2 Zorgprofessional perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Attention for the families' situation			
Orkin, 2020 – Qualitative study	11 Health Care Professionals (8 physicians, 2 nurses, 1 social worker) of following expertise: • 2 complex care • 3 paediatric medicine • 2 respiratory medicine • 1 paediatric haematology and oncology • 1 critical care • 1 neonatal intensive care • 1 palliative care	Qualitative content-analysis study comprising demographic surveys and individual semi-structured interviews.	*Facilitators perceived by HCPs* • HCPs noted the importance of taking time to recognize, understand, and support diversity and individuality between families. • HCPs noted that understanding family's values and believes is a foundational aspect of ACP, allowing them to tailor care individually.' • HCPs expressed that understanding family's hopes and goals in the context of their child's illness is an essential aspect of ACP.
Henderson 2017 - Qualitative study	36 Health Care Professionals (including medical, nursing, and allied health professionals)	Qualitative design using a group interview.	*Facilitators perceived by HCPs* • Be aware of the importance of needs of the child and their family, including significant others. • Clinical history — HCPs should be aware of expectations of family. • HCPs know what key supports for families are in place, e.g., grandparents, close friend, elder from community, spiritual adviser? • HCPs should have facts about families correct.
GRADE CERQual assessment			
Study design:	+4	2 qualitative studies	
Methodological limitations:	-2	Serious methodological limitations. Aim and appropriateness of qualitative evidence: low in 2/2; Study design and theoretical approach: low in 1/2, unclear in 1/2; Sample selection: unclear in 1/2, high in 1/2; Data collection: low in 1/2, unclear in 1/2; Data analysis: low in 1/2, unclear in 1/2; Results: low in 1/2, high in 1/2	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	
Sufficiency of saturation:	0	No concerns on sufficiency of saturation	
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**	
Conclusion:		**HCPs mentioned the importance of acknowledging the values, beliefs, needs and expectations of the child and their family in the context of the child's illness for making ACP and EOL decisions (2 studies).**	

4.2.5.3 Het geven van hoop

4.2.5.3.1 Ouderperspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Provision of hope			
Lotz, 2017 – Qualitative study	11 parents of 9 deceased children with following diagnoses: • 3 cancer • 1 spinal muscular atrophy type I • 1 cystic fibrosis • 1 leukodystrophy • 1 hypo plastic left heart syndrome • 1 complex malformation syndrome • 1 unknown syndrome	Qualitative, practice-informing, semi-structured interview study.	*Facilitators perceived by parents* • Several parents highlighted the importance of strengthening parents by maintaining hope, e.g. that the child lives "longer than expected," that "the days together are good," and that they "can still do a lot for their children" and be good parents.

Cicero-Oneto 2017 – Qualitative study	• 13 parents/primary cares of 13 children with following diagnosis:
	  • 2 haematological neoplasm
	  • 9 extracranial solid tumour
	  • 2 tumour of the CNS
	7 out of 13 children had already died
		Qualitative study with individual, face-to-face, semi-structured, and in-depth interviews.	*Facilitators perceived by parents*
			• Parents expressed the need for messages of hope, messages that "lift the spirits".

Mekelenkamp 2020 – Qualitative study	14 parents of 8 children that died within a year after allogeneic HSCT, with following diagnoses: • 2 bone marrow failure • 4 malignancy • 1 hemoglobinopathy • 1 primary immune deficiency	Qualitative descriptive study with in-depth face-to-face individual interviews and a background questionnaire.	*Facilitators perceived by parents* • Guidance from HCPs in making treatment trajectory as bearable as possible and keep the hope alive, supported parents to keep going and focus on decision-making aiming for cure.
Sisk 2020 – Qualitative study	77 parents and 1 grandparent of 78 children with following diagnoses: • 35 leukaemia or lymphoma • 30 solid tumor • 13 brain tumor	A qualitative study using semistructured telephone interviews using an interview guide.	*Barriers perceived by parents* • Many parents varied in their preferences for how clinicians should support hope. Some parents preferred clinicians to emphasize positives. For some parents, clinicians supported hope by expressing an intention to cure the child, even if cure was unlikely. Other parents expressed the importance of avoiding false hopes. *Facilitators perceived by parents* • Many parents expressed that hope was essential for their coping and wellbeing.
GRADE CERQual assessment (for conclusions reported in more than one study)			
Study design:	+4	4 qualitative studies	
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 4/4; Study design and theoretical approach: low in 4/4; Sample selection: low in 1/4, high in 3/4; Data collection: low in 3/4, unclear in 1/4; Data analysis: low in 3/4, unclear in 1/3; Results: low in 4/4	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	
Sufficiency of saturation:	0	No concerns on sufficiency of saturation	
Overall assessment of		⊕⊕⊕⊖ **MODERATE confidence in the evidence**	

confidence in findings		
Conclusion:		**Parents mentioned the importance of maintaining hope by HCPs (4 studies).**
GRADE CERQual assessment (for conclusions reported in only one study)		
Study design:	+4	1 qualitative study
Methodological limitations:	0	No methodological limitations. Aim and appropriateness of qualitative evidence: low in 1/1; Study design and theoretical approach: low in 1/1; Sample selection: low in 1/1; Data collection: low in 1/1; Data analysis: low in 1/1; Results: low in 1/1
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	-1	Some concerns on sufficiency of saturation. Only 1 study performed.
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**
Conclusion:		**Parents varied in their preferences of how HCPs should support hope: although some wanted them to emphasize positives or wanted them to express an intention to cure the child, others mentioned the importance of avoiding false hopes (1 study).**

4.2.5.4 Aandacht voor verschillende culturen

4.2.5.4.1 Ouderperspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Attention for different cultures			
Murrell 2018 – Qualitative study	19 families, including 29 parents and 22 children with Type 1 SMA: • 11 children living • 11 deceased children	Qualitative descriptive design with individual or small group interviews guided by a semi-structured questionnaire.	*Facilitators perceived by parents* • Families expressed a desire for a medical team that is culturally sensitive and anticipates how families may interpret information given their culture. *Barriers perceived by parents* • Culture was a significant indicator of how parents preferred the diagnosis to be delivered. It also differs between families and education levels. Some families preferred straightforward diagnosis delivery, while others resented receiving the news in a direct manner. • Families had a varied preference for cultural sensitivity at time of diagnosis and treatment.
Zaal-Schuller 2016 – Qualitative study	17 parents of 14 children with following diagnoses: • 3 post-resuscitation • 5 genetic condition • 1 neurologic condition • 2 metabolic condition • 3 unknown	Retrospective, qualitative study, with semi-structured interviews.	*Barriers perceived by parents* • One couple of parents with a Moroccan background reported that the cultural and legislative differences between The Netherlands and Morocco were a complicating factor, which caused disagreement with physicians.
GRADE CERQual assessment			
Study design:	+4	2 qualitative studies	
Methodological limitations:	0	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 2/2; Study design and theoretical approach: low in 2/2; Sample selection: low in 1/2, unclear in 1/2; Data collection: low in 2/2; Data analysis: low in 1/2, unclear in 1/2; Results: low in 2/2	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	
Sufficiency of saturation:	-1	Some concerns on sufficiency of saturation due to small sample size (N=19/N=17). Only 1 study performed.	
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**	
Conclusion:		• **Parents desired HCPs to be culturally sensitive in delivering information (1 study).** • **Differences in cultural background, causing disagreement with HCPs, was perceived as a barrier by parents (1 study).**	

4.2.5.4.2 Zorgprofessional perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Attention for different cultures			
Edwards, 2017 – Qualitative study	15 directors/codirectors of paediatric home ventilation programs at children's hospital of following expertise: • 11 paediatric pulmonologists • 2 paediatric intensivists • 2 specialized in both paediatric pulmonology and critical care Children treated in children's hospital: Children with Chronic Respiratory Failure (CRF)	In-depth, semi-structured interviews over the phone, using an open-ended interview guide.	*Barriers perceived by HCPs* • Fear that parents think that they are being discriminated because of their socioeconomic status (1/15)
Henderson 2017 – Qualitative study	36 Health Care Professionals (including medical, nursing, and allied health professionals)	Qualitative design using a group interview.	*Facilitators perceived by HCPs* • Have cultural humility and curiosity. • Knowing the culture; be aware of cultural awareness and language, how they are used, and what is said.
Zaal-Schuller 2016 – Qualitative study	11 Health Care Professionals of following expertise: • 6 paediatricians • 1 rehabilitation specialists • 1 paediatric Intensive Care specialists • 3 paediatric Neurologists	Retrospective, qualitative study, with semi-structured interviews.	*Barriers perceived by HCPs* • EOL decision-making could be complicated by differences in ethnic, religious and/or linguistic backgrounds.
GRADE CERQual assessment (for conclusions reported in more than one study)			
Study design:	+4	2 qualitative studies	
Methodological limitations:	-2	Serious methodological limitations. Aim and appropriateness of qualitative evidence: low in 2/2; Study design and theoretical approach: low in 1/2, unclear in 1/2; Sample selection: unclear in 2/2; Data collection: low in 1/2, unclear in 1/2; Data analysis: low in 1/2, unclear in 1/2; Results: low in 1/2, high in 1/2	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	
Sufficiency of saturation:	0	No concerns on sufficiency of saturation	
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**	
Conclusion:		**HCPs mentioned that EOL discussions can be complicated by differences in ethnic, religious and/or linguistic backgrounds, and stated the importance of having cultural humility and curiosity, and being aware of cultural awareness and language (2 studies).**	
GRADE CERQual assessment (for conclusions reported in only one study)			
Study design:	+4	1 qualitative study	
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 1/1; Study design and theoretical approach: low in 1/1; Sample selection: high in 1/1; Data collection: unclear in 1/1; Data analysis: low in 1/1; Results: low in 1/1	
Coherence:	0	No concerns on coherence	

Relevance:	0	No concerns on relevance
Sufficiency of saturation:	-1	Some concerns on sufficiency of saturation due to small sample size (N=15). Only 1 study performed.
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**
Conclusion:		**One HCP mentioned parents' fear of being discriminated because of socioeconomic status as a barrier for decision-making (1 study).**

4.2.5.5 Aandacht voor geloof en religie

4.2.5.5.1 Ouderperspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Attention for faith and religion			
Edwards, 2020 – Qualitative study	44 parents of 43 children: • 18 contemporaneous invasive long-term ventilation decision-makers • 10 contemporaneous non-invasive long-term ventilation decision-makers • 8 former invasive long-term ventilation decision-makers • 8 former non-invasive long-term ventilation decision-makers 1 young woman using invasive long-term ventilation 1 adolescent girl being initiated on non-invasive long-term ventilation	Semi-structured interviews using an open-ended interview guide. Interviews were conducted in person or over the phone	*Facilitators perceived by parents* Parents had various approaches to manage stress in decision-making • 5/44 parents put their faith in a higher power. This higher power would guide their decision-making or dictate how things should be.
Superdock 2018 – Qualitative study	28 parents of 17 children with following diagnoses: • 5 complex congenital heart disease • 7 genetic/metabolic disease/HSCT • 5 extreme prematurity	Longitudinal, qualitative, descriptive design, with longitudinal series of one-on-one interviews, field notes, questionnaires, and medical chart data.	*Faith & hope – Facilitators perceived by parents* • Parents believed faith was integral to decision-making, because it gave them confidence in decisions, guarded against regret, and aided joint decision-making with their spouse. • If decisions became more complicated or consequential (e.g. new devices, goals-of-care, end-of-life), parents spoke more emphatically about the importance of maintaining hope and faith. *God is in control – Facilitators perceived by parents* • All mothers and most fathers emphasize the belief that god is in control. This belief empowered parents to make decisions, or at times it motivated parents to abstain from making decisions. • Surrendering control to god freed parents from the burden to control chaotic situations themselves, but parents admitted that it was not easy or straight forward and wanted to remain engaged in their child's care. • Parents did not expect HCPs to surrender control to god, but seemed pleased when physicians acknowledged a higher authority. *Presence or voice of god – Facilitators perceived by parents* • Many parents said they could not have endured their circumstances or made decisions without god's presence. *Belief in miracles/divine intervention* *Facilitators perceived by parents*

		• Belief in miracles was related to beliefs about god and influenced decisions in similar ways. If god is in control, then god can intervene in the world and bring about events that defy medical explanation. • Belief in miracles sometimes pushed parents to pursue aggressive treatment, and other times allowed parents to de-escalate aggressive care. • To parents, if god miraculously brought their child into the world, he would miraculously keep them alive, and were therefore less likely to accept poor prognoses or "give up" hope. *Barriers perceived by parents* • Some parents expressed that they did not feel physicians understood their believes. *Meaning of suffering – Facilitators perceived by parents* • The belief that god is perfectly good affected how parents interpreted suffering. Either god predetermined a purpose for suffering, or he could bring good things from suffering *Life & death – Facilitators perceived by parents* • When parents believed they were "meant to be" their child's parents, they were empowered to trust their instincts about what was best for the child. *Praying – Facilitators perceived by parents* • In four cases, praying played a large role in parents' decisions, incl. treatment initiation decisions, choice of hospital, medical procedures, relocation, resuscitation orders, withdrawal of life-sustaining therapy. • Parents did not always state the way the prayers guided the decisions, but were clear they engendered peace and confidence in their choices. • Faith communities did not directly impact decision-making, but one family suggested that the support of the church community reinforced their decision to leave the hospital and care for their child at home.
GRADE CERQual assessment (for conclusions reported in more than one study)		
Study design:	+4	2 qualitative studies
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 2/2; Study design and theoretical approach: low in 2/2; Sample selection: unclear in 1/2, high in 1/2; Data collection: low in 2/2; Data analysis: low in 2/2; Results: low in 2/2
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	0	No concerns on sufficiency of saturation
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**
Conclusion:		**Parents expressed that hope, faith, religion and praying influenced decision-making (2 studies):** ○ **Faith and belief in god empowered parents to make or abstain from decisions, guarded against regret and aided joint decision-making with their spouse, especially when decisions became more complicated or consequential (2 study).**

		○ **Belief in miracles sometimes pushed parents to pursue or de-escalate aggressive treatment. It could make parents not accept poor prognosis, because they believed god would keep their child miraculously alive (1 study).**
GRADE CERQual assessment (for conclusions reported in only one study)		
Study design:	+4	1 qualitative study
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 1/1; Study design and theoretical approach: low in 1/1; Sample selection: high in 1/1; Data collection: low in 1/1; Data analysis: low in 1/1; Results: low in 1/1
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	-1	Some concerns on sufficiency of saturation. Only 1 study performed.
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**
Conclusion:		**Parents sometimes felt HCPs did not understand their believes. They did not expect HCPs to surrender control to god, but were pleased when HCPs acknowledged their believes (1 study).**

4.2.5.5.2 Zorgprofessional perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Attention for faith and religion			
Edwards, 2017 – Qualitative study	15 directors/codirectors of paediatric home ventilation programs at children's hospital of following expertise: • 11 paediatric pulmonologists • 2 paediatric intensivists • 2 specialized in both paediatric pulmonology and critical care Children treated in children's hospital: Children with Chronic Respiratory Failure (CRF)	In-depth, semi-structured interviews over the phone, using an open-ended interview guide.	*Barriers perceived by HCPs* • Theological fatalism (1/15)
Superdock 2018 – Qualitative study	108 Health Care Professionals of following specialties: • 30 attending physicians • 5 fellow physicians • 25 nurse practitioners • 27 nurses • 22 social workers	Longitudinal, qualitative, descriptive design, with longitudinal series of one-on-one interviews, field notes, questionnaires, and medical chart data.	*1. Faith & hope* *Barriers perceived by HCPs* • HCPs had mixed feelings about parental hope and faith. Faith kept parents hopeful enough to be involved and endure stress, but became problematic when cure was no longer possible from a medical standpoint. Many HCPs began to worry that faith-based hope was allowing parents to disregard medical evidence when making decisions. *2. God is in control* *Barriers perceived by HCPs* • Many HCPs believed sacrificing control should mean letting "nature take its course". *3. Belief in miracles/divine intervention* Belief in miracles was related to beliefs about god and influenced decisions in similar ways. If god is in control, then god can intervene in the world and bring about events that defy medical explanation. *Barriers perceived by HCPs* • HCPs used the term "miracle" reluctantly. Some HCPs said their experience with medical miracles made them less confident in their ability to "predict the future", and more cautious when communicating poor prognosis. *4. Meaning of suffering* *Barriers perceived by HCPs* • The issue of suffering seemed to be the greatest point of contention between HCPs and parents. HCPs believed suffering was only allowed when necessary to prolong a life of good quality. • Physicians felt that parents used religion and spirituality beliefs to "rationalize" the infant's short-term suffering.

		• In one case, a physician stated that the parents “just didn’t care” that the infant was suffering. 5. *Praying* *Barriers perceived by HCPs* • In one case, a HCP reported that a family’s pastor prohibited endotracheal tube removal, and they abided by that condition while de-escalating care in other ways.
GRADE CERQual assessment		
Study design:	+4	2 qualitative studies
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 2/2; Study design and theoretical approach: low in 2/2; Sample selection: high in 2/2; Data collection: low in 1/2, unclear in 1/2; Data analysis: low in 2/2; Results: low in 2/2
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	0	No concerns on sufficiency of saturation
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**
Conclusion:		**HCPs worried that hope, faith, religion and theological fatalism allowed parents to disregard medical evidence in decision-making (2 study).**

4.2.6 Timing

4.2.6.1 Gëincludeerde subthema's

Included subthemes
Timing and initiation
Ongoing process
Sufficient time for decision-making

4.2.6.2 Timing en initiatie

4.2.6.2.1 Ouderperspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Timing and initiation			
Edwards, 2020 – Qualitative study	44 parents of 43 children: • 18 contemporaneous invasive long-term ventilation decision-makers • 10 contemporaneous non-invasive long-term ventilation decision-makers • 8 former invasive long-term ventilation decision-makers • 8 former non-invasive long-term ventilation decision-makers 1 young woman using invasive long-term ventilation 1 adolescent girl being initiated on non-invasive long-term ventilation	Semi-structured interviews using an open-ended interview guide. Interviews were conducted in person or over the phone	*Barriers perceived by parents* • Pressure to make a decision was considered an unhelpful communication practice by contemporaneous decision makers (9/28).
Fahner, 2020 – Qualitative study	20 parents of 17 seriously ill children with following diagnoses: • 7 chromosomal anomaly • 4 congenital heart disease • 2 CNS tumour • 1 cystic fibrosis • 1 neuromuscular disease • 1 epilepsy syndrome • 1 perinatal asphyxia 6 children are deceased. 10 parents participated in a focus group interview.	Interpretive qualitative study, with individual face-to-face interviews and two focus group interviews.	*Barriers perceived by parents* • Some parents addressed treatment limitations themselves because they considered this as an essential part of what they valued as good care. They emphasized they would prefer clinicians to initiate these discussions, because the accompanying emotional distress could be a parental barrier to initiate these conversations.

Hein, 2020 – Qualitative study	9 bereaved parents of children aged 2 to 16 years with following type of conditions: • 3 metabolic • 2 oncological • 2 perinatal • 1 cardiological • 2 neuromuscular	2 transdisciplinary workshops: • First workshop - discussion groups to explore experiences with paediatric advance care planning (6 parents, 14 HCPs). • Second workshop - dialogue groups to discuss topics such as, participation of children and adolescents; paediatric advance care planning documentation; supplementary written materials (5 parents, 14 HCPs).	*Barriers perceived by parents* • 'Timing might never be right'. However, missed opportunities to engage in paediatric advance care planning may lead to regrets. • Even bereaved parents were not able to give a clear definition of a 'right time' to initiate advance care planning. • Parents described in detail what they considered as wrong times: shortly after breaking bad news, shortly after overcoming a crisis or under time pressure. • Most participants favoured an early start of paediatric advance care planning. Some parents questioned this approach and demanded a previous assessment of parental readiness. *Facilitators perceived by parents* • Timing might never be right. One solution might be to offer families timely to participate in paediatric advance care planning and to repeat this offer regularly in case parents do not feel ready. • Parents confirmed that there was a time during which they preferred to avoid thinking about end-of-life issues. However, at some point, they realised that their child was not going to get better. Parents described this moment as a turning point, after which they felt ready to engage in advance care planning. • Parents asked that professionals allow decision-making without pressure.
Lord, 2020 – Qualitative study	13 bereaved parents of 12 children with medical complexity: • 11 genetic or congenital • 1 acquired	Qualitative, semi-structured interviews.	*Facilitators perceived by parents* • Many parents felt discussions should occur early. *Barriers perceived by parents* • Some parents expressed that they felt that they should be the ones indicating when they are ready to engage in such conversations or they felt the conversations were to frequent.
Lotz, 2017 – Qualitative study	11 parents of 9 deceased children with following diagnoses: • 3 cancer • 1 spinal muscular atrophy type I • 1 cystic fibrosis • 1 leukodystrophy • 1 hypo plastic left heart syndrome • 1 complex malformation syndrome • 1 unknown syndrome	Qualitative, practice-informing, semi-structured interview study.	*Facilitators perceived by parents* • Parents indicated that early conversations and planning ahead were helpful through empowering them to make good decisions for their child and be a good parent, facilitating coping, and giving a sense of control and security by preparing for what may come. *Barriers perceived by parents* • Parents mentioned that HCPs should gently introduce and repeatedly offer ACP conversations but should not put pressure on parents.
Mitchell, 2019 – Qualitative study	17 parents of 11 deceased children Child's diagnosis/Together for Short Lives category: • Category 1 (n=5) • Category 2 (n=0) • Category 3 (n=2) • Category 4 (n=4)	In-depth, semi-structured qualitative interview study.	*Barriers perceived by parents* • Parents reported that the timing of conversations with respect to ACP was important, but could be particularly difficult where there was uncertainty about the likely outcome of a treatment or procedure, such as surgery or a new medical intervention. • Parents described the need to be in a 'place of acceptance' in order for ACP conversations to take place.
Orkin, 2020 – Qualitative study	14 mothers of 14 children	Qualitative content-analysis study comprising demographic surveys and individual semi-structured interviews.	*Facilitators perceived by parents and HCPs* • Participants emphasized that ACP should start at time of diagnosis and should occur before a medical crisis.

	11 Health Care Professionals (8 physicians, 2 nurses, 1 social worker) of following expertise: • 2 complex care • 3 paediatric medicine • 2 respiratory medicine • 1 paediatric haematology and oncology • 1 critical care • 1 neonatal intensive care • 1 palliative care		*Barriers perceived by parents* • Parents stated that HCPs should respect their feelings and not push for conversations when they make it clear that they are not ready to engage.
Sisk 2020 – Qualitative study	77 parents and 1 grandparent of 78 children with following diagnoses: • 35 leukaemia or lymphoma • 30 solid tumor • 13 brain tumor	A qualitative study using semistructured telephone interviews using an interview guide.	*Barriers perceived by parents* • Some parents preferred conversations to be tempered or delayed.
Zaal-Schuller 2016 – Qualitative study	17 parents of 14 children with following diagnoses: • 3 post-resuscitation • 5 genetic condition • 1 neurologic condition • 2 metabolic condition • 3 unknown	Retrospective, qualitative study, with semi-structured interviews.	*Barriers perceived by parents* • Half of the 17 parents mentioned that they felt it was a missed opportunity that physicians did not take the initiative to talk about EOL discussions when the child was still in a stable condition.

GRADE CERQual assessment (for conclusions reported in more than one study)		
Study design:	+4	9 qualitative studies
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 9/9; Study design and theoretical approach: low in 9/9; Sample selection: low in 1/9, unclear in 3/9, high in 5/9; Data collection: low in 6/9, unclear in 2/9, high in 1/9; Data analysis: low in 7/9, unclear in 2/9; Results: low in 9/9
Coherence:	-1	Some concerns on coherence, some supported starting ACP and EOL discussions as early as possible, others mentioned they wanted to wait until they felt ready.
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	0	No concerns on sufficiency of saturation
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**
Conclusion:		• **Although some parents find it difficult to define the right timing of initiating ACP and EOL discussions and felt timing might never be right (3 studies), most parents do support early initiation (4 studies), while some preferred delaying or tempering ACP and EOL discussions (1 study).** • **Parents expressed the need to feel ready before starting to engage in ACP and EOL discussions, without feeling pressured (6 studies).** • **Parents considered it a missed opportunity when physicians did not initiate ACP or EOL discussions (2 studies).** • **Parents found it helpful to regularly repeat offering ACP and EOL discussions (2 studies).**

GRADE CERQual assessment (for conclusions reported in only one study)		
Study design:	+4	2 qualitative studies
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 2/2; Study design and theoretical approach: low in 2/2; Sample selection: unclear in 2/2; Data collection: low in 1/2, unclear in 1/2; Data analysis: low in 1/2, unclear in 1/2; Results: low in 2/2
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance

Sufficiency of saturation:	-1	Some concerns on sufficiency of saturation due to small sample size (N=9/N=17). Only 1 study performed.
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**
Conclusion:		**Parents mentioned that wrong timing of initiating ACP or EOL discussions includes shortly after breaking bad news (1 study), shortly after overcoming a crisis (1 study), or when the child is in an 'unstable' condition (1 study).**

4.2.6.2.2 Zorgprofessional perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Timing and initiation			
Edwards, 2017 – Qualitative study	15 directors/codirectors of paediatric home ventilation programs at children's hospital of following expertise: • 11 paediatric pulmonologists • 2 paediatric intensivists • 2 specialized in both paediatric pulmonology and critical care Children treated in children's hospital: Children with Chronic Respiratory Failure (CRF)	In-depth, semi-structured interviews over the phone, using an open-ended interview guide.	*Facilitators perceived by HCPs* • Directors emphasized that the decision-making process around long-term ventilation should be unhurried and that it should start as soon as CRF is anticipated or diagnosed—either early during the hospitalization or, ideally, during a period of relative wellness before acute illness pushes the susceptible child into CRF. • HCPs rushing families to make decisions (3/15)
Odeniyi, 2017 – Qualitative study	10 Health Care Professionals of following expertise: • 2 intensivist attendings • 1 intensive care fellow • 4 oncologist attendings • 3 oncologist fellows	Qualitative study using semi-structured interviews.	*Barriers perceived by HCPs* • Both groups of professionals struggles with the timing and mechanics of communicating bad news to families, e.g. when to shift to palliative care, and providing support. • Oncologist were often uncertain about continuing offering additional treatments when cure was unlikely, and struggled with if they should recommend a shift in goals-of-care.
Hein, 2020 – Qualitative study	9 bereaved parents of children aged 2 to 16 years with following type of conditions: • 3 metabolic • 2 oncological • 2 perinatal • 1 cardiological • 2 neuromuscular 14 Health Care Professionals of following expertise: • 4 paediatricians • 1 emergency physician • 1 psychologist • 1 chaplain • 3 nurses (intensive care, out-patient) • 2 social workers • 2 special education teachers	2 transdisciplinary workshops: • First workshop - discussion groups to explore experiences with paediatric advance care planning (6 parents, 14 HCPs). • Second workshop - dialogue groups to discuss topics such as, participation of children and adolescents; paediatric advance care planning documentation; supplementary written materials (5 parents, 14 HCPs).	*Barriers perceived by HCPs* • Professionals were concerned about the possible lack of readiness of parents to engage in paediatric advance care planning. • According to professionals, when parents are not ready, they are more likely to reject treatment limitations for their child and less likely to participate in paediatric advance care planning discussions or to complete advance directives.
Jack, 2018 – Qualitative study	21 Health Care Professionals of following expertise: • 1 hospice nurse • 1 obstetrics and gynaecology consultant • 1 hospice nurse	A qualitative methodological approach which drew upon a naturalistic interpretative design, with semi-structured interviews.	*Facilitators perceived by HCPs* • For children with life-limiting conditions it was recognised that the timing for the conversations to start needed to be related to the health of the child, and the professional needs to be aware of any deterioration, which emphasises the ongoing need for review. • Some professionals suggested that the ideal time to start ACP conversations should be after the relationship with the family is formed and allow the family to go at their pace.

	• 1 consultant paediatrician • 1 midwife • 1 community midwife • 1 neonatal nurse • 1 consultant paediatric oncologist • 1 complimentary therapist • 1 hospice nurse • 1 paediatric palliative care nurse • 1 bereavement specialist • 1 senior hospice nurse • 1 practitioner • 1 health visitor • 1 care assistant • 1 support worker • 1 consultant neonatologist • 1 palliative care nurse specialist • 1 neonatal nurse • 1 hospice nurse		• Some participant stated that ACP conversations should starts as soon as possible, even at point of diagnosis. Which could avoid the conversation having to take place at a critical time for the parents in the situation that when a child suddenly deteriorates. • Timing was important in starting ACP conversations as soon as possible to allow for a more flexible approach to the conversation, allowing a staged approach. • Another participant suggested the need to look for cues, e.g. when families start to ask questions that could help to open-up the conversation to approach a discussion around ACP. *Barriers perceived by HCPs* • A participant pointed out that conversation should ideally not take place in crises when parents are under incredible stress.
Orkin, 2020 – Qualitative study	14 mothers of 14 children 11 Health Care Professionals (8 physicians, 2 nurses, 1 social worker) of following expertise: • 2 complex care • 3 paediatric medicine • 2 respiratory medicine • 1 paediatric haematology and oncology • 1 critical care • 1 neonatal intensive care • 1 palliative care	Qualitative content-analysis study comprising demographic surveys and individual semi-structured interviews.	*Facilitators perceived by parents and HCPs* • Participants emphasized that ACP should start at time of diagnosis, should occur before a medical crisis, and be an ongoing and dynamic part of the child's care. *Barriers perceived by HCPs* • Some HCPs mentioned the need to gauge family readiness and follow the family's lead. Others felt that families might never feel ready.
Day 2018 – Qualitative study	58 Health Care Professionals specialised in haematology, haematopoietic stem cell transplantation or palliative care, working principally with patients aged 13-25 years. • 6 consultants • 19 junior doctors (foundation year, registrar/resident and specialty registrar/fellow) • 9 Clinical Nurse Specialists • 10 ward nurses • 14 allied HCP (psychologists, physiotherapists, dieticians and social workers)	In-depth, semi-structured interviews and participant observations (during psycho-social meetings, day-care meetings and pre-ward round meeting, and informal conversations).	*Facilitators perceived by HCPs* • HCPs suggested that at the point that treatment begins to fail, families and teenagers are pulled into the decision-making, and are asked to voice their opinions and preferences.

Henderson 2017 – Qualitative study	36 Health Care Professionals (including medical, nursing, and allied health professionals)	Qualitative design using a group interview.	*Facilitators perceived by HCPs* • The timing has to be right for the family rather than HCPs.
Zaal-Schuller 2016 – Qualitative study	11 Health Care Professionals of following expertise: • 6 paediatricians • 1 rehabilitation specialists • 1 paediatric Intensive Care specialists • 3 paediatric Neurologists	Retrospective, qualitative study, with semi-structured interviews.	*Facilitators perceived by HCPs* • Many physicians named acute deterioration of a child the most common reason to discuss withholding or withdrawing certain treatments. • 2/11 HCPs named improvement of physical condition as a reason to reassess the agreements and to sometimes reverse decisions. *Barriers perceived by HCPs* • Many physicians had an idea about how parents felt about EOL discussions, but found it very difficult to identify when parents were 'ready' to discuss these decisions.

GRADE CERQual assessment (for conclusions reported in more than one study)		
Study design:	+4	8 qualitative studies
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 8/8; Study design and theoretical approach: low in 7/8, unclear in 1/8; Sample selection: unclear in 5/8, high in 3/8; Data collection: low in 4/8, unclear in 4/8; Data analysis: low in 4/8, unclear in 4/8; Results: low in 7/8, high in 1/8
Coherence:	-1	Some concerns on coherence, some supported starting ACP and EOL discussions as early as possible, others mentioned they wanted to wait until the family felt ready.
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	0	No concerns on sufficiency of saturation
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**
Conclusion:		• **Although some HCPs supported initiation of ACP discussions as early as possible, ideally at time of diagnosis or when the child is in a period of relative wellness (3 studies), others gave priority to parent's readiness before starting ACP or EOL discussions, and mentioned timing should be right for family rather than HCPs and discussions should go at the parents' pace (6 studies).** • **Heath care professionals suggested that changes in the child's condition or specific events, such as failing of treatment, could be seen as a prompt for ACP and EOL discussions (4 studies).** • **HCPs stated that a wrong timing of initiating ACP discussions is during a crisis (2 studies).**

GRADE CERQual assessment (for conclusions reported in one study only)		
Study design:	+4	1 qualitative study
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 1/1; Study design and theoretical approach: low in 1/1; Sample selection: high in 1/1; Data collection: low in 1/1; Data analysis: unclear in 1/1; Results: low in 1/1
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	-1	Some concerns on sufficiency of saturation. Only 1 study performed.
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**
Conclusion:		**HCPs mentioned that readiness could be difficult to assess, and cues could be used, such as parents asking questions that could open-up discussions (1 study).**

4.2.6.3 Dynamisch proces

4.2.6.3.1 Ouderperspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Ongoing process			
Hein, 2020 – Qualitative study	9 bereaved parents of children aged 2 to 16 years with following type of conditions: • 3 metabolic • 2 oncological • 2 perinatal • 1 cardiological • 2 neuromuscular 14 Health Care Professionals of following expertise: • 4 paediatricians • 1 emergency physician • 1 psychologist • 1 chaplain • 3 nurses (intensive care, out-patient) • 2 social workers • 2 special education teachers	2 transdisciplinary workshops: • First workshop - discussion groups to explore experiences with paediatric advance care planning (6 parents, 14 HCPs). • Second workshop - dialogue groups to discuss topics such as, participation of children and adolescents; paediatric advance care planning documentation; supplementary written materials (5 parents, 14 HCPs).	*Facilitators perceived by parents* • Parents found it helpful to have several paediatric advance care planning meetings with HCPs that are regularly involved in care of children with life-limiting diseases. • Parents may not be aware of the necessity of updating documents; thus, professionals should take the initiative and guide parents through process iteration. *Facilitators perceived by parents and HCPs* • Participants recommended embedding paediatric advance care planning in the continuous care of families. • Care should start as soon as possible and respond to the emerging needs and increasing awareness and acceptance of the situation during the course of the disease.
Lord, 2020 – Qualitative study	13 bereaved parents of 12 children with medical complexity: • 11 genetic or congenital 1 acquired	Qualitative, semi-structured interviews.	*Facilitators perceived by parents* • Many parents felt discussions should continue regularly.
Lotz, 2017 – Qualitative study	11 parents of 9 deceased children with following diagnoses: • 3 cancer • 1 spinal muscular atrophy type I • 1 cystic fibrosis • 1 leukodystrophy • 1 hypo plastic left heart syndrome • 1 complex malformation syndrome • 1 unknown syndrome	Qualitative, practice-informing, semi-structured interview study.	*Facilitators perceived by parents* • Parents unanimously wished for a step-by-step process with repeated discussions and sensitive communication respecting their needs and reservations.
Orkin, 2020 – Qualitative study	14 mothers of 14 children 11 Health Care Professionals (8 physicians, 2 nurses, 1 social worker) of following expertise: • 2 complex care • 3 paediatric medicine • 2 respiratory medicine	Qualitative content-analysis study comprising demographic surveys and individual semi-structured interviews.	*Facilitators perceived by parents and HCPs* • Participants emphasized that ACP should be an ongoing and dynamic part of the child's care.

• 1 paediatric haematology and oncology • 1 critical care • 1 neonatal intensive care • 1 palliative care		
GRADE CERQual assessment		
Study design:	+4	4 qualitative studies
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 4/4; Study design and theoretical approach: low in 4/4; Sample selection: unclear in 1/4, high in 3/4; Data collection: low in 2/4, unclear in 2/4; Data analysis: low in 2/4, unclear in 2/4; Results: low in 4/4
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	0	No concerns on sufficiency of saturation
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**
Conclusion:		**Parents mentioned that ACP and EOL discussions should be an ongoing process and a continuous part of the child's care (4 studies).**

4.2.6.3.2 Zorgprofessional perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Ongoing process			
Hein, 2020 – Qualitative study	9 bereaved parents of children aged 2 to 16 years with following type of conditions: • 3 metabolic • 2 oncological • 2 perinatal • 1 cardiological • 2 neuromuscular 14 Health Care Professionals of following expertise: • 4 paediatricians • 1 emergency physician • 1 psychologist • 1 chaplain • 3 nurses (intensive care, out-patient) • 2 social workers • 2 special education teachers	2 transdisciplinary workshops: • First workshop - discussion groups to explore experiences with paediatric advance care planning (6 parents, 14 HCPs). • Second workshop - dialogue groups to discuss topics such as, participation of children and adolescents; paediatric advance care planning documentation; supplementary written materials (5 parents, 14 HCPs).	*Facilitators perceived by parents and HCPs* • Participants recommended embedding paediatric advance care planning in the continuous care of families. • Care should start as soon as possible and respond to the emerging needs and increasing awareness and acceptance of the situation during the course of the disease.
Jack, 2018 – Qualitative study	21 Health Care Professionals of following expertise: • 1 hospice nurse • 1 obstetrics and gynaecology consultant • 1 hospice nurse • 1 consultant paediatrician • 1 midwife • 1 community midwife • 1 neonatal nurse • 1 consultant paediatric oncologist • 1 complimentary therapist • 1 hospice nurse • 1 paediatric palliative care nurse • 1 bereavement specialist • 1 senior hospice nurse • 1 practitioner • 1 health visitor • 1 care assistant • 1 support worker • 1 consultant neonatologist • 1 palliative care nurse specialist • 1 neonatal nurse	A qualitative methodological approach which drew upon a naturalistic interpretative design, with semi-structured interviews.	*Facilitators perceived by HCPs* • The need to slowly have the conversations and building up overtime allowed the news to be absorbed. • Timing was important in starting ACP conversations as soon as possible to allow for a more flexible approach to the conversation, allowing a staged approach.

	• 1 hospice nurse		
Henderson 2017 – Qualitative study	36 Health Care Professionals (including medical, nursing, and allied health professionals)	Qualitative design using a group interview.	*Facilitators perceived by HCPs* • It takes more than one discussion
GRADE CERQual assessment			
Study design:	+4	3 qualitative studies	
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 3/3; Study design and theoretical approach: low in 2/3, unclear in 1/3; Sample selection: unclear in 2/3, high in 1/3; Data collection: low in 1/3, unclear in 2/3; Data analysis: unclear in 3/3; Results: low in 2/3, high in 1/3	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	
Sufficiency of saturation:	0	No concerns on sufficiency of saturation	
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**	
Conclusion:		**HCPs mentioned that ACP and EOL discussions should be an ongoing process and a continuous part of the child's care (3 studies).**	

4.2.6.4 Voldoende tijd voor besluitvorming

4.2.6.4.1 Ouderperspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Sufficient time for decision-making			
Beecham, 2017 – Qualitative study	18 parents • 9 parents whose child was currently receiving palliative care • 9 bereaved parents whose child had received palliative care Children had following type of conditions: ○ 10 neurologic ○ 2 metabolic ○ 2 oncologic ○ 1 gastroenterological ○ 1 immunologic ○ 1 respiratory ○ 1 chromosomal abnormality	Open-ended, semi-structured interviews.	*Facilitators perceived by parents* • Parents suggested the need for clinicians to give parents sufficient time to make decisions, allowing them time to adjust to their child's diagnosis and prognosis.
Edwards, 2020 – Qualitative study	44 parents of 43 children: • 18 contemporaneous invasive long-term ventilation decision-makers • 10 contemporaneous non-invasive long-term ventilation decision-makers • 8 former invasive long-term ventilation decision-makers • 8 former non-invasive long-term ventilation decision-makers 1 young woman using invasive long-term ventilation 1 adolescent girl being initiated on non-invasive long-term ventilation	Semi-structured interviews using an open-ended interview guide. Interviews were conducted in person or over the phone	*Facilitators perceived by parents* Following provider practices/qualities regarding communication were considered helpful by contemporaneous decision makers (n=28) • Allowing time for processing information and asking questions. 9/28 • Share information before decisions or crises. 4/28
GRADE CERQual assessment			
Study design:	+4	2 qualitative studies	
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 2/2; Study design and theoretical approach: low in 2/2; Sample selection: unclear in 1/2, high in 1/2; Data collection: low in 2/2; Data analysis: low in 1/2, unclear in 1/2; Results: low in 2/2	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	
Sufficiency of saturation:	0	No concerns on sufficiency of saturation	
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**	
Conclusion:		**Parents mentioned the need to have sufficient time between receiving information and making decisions, to process information and ask questions (2 studies).**	

4.2.7 Voorbereiding

4.2.7.1.1 Zorgprofessional perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Preparation			
Jack, 2018 – Qualitative study	21 Health Care Professionals of following expertise: • 1 hospice nurse • 1 obstetrics and gynaecology consultant • 1 hospice nurse • 1 consultant paediatrician • 1 midwife • 1 community midwife • 1 neonatal nurse • 1 consultant paediatric oncologist • 1 complimentary therapist • 1 hospice nurse • 1 paediatric palliative care nurse • 1 bereavement specialist • 1 senior hospice nurse • 1 practitioner • 1 health visitor • 1 care assistant • 1 support worker • 1 consultant neonatologist • 1 palliative care nurse specialist • 1 neonatal nurse • 1 hospice nurse	A qualitative methodological approach which drew upon a naturalistic interpretative design, with semi-structured interviews.	*Facilitators perceived by HCPs* • Participants mentioned the need for parallel planning to ensure the best plan for the future care of children, so different plans were ready for potential outcomes.

Henderson 2017 – Qualitative study	36 Health Care Professionals (including medical, nursing, and allied health professionals)	Qualitative design using a group interview.	Facilitators perceived by HCP
			• Team prebriefing
			  ○ Prepare behind the scenes.
			  ○ Build strong foundations for the EOL discussion.
			  ○ Work out who is the most appropriate person (to lead the discussion).
			• We have our agenda of what we need to achieve.

GRADE CERQual assessment			
Study design:	+4	2 qualitative studies	
Methodological limitations:	-2	Serious methodological limitations. Aim and appropriateness of qualitative evidence: low in 2/2; Study design and theoretical approach: low in 1/2, unclear in 1/2; Sample selection: unclear in 1/2, high in 1/2; Data collection: low in 1/2, unclear in 1/2; Data analysis: unclear in 2/2; Results: low in 1/2, high in 1/2	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	

Sufficiency of saturation:	0	No concerns on sufficiency of saturation
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**
Conclusion:		**HCPs mentioned preparation and planning of ACP and EOL discussions as helpful (2 studies), such as having an agenda, assigning an appropriate person to lead the discussion, and parallel planning to prepare different plans for potential outcomes (1 study).**

4.2.8 Documentatie

4.2.8.1.1 Ouderperspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Documentation			
Hein, 2020 – Qualitative study	9 bereaved parents of children aged 2 to 16 years with following type of conditions: • 3 metabolic • 2 oncological • 2 perinatal • 1 cardiological • 2 neuromuscular 14 Health Care Professionals of following expertise: • 4 paediatricians • 1 emergency physician • 1 psychologist • 1 chaplain • 3 nurses (intensive care, out-patient) • 2 social workers • 2 special education teachers	2 transdisciplinary workshops: • First workshop - discussion groups to explore experiences with paediatric advance care planning (6 parents, 14 HCPs). • Second workshop - dialogue groups to discuss topics such as, participation of children and adolescents; paediatric advance care planning documentation; supplementary written materials (5 parents, 14 HCPs).	*Facilitators perceived by professionals and parents* • All participants agreed that all parties involved should sign the documents. • All participants recommended keeping minutes of all discussions to ensure continuity of the process. • Participants did not approve for supplementary written materials to be handed out without a personal conversation.
Lotz, 2017 – Qualitative study	11 parents of 9 deceased children with following diagnoses: • 3 cancer • 1 spinal muscular atrophy type I • 1 cystic fibrosis • 1 leukodystrophy • 1 hypo plastic left heart syndrome • 1 complex malformation syndrome • 1 unknown syndrome	Qualitative, practice-informing, semi-structured interview study.	*Facilitators perceived by parents* • Parents ascribed little importance to documenting decisions in a written plan and preferred oral agreements with the care professionals.
GRADE CERQual assessment (for conclusions reported in more than one study)			
Study design:	+4	2 qualitative studies	
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 2/2; Study design and theoretical approach: low in 2/2; Sample selection: unclear in 1/2, high in 1/2; Data collection: unclear in 2/2; Data analysis: unclear in 2/2; Results: low in 2/2	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	
Sufficiency of saturation:	0	No concerns on sufficiency of saturation	
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**	
Conclusion:		**Parents preferred a personal conservation when handing out supplementary written materials (2 studies).**	

GRADE CERQual assessment (for conclusions reported in only one study)		
Study design:	+4	1 qualitative study
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 1/1; Study design and theoretical approach: low in 1/1; Sample selection: unclear in 1/1; Data collection: unclear in 1/1; Data analysis: unclear in 1/1; Results: low in 1/1
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	-1	Some concerns on sufficiency of saturation. Only 1 study performed.
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**
Conclusion:		**Parents agreed that all parties should sign the documents and prefer to keep minutes of all discussion to ensure continuity of the advance care planning (1 study).**

4.2.8.1.2 Zorgprofessional perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Documentation			
Hein, 2020 – Qualitative study	9 bereaved parents of children aged 2 to 16 years with following type of conditions: • 3 metabolic • 2 oncological • 2 perinatal • 1 cardiological • 2 neuromuscular 14 Health Care Professionals of following expertise: • 4 paediatricians • 1 emergency physician • 1 psychologist • 1 chaplain • 3 nurses (intensive care, out-patient) • 2 social workers • 2 special education teachers	2 transdisciplinary workshops: • First workshop - discussion groups to explore experiences with paediatric advance care planning (6 parents, 14 HCPs). • Second workshop - dialogue groups to discuss topics such as, participation of children and adolescents; paediatric advance care planning documentation; supplementary written materials (5 parents, 14 HCPs).	*Barriers Identified by HCPs* • Professionals worried about the unclear legal status of advance care planning documents for children. *Barriers identified by HCPs and parents* • Participants did not approve for supplementary written materials to be handed out without a personal conversation. *Facilitators perceived by HCPs* • Stakeholders wanted to receive and be informed about the documents in a personal conversation, in order to ask questions, to discuss emergency procedures and to address in advance potential conflicts between institutional policies and the family's wishes. • Professionals recommended the use of brief recommendations for emergencies, supplemented by larger advance directives containing a characterisation of the child, the diagnosis and the course of the disease. • Contact information should be easily retrievable and organised in accordance to priority. *Facilitators perceived by HCPs and parents* • All participants agreed that all parties involved should sign the documents. • All participants recommended keeping minutes of all discussions to ensure continuity of the process.

GRADE CERQual assessment		
Study design:	+4	1 qualitative study
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 1/1; Study design and theoretical approach: low in 1/1; Sample selection: unclear in 1/1; Data collection: unclear in 1/1; Data analysis: unclear in 1/1; Results: low in 1/1
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	-1	Some concerns on sufficiency of saturation. Only 1 study performed.
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**
Conclusion:		• **HCPs preferred a personal conservation when handing out supplementary written materials (1 study).** • **HCPs agreed that all parties should sign the documents and prefer to keep minutes of all discussion to ensure continuity of the advance care planning (1 study).** • **HCPs want to receive and be informed about advance care planning documents in a personal conversation, and recommend using brief recommendations for emergencies, supplemented by larger advance directives with easily retrievable and organised contact information (1 study).** • **HCPs worried about the unclear legal status of advance care planning documents for children (1 study).**

4.2.9 Setting

4.2.9.1 Included subthemes

Included subthemes
Location
Attendees

4.2.9.2 Locatie

4.2.9.2.1 Ouderperspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Location			
Lord, 2020 – Qualitative study	13 bereaved parents of 12 children with medical complexity: • 11 genetic or congenital • 1 acquired	Qualitative, semi-structured interviews.	*Facilitators perceived by parents* • A comfortable setting, e.g. a quiet room with adequate seating.
Orkin, 2020 – Qualitative study	14 mothers of 14 children 11 Health Care Professionals (8 physicians, 2 nurses, 1 social worker) of following expertise: • 2 complex care • 3 paediatric medicine • 2 respiratory medicine • 1 paediatric haematology and oncology • 1 critical care • 1 neonatal intensive care • 1 palliative care	Qualitative content-analysis study comprising demographic surveys and individual semi-structured interviews.	*Facilitators perceived by parents and HCPs* • Ensuring a comfortable and appropriate location and budget enough time.
Sisk 2020 – Qualitative study	77 parents and 1 grandparent of 78 children with following diagnoses: • 35 leukaemia or lymphoma • 30 solid tumor • 13 brain tumor	A qualitative study using semistructured telephone interviews using an interview guide.	*Facilitators perceived by parents* • Parents highlighted the importance of meeting their unique information needs, especially related to the setting of the conversation.
GRADE CERQual assessment			
Study design:	+4	3 qualitative studies	
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 3/3; Study design and theoretical approach: low in 3/3; Sample selection: low in 1/3, high in 2/3; Data collection: low in 1/1; Data analysis: low in 3/3; Results: low in 3/3	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	
Sufficiency of saturation:	0	No concerns on sufficiency of saturation	

Overall assessment of confidence in findings	**⊕⊕⊕⊖ MODERATE confidence in the evidence**
Conclusion:	**Parents mentioned the importance of a comfortable and appropriate setting including a quiet room with adequate seating and having enough time for the discussion (3 studies).**

4.2.9.2.2 Zorgprofessional perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Locatie			
Jack, 2018 – Qualitative study	21 Health Care Professionals of following expertise: • 1 hospice nurse • 1 obstetrics and gynaecology consultant • 1 hospice nurse • 1 consultant paediatrician • 1 midwife • 1 community midwife • 1 neonatal nurse • 1 consultant paediatric oncologist • 1 complimentary therapist • 1 hospice nurse • 1 paediatric palliative care nurse • 1 bereavement specialist • 1 senior hospice nurse • 1 practitioner • 1 health visitor • 1 care assistant • 1 support worker • 1 consultant neonatologist • 1 palliative care nurse specialist • 1 neonatal nurse • 1 hospice nurse	A qualitative methodological approach which drew upon a naturalistic interpretative design, with semi-structured interviews.	*Facilitators perceived by HCPs* • Good practice was to consider the environment in which the conversation was to take place. • A professional mentioned that some families prefer to have the conversations in a quieter environment, away from the child in hospital, or another location such as home.
Orkin, 2020 – Qualitative study	14 mothers of 14 children 11 Health Care Professionals (8 physicians, 2 nurses, 1 social worker) of following expertise: • 2 complex care • 3 paediatric medicine • 2 respiratory medicine • 1 paediatric haematology and oncology • 1 critical care • 1 neonatal intensive care • 1 palliative care	Qualitative content-analysis study comprising demographic surveys and individual semi-structured interviews.	*Facilitators perceived by parents and HCPs* • Ensuring a comfortable and appropriate location and budget enough time.
Henderson 2017 –	36 Health Care Professionals (including medical, nursing, and allied health professionals)	Qualitative design using a group interview.	*Facilitators perceived by HCPs* • Find space to do EOL discussions, nothing is worse than having to do discussions in a busy ward area

Qualitative study		• Leave practitioner distractors such as mobile phones and pagers with someone else.
GRADE CERQual assessment		
Study design:	+4	3 qualitative studies
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 3/3; Study design and theoretical approach: low in 2/3, unclear in 1/3; Sample selection: unclear in 1/3, high in 2/3; Data collection: low in 2/3, unclear in 1/3; Data analysis: low in 1/3, unclear in 2/3; Results: low in 2/3, high in 1/3
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	0	No concerns on sufficiency of saturation
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**
Conclusion:		**HCPs mentioned the importance of a comfortable and appropriate setting including a quiet room with adequate seating, without distractors such as mobile phones and pagers, possibly away from the hospital or at home, and having enough time for the discussion (3 studies).**

4.2.9.3 Aanwezigen

4.2.9.3.1 Ouderperspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Attendees during ACP meeting			
Lord, 2020 – Qualitative study	13 bereaved parents of 12 children with medical complexity: • 11 genetic or congenital • 1 acquired	Qualitative, semi-structured interviews.	*Facilitators perceived by parents* • Having appropriate people present, e.g. HCPs who know the patient and family well and key family caregiver (ensuring both parents are present).
Lotz, 2017 – Qualitative study	11 parents of 9 deceased children with following diagnoses: • 3 cancer • 1 spinal muscular atrophy type I • 1 cystic fibrosis • 1 leukodystrophy • 1 hypo plastic left heart syndrome • 1 complex malformation syndrome • 1 unknown syndrome	Qualitative, practice-informing, semi-structured interview study.	*Facilitators perceived by parents* • Parents mentioned bringing in an additional, uninvolved "listener" (e.g. a friend), involving nurses for support and exchange with other parents in similar situations as helpful.
Orkin, 2020 – Qualitative study	14 mothers of 14 children 11 Health Care Professionals (8 physicians, 2 nurses, 1 social worker) of following expertise: • 2 complex care • 3 paediatric medicine • 2 respiratory medicine • 1 paediatric haematology and oncology • 1 critical care • 1 neonatal intensive care • 1 palliative care	Qualitative content-analysis study comprising demographic surveys and individual semi-structured interviews.	*Facilitators perceived by parents and HCPs* • Provide the opportunity for all key team and family members to be present, and ensure that the family feels supported.
GRADE CERQual assessment			
Study design:	+4	3 qualitative studies	
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 3/3; Study design and theoretical approach: low in 3/3; Sample selection: high in 3/3; Data collection: low in 2/3, unclear in 1/3; Data analysis: low in 2/3, unclear in 1/3; Results: low in 3/3	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	
Sufficiency of saturation:	0	No concerns on sufficiency of saturation	
Overall assessment of confidence in findings		⊕⊕⊕⊖ **MODERATE confidence in the evidence**	

Conclusion:	**All key family members and HCPs should be given the opportunity to be present during ACP discussions. Additionally, family support should be ensured by inviting an uninvolved “listener” like a friend or nurse (3 studies).**

4.2.9.3.2 Zorgprofessional perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Attendees			
Orkin, 2020 – Qualitative study	14 mothers of 14 children 11 Health Care Professionals (8 physicians, 2 nurses, 1 social worker) of following expertise: • 2 complex care • 3 paediatric medicine • 2 respiratory medicine • 1 paediatric haematology and oncology • 1 critical care • 1 neonatal intensive care • 1 palliative care	Qualitative content-analysis study comprising demographic surveys and individual semi-structured interviews.	*Facilitators perceived by parents and HCPs* • Provide the opportunity for all key team and family members to be present, and ensure that the family feels supported.
GRADE CERQual assessment			
Study design:	+4	1 qualitative study	
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 1/1; Study design and theoretical approach: low in 1/1; Sample selection: high in 1/1; Data collection: low in 1/1; Data analysis: low in 1/1; Results: low in 1/1	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	
Sufficiency of saturation:	-1	Some concerns on sufficiency of saturation. Only 1 study performed.	
Overall assessment of confidence in findings		⊕⊕⊖⊖ **LOW confidence in the evidence**	
Conclusion:		**All key HCPs and family members should be given the opportunity to be present, and family support should be ensured (1 study).**	

4.2.10 Ondersteuning

4.2.10.1.1 Ouderperspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Support			
Edwards, 2020 – Qualitative study	44 parents of 43 children: • 18 contemporaneous invasive long-term ventilation decision-makers • 10 contemporaneous non-invasive long-term ventilation decision-makers • 8 former invasive long-term ventilation decision-makers • 8 former non-invasive long-term ventilation decision-makers 1 young woman using invasive long-term ventilation 1 adolescent girl being initiated on non-invasive long-term ventilation	Semi-structured interviews using an open-ended interview guide. Interviews were conducted in person or over the phone	*Facilitators perceived by parents* Parents had various approaches to manage stress in decision-making • Several parents drew emotional support from other family members
Lotz, 2017 – Qualitative study	11 parents of 9 deceased children with following diagnoses: • 3 cancer • 1 spinal muscular atrophy type I • 1 cystic fibrosis • 1 leukodystrophy • 1 hypo plastic left heart syndrome • 1 complex malformation syndrome • 1 unknown syndrome	Qualitative, practice-informing, semi-structured interview study.	*Facilitators perceived by parents* • Parents mentioned exchange with other parents in similar situations as helpful.
Murrell 2018 – Qualitative study	19 families, including 29 parents and 22 children with Type 1 SMA: • 11 children living • 11 deceased children	Qualitative descriptive design with individual or small group interviews guided by a semi-structured questionnaire.	*Facilitators perceived by parents* • 18/19 families talked about the value of being connected to another family with a child with Type 1 SMA, so they could share stories and ask questions. Interactions ranged from acquiring simple information to making life-altering treatment decisions.
Zaal-Schuller 2016 – Qualitative study	17 parents of 14 children with following diagnoses: • 3 post-resuscitation • 5 genetic condition • 1 neurologic condition • 2 metabolic condition • 3 unknown	Retrospective, qualitative study, with semi-structured interviews.	*Facilitators perceived by parents* • Many parents indicated that conversations with other parents who had been through the same would have been informative and supportive, because they would understand their feelings and complexity of their considerations.
GRADE CERQual assessment			
Study design:	+4	4 qualitative studies	
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 4/4; Study design and theoretical approach: low in 4/4; Sample selection: low in 1/4, unclear in 2/4, high in 1/4; Data collection: low in 3/4, unclear in 1/4; Data analysis: low in 2/4, unclear in 2/4; Results: low in 4/4	
Coherence:	0	No concerns on coherence	

Relevance:	0	No concerns on relevance
Sufficiency of saturation:	0	No concerns on sufficiency of saturation
Overall assessment of confidence in findings		⊕⊕⊕⊖ **MODERATE confidence in the evidence**
Conclusion:		**Parents mentioned being connected to family-members and other parents in similar situations as valuable for making-decisions (4 studies).**

4.2.11 Onderwijs

4.2.11.1 Ouderperspectief

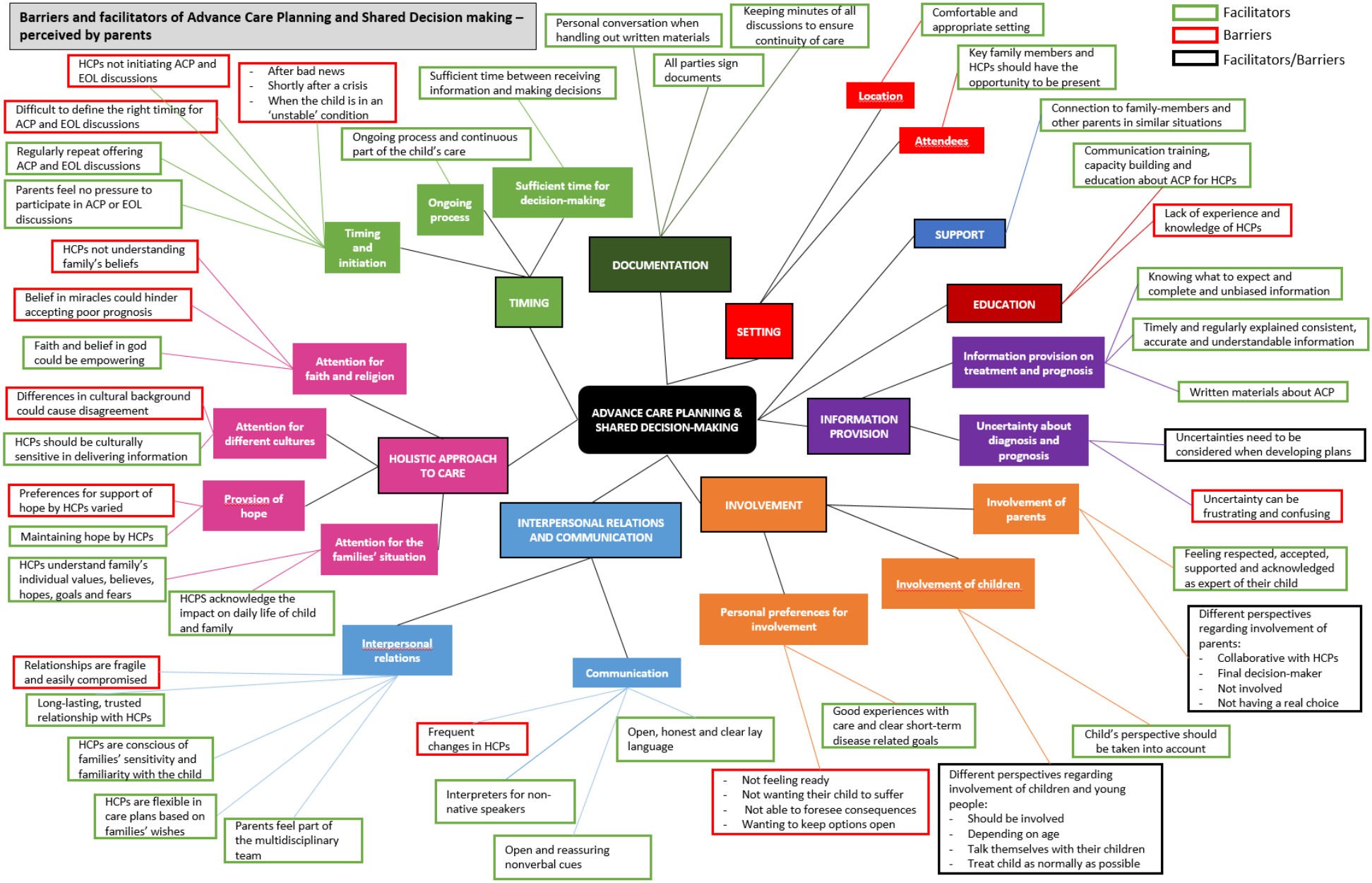
Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Education			
Fahner, 2021 – Qualitative study	20 parents of 17 children with life-limiting conditions (10 bereaved parents of 6 children who died) with following diagnoses: • 7 chromosomal anomaly • 4 congenital heart disease • 2 CNS tumour • 1 cystic Fibrosis • 1 neuromuscular disease • 1 epilepsy syndrome • 1 perinatal asphyxia	Qualitative interviews; focus group interviews and individual interviews.	*Facilitators perceived by parents* • Education for HCPs is required about the holistic nature of ACP.
Hein, 2020 – Qualitative study	9 bereaved parents of children aged 2 to 16 years with following type of conditions: • 3 metabolic • 2 oncological • 2 perinatal • 1 cardiological • 2 neuromuscular	2 transdisciplinary workshops: • First workshop - discussion groups to explore experiences with paediatric advance care planning (6 parents, 14 HCPs). • Second workshop - dialogue groups to discuss topics such as, participation of children and adolescents; paediatric advance care planning documentation; supplementary written materials (5 parents, 14 HCPs).	*Barriers perceived by parents* • Parents disapproved lack of experience or knowledge on the part of professionals.
Lotz, 2017 – Qualitative study	11 parents of 9 deceased children with following diagnoses: • 3 cancer • 1 spinal muscular atrophy type I • 1 cystic fibrosis • 1 leukodystrophy • 1 hypo plastic left heart syndrome • 1 complex malformation syndrome • 1 unknown syndrome	Qualitative, practice-informing, semi-structured interview study.	*Facilitators perceived by parents* • Communication trainings for physicians to improve their communication skills.
Orkin, 2020 – Qualitative study	14 mothers of 14 children 11 Health Care Professionals (8 physicians, 2 nurses, 1 social worker) of following expertise: • 2 complex care • 3 paediatric medicine • 2 respiratory medicine • 1 paediatric haematology and oncology	Qualitative content-analysis study comprising demographic surveys and individual semi-structured interviews.	*Barriers perceived by parents and HCPs* • Some HCPs and parents stated that specific training and capacity building would be beneficial for HCPs.

• 1 critical care • 1 neonatal intensive care • 1 palliative care		
GRADE CERQual assessment (for conclusions reported in more than one study)		
Study design:	+4	3 qualitative studies
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 3/3; Study design and theoretical approach: low in 3/3; Sample selection: high in 3/3; Data collection: low in 1/3, unclear in 2/3; Data analysis: low in 1/3, unclear in 2/3; Results: low in 3/3
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	0	No concerns on sufficiency of saturation
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**
Conclusion:		**Parents felt that communication trainings, capacity building and education about ACP would be beneficial for HCPs (3 studies).**
GRADE CERQual assessment (for conclusions reported in only one study)		
Study design:	+4	1 qualitative study
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 1/1; Study design and theoretical approach: low in 1/1; Sample selection: unclear in 1/1; Data collection: unclear in 1/1; Data analysis: unclear in 1/1; Results: low in 1/1
Coherence:	0	No concerns on coherence
Relevance:	0	No concerns on relevance
Sufficiency of saturation:	-1	Some concerns on sufficiency of saturation due to small sample size (N=9). Only 1 study performed.
Overall assessment of confidence in findings		**⊕⊕⊖⊖ LOW confidence in the evidence**
Conclusion:		**Parents disapproved lack of experience or knowledge of HCPs (1 study).**

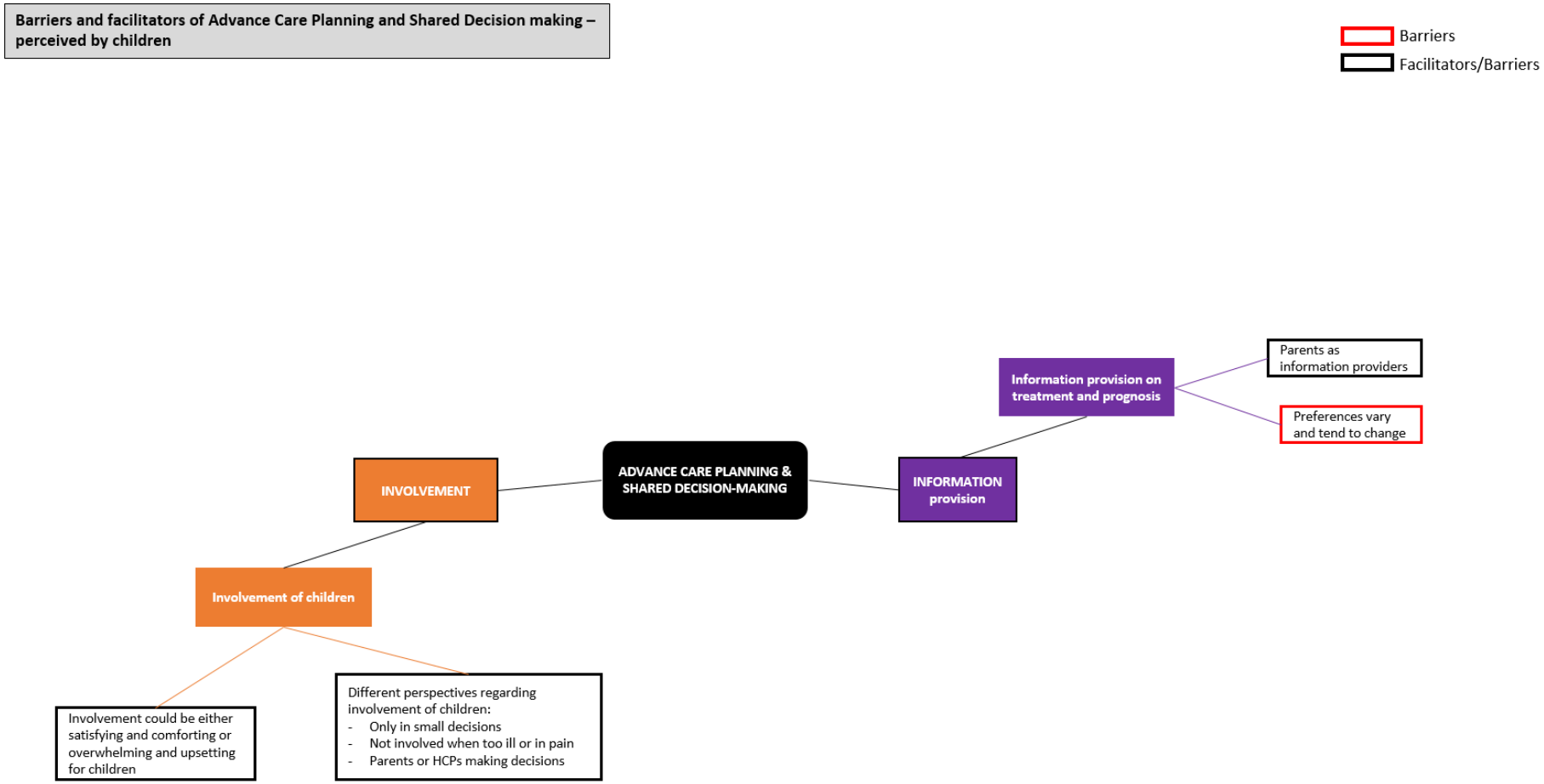
4.2.11.2 Zorgprofessional perspectief

Facilitating and impeding factors of Advance Care Planning and shared decision-making			
Study	Number and type of participants	Method	Summary of findings
Education			
Odeniyi, 2017 – Qualitative study	10 Health Care Professionals of following expertise: • 2 intensivist attendings • 1 intensive care fellow • 4 oncologist attendings • 3 oncologist fellows	Qualitative study using semi-structured interviews.	*Barriers perceived by HCPs* • All professionals reported lack of formal training in communication.
Orkin, 2020 – Qualitative study	11 Health Care Professionals (8 physicians, 2 nurses, 1 social worker) of following expertise: • 2 complex care • 3 paediatric medicine • 2 respiratory medicine • 1 paediatric haematology and oncology • 1 critical care • 1 neonatal intensive care • 1 palliative care	Qualitative content-analysis study comprising demographic surveys and individual semi-structured interviews.	*Barriers perceived by HCPs* • Many caregivers had never heard of the term ACP. • HCP held varied perspective regarding ACP's definition; some felt it was geared towards end-of-life specifically. Others had a more general definition, like understanding the family and their goals. • Some HCPs and parents stated that specific training and capacity building would be beneficial for HCPs. *Facilitators perceived by HCPs* • All HCPs agreed that expertise can enhance ACP conversations.
Cicero-Oneto 2017 – Qualitative study	• 13 paediatric oncologists	Qualitative study with individual, face-to-face, semi-structured, and in-depth interviews.	*Barriers percieved by HCPs* • Oncologists mentioned their own lack of training in psychology and/or palliative care.
GRADE CERQual assessment			
Study design:	+4	3 qualitative studies	
Methodological limitations:	-1	Some methodological limitations. Aim and appropriateness of qualitative evidence: low in 3/3; Study design and theoretical approach: low in 3/3; Sample selection: unclear in 1/3, high in 2/3; Data collection: low in 2/3, unclear in 1/3; Data analysis: low in 3/3; Results: low in 3/3	
Coherence:	0	No concerns on coherence	
Relevance:	0	No concerns on relevance	
Sufficiency of saturation:	0	No concerns on sufficiency of saturation.	
Overall assessment of confidence in findings		**⊕⊕⊕⊖ MODERATE confidence in the evidence**	
Conclusion:		**HCPs mentioned a lack in communication, psychology, palliative care and ACP training. They felt trainings and capacity building would be beneficial, and agreed that expertise can enhance ACP and EOL discussions (3 studies).**	

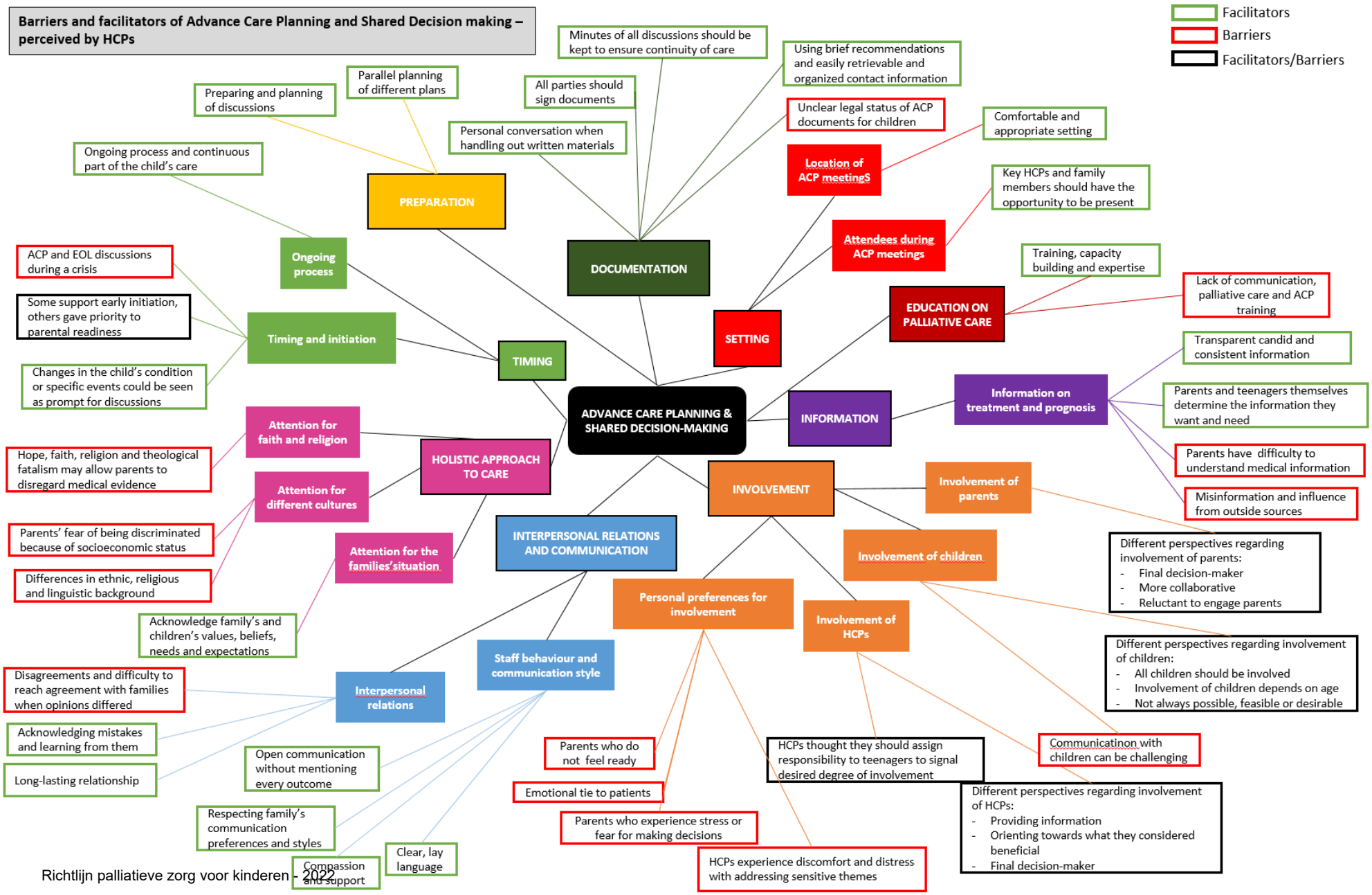
4.2.12 *Samenvatting belemmerende en bevorderende factoren van ACP en gezamenlijke besluitvorming - ouderperspectief*



4.2.13 *Samenvatting belemmerende en bevorderende factoren van ACP en gezamenlijke besluitvorming –kindrperspectief*



4.2.14 *Samenvatting belemmerende en bevorderende factoren van ACP en gezamenlijke besluitvorming –zorg professional rperspectief*



5 Conclusies van evidence

5.1 Effectiviteit van ACP interventies

Effectivity of advance care planning interventions			
Intervention		**Conclusions of evidence**	**Quality of evidence**
Family-centred Advance Care planning	*vs. control or usual care*	↑ completion of a legal statement of treatment preferences among adolescents with *HIV-infection* or *cancer* and their adult surrogates after intervention.	⊕⊖⊖⊖ VERY LOW (2 RCTs)
Family-centred Advance Care planning	*vs. control*	↑ congruence in treatment preferences post-session-2 among adolescents with *HIV-infection* and their adult surrogates in the situations long hospitalization, functional impairment, and mental impairment after intervention. Unclear if effect was significant.	⊕⊖⊖⊖ VERY LOW (1 RCT)
		↑ congruence in treatment preferences at 3 month follow-up among adolescents with *HIV-infection* and their adult surrogates in the situations long hospitalization, functional impairment and mental impairment after intervention. Unclear if effect was significant.	
Family-centred Advance Care planning	*vs. usual care*	↑ congruence in treatment preferences post-session-3 among adolescents with *cancer* and their adult surrogates in the situations long hospitalization, treatment would extend my life, functional impairment, mental impairment, attempting cardiopulmonary resuscitation and mechanical ventilation after intervention. This effect was not significant for the situation attempting cardiopulmonary resuscitation.	⊕⊖⊖⊖ VERY LOW (1 RCT)
Family-centred Advance Care planning	*vs. control*	↑ agreement to limit treatment post-session-2 among adolescents with HIV-infection and their adult surrogates in following situations, long hospitalization and mental impairment after intervention. This effect was not significant in the situation functional impairment.	⊕⊕⊖⊖ LOW (2 RCTs)
Family-centred Advance Care planning	*vs. control*	↑ agreement to limit treatment at 3 month follow-up among adolescents with *HIV-infection and* their adult surrogates in the situation functional impairment, after intervention. This effect was not significant in the situations long hospitalization and mental impairment.	⊕⊕⊖⊖ LOW (2 RCTs)
Family-centred Advance Care planning	*vs. control or usual care*	↑agreement to give family leeway post-session-2/3 among adolescents with *cancer* and their adult surrogates after intervention. This effect was not significant among adolescents with *HIV-infection.*	⊕⊕⊖⊖ LOW (2 RCTs)
Family-centred Advance Care planning	*vs. control*	No significant effect on agreement to give family leeway in decision making at 3 month follow-up among adolescents with *HIV-infection* and their adult surrogates	⊕⊖⊖⊖ VERY LOW (1 RCT)
Family-centred Advance Care planning	*vs. control or usual care*	No significant effect on anxiety at 3 month follow-up among adolescents with *HIV-infection* or *cancer*.	⊕⊖⊖⊖ VERY LOW (2 RCTs)
		No significant effect on anxiety at 3 month follow-up among adult surrogates of adolescents with *HIV-infection* or *cancer.*	
		↓ depression at 3 month follow-up among adolescents with *cancer* after intervention. No significant effect among adolescents with *HIV-infection.*	
		No significant effect on depression at 3 month follow-up among adult surrogates of adolescents with *HIV-infection* or *cancer.*	
		No significant effect on quality of life at 3 month follow-up among adolescents with *HIV-infection* or *cancer.*	
Family-centred Advance Care planning	*vs. usual care*	↑ spiritual well-being at 3 month follow-up among adolescents with *cancer*.	⊕⊖⊖⊖ VERY LOW (1 RCT)

5.2 Belemmerende en bevorderende factoren van ACP en gezamenlijke besluitvorming

5.2.1 Informatievoorziening

Barriers and facilitators of shared decision-making and Advance Care Planning			
Sub-theme	**Perspective**	**Conclusions of evidence**	**Quality of evidence**
Information provision on treatment and prognosis	Parents	Parents expressed the need to know what to expect and **wished complete and unbiased information** about the child's condition, likely outcomes and treatment options (including the option to stop or not initiate treatment).	⊕⊕⊕⊖ MODERATE (6 studies); NICE 2016
		Parents needed **consistent, accurate and understandable information** that is timely and regularly explained, and in accordance with the unique situation of the child (4 studies). When parents lacked medical background or did not understand the complexity of treatment, they felt unable to take decision-making responsibility (3 studies).	⊕⊕⊕⊖ MODERATE (6 studies); NICE 2016
		A minority of parents only wanted to **receive negative information when it was relevant** for a specific decision.	⊕⊕⊖⊖ LOW (1 study)
		Written materials about ACP help parents to determine what they are ready to address.	⊕⊕⊖⊖ LOW (1 study)
	Children	Some children preferred to hear **information from their parents**, and mentioned their parents' and clinicians' central roles in meeting their communication needs.	⊕⊕⊖⊖ LOW (2 studies)
		Children's information **preferences varied and tended to change** as children learned about their condition: • Some children wanted to know everything including prognosis and test results, and needed their HCPs to speak truthfully to them (2 studies). • Some children did not want to receive information (1 study).	⊕⊕⊖⊖ LOW (2 studies)
	Healthcare professionals	Although HCPs mentioned it is complicated to give clear and consistent information due to prognostic uncertainty (3 studies), they acknowledge the need to deliver **transparent, candid and consistent information** to parents (3 studies).	⊕⊕⊕⊖ MODERATE (5 studies); NICE 2016
		Although HCPs prefer **parents and teenagers to determine the type and amount of information** they want and need at different times (2 studies), not fully informing families was perceived as a barrier in ACP discussions (1 study).	⊕⊕⊕⊖ MODERATE (3 studies); NICE 2016
		Some HCPs mentioned that **understanding medical information and prognosis is difficult** for parents (3 studies), especially parents with non-Dutch backgrounds, other HCPs did consider parents **capable of understanding medical information**, because of their knowledge and experience with their child's medical condition (1 study).	⊕⊕⊕⊖ MODERATE (3 studies)
		Misinformation or influence from outside sources and people were mentioned as barriers.	⊕⊕⊖⊖ LOW (1 study)

Uncertainty about diagnosis and prognosis	Parents	Parents mentioned that **uncertainty on the child's prognosis can be frustrating and confusing** during ACP and EOL discussions, as it often led to guesses or disagreement among HCPs.	⊕⊕⊕⊖ MODERATE (3 studies); NICE 2016
		Parents mentioned that **uncertainties on diagnosis and prognosis need to be taken into account** as an aspect of the child's unique situation and need to be explored by HCPs to develop contingent plans.	⊕⊕⊕⊖ MODERATE (3 studies); NICE 2016
		Parents mentioned that a **prognosis given in terms of death and not wanting to see their child suffer anymore are helpful** for making decisions.	⊕⊕⊖⊖ LOW (1 study)
	Children	Not reported	No studies
	Healthcare professionals	Not reported	No studies

5.2.2 Betrokkenheid

Barriers and facilitators of shared decision-making and Advance Care Planning			
Sub-theme	**Perspective**	**Conclusions of evidence**	**Quality of evidence**
Involvement of parents	Parents	Parents wanted to be acknowledged as the **expert of their child**, and mentioned the importance of **feeling respected, accepted and supported** during decision-making in ACP and EOL discussions.	⊕⊕⊕⊖ MODERATE (12 studies); NICE 2016
		Parents had different perspectives regarding their level of involvement in ACP and EOL decision-making: • Some parents wanted to make decisions **in collaboration with HCPs** (6 studies). • Some parents wanted to be the **final decision-maker** (2 studies). • Some parents **did not want to be involved** and wanted HCPs to make the decisions (2 studies). • Some parents felt like they **did not have a choice**, as there was only one option due to the treatment process (2 studies).	⊕⊕⊕⊖ MODERATE (7 studies); NICE 2016
		Parents saw themselves as the **best advocates** for their child, but **struggled to define their child's best interest**.	⊕⊕⊖⊖ LOW (1 study); NICE 2016
	Children	Not reported	No studies
	Healthcare professionals	HCPs had different perspectives regarding the level of involvement of parents in ACP and EOL decision-making: • Some HCPs felt that parents should be the **final decision-makers** (3 studies). • Some HCPs felt the decision-making process should be **more collaborative with parents and children**, and parents should be acknowledging as their child's expert and translator (5 studies). • Some HCPs were **reluctant to engage parents** in ACP or EOL decision-making because they felt it would burden parents giving them too much responsibility (3 studies), or because they thought they already knew how parents felt about these discussions (1 study).	⊕⊕⊕⊖ MODERATE (7 studies); NICE 2016

Involvement of children and young people	Parents	Parents felt that their **child's perspective should be taken into account** when making ACP and EOL decisions.	⊕⊕⊕⊖ MODERATE (3 studies); NICE 2016
		Parents felt that their child could be involved in decision-making, but had different perspectives regarding their level of involvement in ACP and EOL discussions: • Some parents felt children **should be involved** in decision making (2 studies). • Some parents felt the level of involvement is **dependent on the child's age**. They appreciate age-appropriate information, but were sceptical about involving young children, while they thought teenagers should be involved (3 studies). • Some parents wanted to **talk themselves with their children** about sensitive issues (1 study). • Some parents wanted their child to be **treated as normally as possible** (1 study).	⊕⊕⊕⊖ MODERATE (5 studies); NICE 2016
	Children	Children had different perspectives on their own level of involvement in ACP and EOL decision-making: • Some children wanted to be involved in **making smaller decisions**, and not in making "big" decisions. • Some children **did not want to make decisions** when they were too ill or in pain. • Some children felt **ignored, worried and powerless when not involved** in EOL discussions. • Some children were more comfortable with **their parents or HCPs making decisions**, since they always act in their best interest.	⊕⊕⊖⊖ LOW (1 study); NICE 2016
		Although some children perceived being involved in EOL discussions as **satisfying and comforting**, others felt this could be **overwhelming and upsetting**.	⊕⊕⊖⊖ LOW (1 study); NICE 2016
	Healthcare professionals	HCPs had different perspectives regarding the level of involvement of children in ACP and EOL decision-making: Some HCPs felt that children of all ages should participate in discussions (4 studies), other felt cognitively capable older children should be involved, but found it **difficult to specify an age** at which the child should be informed about their prognosis (2 studies). • Some HCPs felt that involving teenagers might **not be always possible, feasible or desirable**, like when internationally agreed protocols are in place, when it could impose harm, death or suffering, or when involvement from other professionals was prioritised (1 study).	⊕⊕⊕⊖ MODERATE (5 studies); NICE 2016
		HCPs mentioned **challenges when communicating with children,** including understanding their perspectives and the role of parents as gatekeepers and influencing their child's choices (4 studies).	⊕⊕⊕⊖ MODERATE (4 studies)
Involvement of HCPs	Parents	Not reported	No studies
	Children	Not reported	No studies
	Healthcare professionals	HCPs had different perspectives regarding their level of involvement in ACP and EOL decision-making: • Some HCPs felt their role was **solely providing information**, enabling parents to make the best decisions (1 study).	⊕⊕⊕⊖ MODERATE (2 studies); NICE 2016

		• Some HCPs felt they had an **"orienting" role**, directing parents towards what they thought is beneficial for the child (1 study). • Some HCPs mentioned **making the final decision alone in certain situations** when they wanted to protect the child from further suffering (1 study).	
		HCPs felt they should take the lead about what to disclose from teenagers, and **assigned responsibility to the teenager for signalling their desired degree of involvement** in decision-making (1 study).	⊕⊕⊖⊖ LOW (1 study)
Personal facilitators/barriers to ACP/EOL decision-making	Parents	Parents experienced difficulty in EOL and ACP decision-making because: • Parents **did not feel ready** to make decision because they could not acknowledge the child's situation, wanted to focus on the present, suppressed burdensome thoughts and had intense emotions (4 studies). • Parents **did not want their child to suffer** but also wanted to do everything possible to try to increase the length of their child's life (3 studies). • Parents **could not foresee consequences** of some decisions and would feel regret (2 studies). • Parents wanted to **keep options open**, because they were afraid to bind themselves when their preferences might change (2 studies).	⊕⊕⊕⊖ MODERATE (7 studies); NICE 2016
		Parents' **decisions about future care were influenced by past experiences** with the child's care. Parents mentioned decision-making was easier when these experiences were good and when they had clear short-term disease related goals.	⊕⊕⊕⊖ MODERATE (2 studies)
	Children	Not reported	No studies
	Healthcare professionals	HCPs experienced **discomfort and distress with addressing sensitive themes and assessing the child's best interest** during and after ACP and EOL decision-making.	⊕⊕⊕⊖ MODERATE (6 studies)
		HCPs mentioned that parents had difficulty with making EOL and ACP decisions because **parents experienced stress or fear** for making decisions.	⊕⊕⊕⊖ MODERATE (2 studies)
		HCPs mentioned an **emotional tie to patients** as a barrier for EOL discussions.	⊕⊕⊖⊖ LOW (1 study)
		HCPs mentioned that parents had difficulty with making EOL and ACP decisions because parents **did not feel ready** to make decisions because they could not acknowledge their child's situation, wanted to focus on the present or had unrealistic expectations.	⊕⊕⊖⊖ LOW (1 study)

5.2.3 Interpersoonlijke relaties en communicatie

Barriers and facilitators of shared decision-making and Advance Care Planning			
Sub-theme	**Perspective**	**Conclusions of evidence**	**Quality of evidence**
Staff behaviour and communication style	Parents	Parents valued **open, honest and clear lay language and information**, even if it was uncertain or potentially upsetting.	⊕⊕⊕⊖ MODERATE (4 studies); NICE 2016

		Parents found it helpful when information was provided by **a trusted HCP**, and mentioned frequent changes in HCPs as a barrier for communication.	⊕⊕⊕⊖ MODERATE (2 studies); NICE 2016
		Parents considered using **interpreters for non-English speakers** helpful.	⊕⊕⊕⊖ MODERATE (1 study)
		Parents mentioned the importance of **open and reassuring nonverbal cues** including sitting, making eye contact, smiling, and maintaining an open posture.	⊕⊕⊕⊖ MODERATE (1 study); NICE 2016
	Healthcare professionals	HCPs mentioned the importance of **using clear, lay language** that is consistent and unambiguous.	⊕⊕⊕⊖ MODERATE (3 studies); NICE 2016
		HCPs mentioned the importance of **being compassionate and supportive**, listen actively to families, thinking before you speak and knowing what not to say, such as 'things happen for a reason'.	⊕⊕⊕⊖ MODERATE (2 studies); NICE 2016
		HCPs mentioned the importance of respecting the **individual family's communication preferences and styles**.	⊕⊕⊖⊖ LOW (1 study); NICE 2016
		HCPs stated that **open communication** is important for involving children in decision-making, but mentioned that not every outcome has to be explicitly mentioned.	⊕⊕⊖⊖ LOW (1 study); NICE 2016
Family-provider relationship	Parents	Parents mentioned the importance of **long-lasting, trusted relationships** with HCPs.	⊕⊕⊕⊖ MODERATE (5 studies); NICE 2016
		Relationships were considered **fragile and were easily compromised** when parents felt not heard by HCPs. This included situations in which parents felt that their child's quality of life was underestimated or felt that they were excluded from conversations about the child.	⊕⊕⊕⊖ MODERATE (4 studies); NICE 2016
		When parents felt **part of the multidisciplinary team** when discussing care goals, this positively influenced their openness to share perspectives (1 study). Involvement of a subspecialty palliative care team was considered helpful (1 study).	⊕⊕⊖⊖ LOW (2 studies); NICE 2016
		Parents sometimes experienced **disagreements with HCPs**. Not all disagreements were considered disturbing, it could also make parents reconsider options. Disturbing disagreements arose when: parents still wanted 'everything to be done' but HCPs thought it was futile; when decisions had to be made under time pressure because of acute deterioration of the child's condition and when parents wanted a treatment to be forgone when there was still a realistic chance of improvement.	⊕⊕⊖⊖ LOW (1 study); NICE 2016
		Parents preferred HCPs who are **conscious of the family's sensitivity and familiarity** with the child, and desired HCPs who are **flexible in their care plans** based on the family's wishes.	⊕⊕⊖⊖ LOW (1 study)
	Healthcare professionals	HCPs mentioned a **long-lasting treatment relationship** with parents as a facilitator for decision-making.	⊕⊕⊕⊖ MODERATE (4 studies); NICE 2016
		HCPs experienced **disagreements with families** (3 studies). Not all disagreements were considered disturbing, it could also challenge HCPs to think of more suitable alternatives. Disturbing disagreements arose when: parents were unrealistic or	⊕⊕⊕⊖ MODERATE (3 studies); NICE 2016

		overly optimistic and when parents wanted a treatment to be forgone when there was still a realistic chance of improvement (1 study).	
		HCPs mentioned that it can be **difficult to reach agreement** with parents and/or children when opinions about ACP or EOL decisions differed.	⊕⊕⊕⊖ MODERATE (3 studies); NICE 2016
		Acknowledging mistakes and learning from it is considered helpful by HCPs.	⊕⊕⊖⊖ LOW (1 study)

5.2.4 Holitistische benadering van zorg

Barriers and facilitators of shared decision-making and Advance Care Planning			
Sub-theme	**Perspective**	**Conclusions of evidence**	**Quality of evidence**
Attention for the families' situation	Parents	Parents mentioned the need for HCPs to **understand and acknowledge the impact on daily life of the child and family** including psychological and social issues, such as work, school and other children, rather than simply focusing on medical problems only.	⊕⊕⊕⊖ MODERATE (7 studies); NICE 2016
		Parents mentioned the importance of HCPs **understanding family's individual values, believes, hopes, goals and fears** for making ACP and EOL decisions and preparing parents for worst-case scenarios.	⊕⊕⊕⊖ MODERATE (2 studies); NICE 2016
	Healthcare professionals	HCPs mentioned the importance of acknowledging the **values, beliefs, needs and expectations of the child and their family** in the context of the child's illness for making ACP and EOL decisions.	⊕⊕⊖⊖ LOW (2 studies); NICE 2016
Provision of hope	Parents	Parents mentioned the **importance of maintaining hope** by HCPs.	⊕⊕⊕⊖ MODERATE (4 studies)
		Parents **varied in their preferences of how HCPs should support hope**: although some wanted them to emphasize positives or wanted them to express an intention to cure the child, others mentioned the importance of avoiding false hopes.	⊕⊕⊕⊖ MODERATE (1 study)
	Healthcare professionals	Not reported	No studies
Attention for different cultures	Parents	Parents desired HCPs to be **culturally sensitive** in delivering information.	⊕⊕⊕⊖ MODERATE (1 study); NICE 2016
		Differences in cultural background, causing disagreement with HCPs, was perceived as a barrier by parents.	⊕⊕⊕⊖ MODERATE (1 study); NICE 2016
	Healthcare professionals	HCPs mentioned that EOL discussions can be complicated by **differences in ethnic, religious and/or linguistic backgrounds**, and stated the importance of having cultural humility and curiosity, and being aware of cultural awareness and language.	⊕⊕⊖⊖ LOW (2 studies); NICE 2016
		One HCP mentioned **parents' fear of being discriminated because of socioeconomic status** as a barrier for decision-making.	⊕⊕⊖⊖ LOW (1 study); NICE 2016

Attention for faith and religion	Parents	Parents expressed that **hope, faith, religion and praying influenced decision-making**: • Faith and belief in god empowered parents to make or abstain from decisions, guarded against regret and aided joint decision-making with their spouse, especially when decisions became more complicated or consequential (2 study). • Belief in miracles sometimes pushed parents to pursue or de-escalate aggressive treatment. It could make parents not accept poor prognosis, because they believed god would keep their child miraculously alive (1 study).	⊕⊕⊕⊖ MODERATE (2 studies); NICE 2016
		Parents sometimes felt **HCPs did not understand their believes**. They did not expect HCPs to surrender control to god, but were pleased when HCPs acknowledged their believes.	⊕⊕⊖⊖ LOW (1 study); NICE 2016
	Healthcare professionals	HCPs worried that **hope, faith, religion and theological fatalism allowed parents to disregard medical evidence** in decision-making.	⊕⊕⊕⊖ MODERATE (2 studies); NICE 2016

5.2.5 Timing

Barriers and facilitators of shared decision-making and Advance Care Planning			
Sub-theme	**Perspective**	**Conclusions of evidence**	**Quality of evidence**
Timing and initiation	Parent	Although some parents find it **difficult to define the right timing** of initiating ACP and EOL discussions and felt timing might never be right (3 studies), most parents do support early initiation (4 studies), while some preferred delaying or tempering ACP and EOL discussions (1 study).	⊕⊕⊖⊖ LOW (6 studies); NICE 2016
		Parents expressed the need to **feel ready before starting to engage** in ACP and EOL discussions, without feeling pressured.	⊕⊕⊖⊖ LOW (6 studies); NICE 2016
		Parents considered it a **missed opportunity when physicians did not initiate** ACP or EOL discussions.	⊕⊕⊖⊖ LOW (2 studies); NICE 2016
		Parents found it helpful to **regularly repeat offering** ACP and EOL discussions.	⊕⊕⊖⊖ LOW (2 studies); NICE 2016
		Parents mentioned that wrong timing of initiating ACP or EOL discussions includes shortly after breaking bad news (1 study), shortly after overcoming a crisis (1 study), or when the child is in an 'unstable' condition (1 study).	⊕⊕⊖⊖ LOW (2 studies)
	Healthcare professional	Although some HCPs supported initiation of ACP discussions **as early as possible**, ideally at time of diagnosis or when the child is in a period of relative wellness (3 studies), others gave priority to parent's readiness before starting ACP or EOL discussions, and mentioned **timing should be right for family** rather than HCPs and discussions should go at the parents' pace (6 studies).	⊕⊕⊖⊖ LOW (6 studies); NICE 2016
		Heath care professionals suggested that **changes in the child's condition or specific events**, such as failing of treatment, could be seen as a prompt for ACP and EOL discussions.	⊕⊕⊖⊖ LOW (4 studies); NICE 2016

		HCPs mentioned that a wrong timing of initiating ACP discussions is during a crisis.	⊕⊕⊖⊖ LOW (2 studies)
		HCPs mentioned that **readiness could be difficult to assess**, and cues could be used, such as parents asking questions that could open-up discussions.	⊕⊕⊖⊖ LOW (1 study)
Ongoing process	Parent	Parents mentioned that ACP and EOL discussions should be an **ongoing process and a continuous part of the child's care**.	⊕⊕⊕⊖ MODERATE (4 studies); NICE 2016
	Healthcare professional	HCPs mentioned that ACP and EOL discussions should be an **ongoing process and a continuous part of the child's care**.	⊕⊕⊕⊖ MODERATE (3 studies); NICE 2016
Sufficient time for decision-making	Parent	Parents mentioned the need to have **sufficient time between receiving information and making decisions**, to process information and ask questions.	⊕⊕⊕⊖ MODERATE (2 studies)
	Healthcare professionals	Not reported	No studies

5.2.6 Voorbereiding

Barriers and facilitators of shared decision-making and Advance Care Planning			
Sub-theme	**Perspective**	**Conclusions of evidence**	**Quality of evidence**
Voorbereiding	Parents	Not reported	No studies
	Healthcare professionals	HCPs mentioned **preparation and planning of ACP and EOL discussions** as helpful (2 studies), such as having an agenda, assigning an appropriate person to lead the discussion, and **parallel planning to prepare different plans** for potential outcomes (1 study).	⊕⊕⊖⊖ LOW (2 study); NICE 2016

5.2.7 Documentatie

Barriers and facilitators of shared decision-making and Advance Care Planning			
Sub-theme	**Perspective**	**Conclusions of evidence**	**Quality of evidence**
Documentatie	Parents	Parents preferred a **personal conservation** when handing out supplementary written materials.	⊕⊕⊕⊖ MODERATE (2 studies)
		Parents agreed that **all parties should sign the documents** and prefer to keep minutes of all discussion to **ensure continuity** of the advance care planning.	⊕⊕⊖⊖ LOW (1 study); NICE 2016
	Healthcare professionals	HCPs preferred a **personal conservation** when handing out supplementary written materials.	⊕⊕⊖⊖ LOW (1 study)
		HCPs agreed that **all parties should sign the documents** and prefer to keep minutes of all discussion to **ensure continuity** of the advance care planning.	⊕⊕⊖⊖ LOW (1 study); NICE 2016
		HCPs want to receive and be informed about advance care planning documents in a **personal conversation**, and recommend using brief recommendations for	⊕⊕⊖⊖ LOW (1 study); NICE 2016

		emergencies, supplemented by larger advance directives with **easily retrievable and organised contact information**.	
		HCPs worried about the **unclear legal status** of advance care planning documents for children.	⊕⊕⊖⊖ LOW (1 study)

5.2.8 Setting

Barriers and facilitators of shared decision-making and Advance Care Planning			
Sub-theme	**Perspective**	**Conclusions of evidence**	**Quality of evidence**
Location	Parents	Parents mentioned the importance of a **comfortable and appropriate setting** including a quiet room with adequate seating and having enough time for the discussion.	⊕⊕⊕⊖ MODERATE (3 studies); NICE 2016
	Healthcare professionals	HCPs mentioned the importance of a **comfortable and appropriate setting** including a quiet room with adequate seating, without distractors such as mobile phones and pagers, possibly away from the hospital or at home, and having enough time for the discussion.	⊕⊕⊕⊖ MODERATE (3 studies); NICE 2016
Attendees	Parents	All key family members and HCPs should be given the **opportunity to be present** during ACP discussions. Additionally, family support should be ensured by inviting an uninvolved “listener” like a friend or nurse.	⊕⊕⊕⊖ MODERATE (3 studies)
	Healthcare professionals	All key HCPs and family members should be given the **opportunity to be present**, and family support should be ensured.	⊕⊕⊖⊖ LOW (1 study)

5.2.9 Ondersteuning

Barriers and facilitators of shared decision-making and Advance Care Planning			
Sub-theme	**Perspective**	**Conclusions of evidence**	**Quality of evidence**
Support	Parents	Parents mentioned **being connected to family-members and other parents in similar situations** as valuable for making-decisions.	⊕⊕⊕⊖ MODERATE (4 studies)
	Healthcare professionals	Not reported	No studies

5.2.10 Onderwijs

Barriers and facilitators of shared decision-making and Advance Care Planning			
Sub-theme	**Perspective**	**Conclusions of evidence**	**Quality of evidence**
Education	Parents	Parents felt that communication **trainings, capacity building and education about ACP would be beneficial** for HCPs.	⊕⊕⊕⊖ MODERATE (3 studies)
		Parents disapproved **lack of experience or knowledge** of HCPs.	⊕⊕⊖⊖ LOW (1 study)

	Healthcare professionals	HCPs mentioned a lack in communication, psychology, palliative care and ACP training. They felt **trainings and capacity building would be beneficial**, and agreed that expertise can enhance ACP and EOL discussions.	⨁⨁⨁⊖ MODERATE (3 studies)

6 Aanbevelingen uit Richtlijnen

Shared decision-making and Advance Care Planning	
National Institute for Health and Care Excellence (NICE). End of life care for infants, children and young people with life-limiting conditions: planning and management. 2016	
Recommendation	**Level of evidence[1]**
Shared decision-making and advance care planning	
Clinical evidence: 11 studies were identified for inclusion. Different (combinations of) perspectives of barriers and facilitators on decision making were studied: perspective of parents caring for a child with a life-limiting condition or whose child had died due to a life-limiting condition (five studies); perspective of health care professionals (2 studies); perspective of children or young people living with a life-limiting condition (1 study); Perspective of both parents and child or young person living with a life-limiting condition (1 study); perspective of both parents and child or young person as well as the physicians involved in their care (1 study). *Moderate to very low quality evidence was presented in the review. The main reasons leading to downgrading of the evidence included limitations in how the data were collected, a low response rate from participants, self-selection bias and an awareness that people who chose to participate may differ from those who refused to be interviewed. On the other hand, in some studies participants were selected by the physicians who provided care to the child, and those who were not selected may have provided a different perspective.*	
Recognise that children and young people with life-limiting conditions and their parents or carers have a central role in decision-making and care planning.	Level B/C: Moderate to low quality evidence
Discuss and regularly review with children and young people and their parents or carers how they want to be involved in making decisions about their care, because this varies between individuals, at different times, and depending on what decisions are being made.	Level B/C: Moderate to low quality evidence
Explain to children and young people and to their parents or carers that their contribution to decisions about their care is very important, but that they do not have to make decisions alone and the multidisciplinary team will be involved as well.	Level B/C: Moderate to low quality evidence
When developing plans for the care of the child or the young person with a life-limiting condition, use parallel planning to take account of possible unpredictability in the course of the condition.	Level B/C: Moderate to low quality evidence
Manage transition from children's to adult's services in line with the NICE guideline on transition from children's to adult's services.	Level B/C: Moderate to low quality evidence

Develop and record an Advance Care Plan at an appropriate time for the current and future care of each child or young person with a life-limiting condition. The Advance Care Plan should include: demographic information about the child or young person and their family
• up-to-date contact information for:
  o the child or young person's parents or carers and
  o the key professionals involved in care
• a statement about who has responsibility for giving consent
• a summary of the life-limiting condition
• an agreed approach to communicating with and providing information to the child or young person and their parents or carers
• an outline of the child or young person's life ambitions and wishes, for example on:
  o family and other relationships
  o social activities and participation
  o education
  o how to incorporate their religious, spiritual, and cultural beliefs and values into their care
• a record of significant discussions with the child or young person and their parents or carers
• agreed treatment plans and objectives
• education plans, if relevant
• a record of any discussions and decisions that have taken place on:
  o preferred place of care and place of death
  o organ and tissue donation
	Level B/C: Moderate to low quality evidence

○ management of life-threatening events, including plans for resuscitation or life support ○ specific wishes, for example on funeral arrangements and care of the body • a distribution list for the Advance Care Plan.	
Begin discussing an Advance Care Plan with parents during the pregnancy if there is an antenatal diagnosis of a life-limiting condition. For each individual think about who should take part in the discussion, for example: • obstetricians • midwives • neonatologists • specialists in the life-limiting condition • a member of the specialist paediatric palliative care team	Level B/C: Moderate to low quality evidence
Develop and regularly review Advance Care Plans: • with relevant members of the multidisciplinary team and • in discussion with the child or young person and their parents or carers.	Level B/C: Moderate to low quality evidence
When developing the Advance Care Plan, take account of the beliefs and values of the child or young person and their parents or carers.	Level B/C: Moderate to low quality evidence
Explain to children and young people and their parents or carers that Advance Care Planning should: • help them be involved in planning their care and give them time to think about their views carefully • help them to understand the life-limiting condition and its management • help to prepare for possible future difficulties or complications • support continuity of care, for example if there are changes in the professionals involved or in the care setting (such as a hospital admission or discharge).	
Share the Advance Care Plan with the child or young person and their parents or carers (as appropriate), and think about which professionals and services involved in the individual child or young person's care should also see it, for example: • GPs • hospital consultants • hospices • respite centres • nursing services (community or specialist) • school and other education services • ambulance services	Level B/C: Moderate to low quality evidence
Update the Advance Care Plan when needed, for example if: • new professionals become involved • the care setting changes (for example hospital admission or discharge) • the child or young person and their parents or carers move home. Discuss the changes with the child or young person (if appropriate) and their parents or carers.	Level B/C: Moderate to low quality evidence
Share the Advance Care Plan with everyone involved each time it is updated.	Level B/C: Moderate to low quality evidence
When making an Advance Care Plan, discuss with the child or young person and their parents or carers: • the nature of the life-limiting condition, its likely consequences and its prognosis • the expected benefits and possible harms of the management options.	Level B/C: Moderate to low quality evidence
Be aware that all children and young people with life-limiting conditions should have an Advance Care Plan in their medical record, and that this should not be confused with a do-not-attempt-resuscitation order.	Level B/C: Moderate to low quality evidence

Be aware that any existing resuscitation plan for a child or young person may need to be changed in some circumstances, for example if they are undergoing general anaesthesia.	Level B/C: Moderate to low quality evidence
Attempt resuscitation for children and young people with life-limiting conditions, unless there is a 'do not attempt resuscitation' order in place	Level B/C: Moderate to low quality evidence
• Be aware that discussing the Advance Care Plan can be distressing for children and young people who are approaching the end of life and their parents or carers, and they may: • be reluctant to think about end of life care • have difficulties discussing end of life care with the professionals or with one another • have differences of opinion about the care plan.	Level B/C: Moderate to low quality evidence
When making or reviewing the Advance Care Plan for a child or young person approaching the end of life, talk to the parents or carers about the care and support they can expect when the child or young person dies. Discuss their personal needs and feelings about this.	Level B/C: Moderate to low quality evidence
When a child or young person is approaching the end of life, think about and discuss with them and their parents or carers their specific support needs. Review these needs regularly.	Level B/C: Moderate to low quality evidence

[1] **Level of evidence adapted from GRADE**
A: High; further research is very unlikely to change confidence in the estimate of the clinical effect.
B: Moderate; Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
C: Low or very low; further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain.

3. PSYCHOSOCIALE ZORG

Inhoudsopgave

1 Uitgangsvragen

1.1 Psychologische interventies

Vraag 1A: Wat is de effectiviteit van psychologische interventies voor kinderen tussen de 0 en 18 jaar in de palliatieve fase?
P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Psychologische interventies
C: Standaardbehandeling of placebo
O: Kwaliteit van leven, psychosociale uitkomsten

Vraag 1B: Wat is de effectiviteit van psychologische interventies voor familieleden en verzorgers van kinderen tussen 0 en 18 jaar in de palliatieve fase?
P: Familieleden en verzorgers van kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Psychologische interventies
C: Geen behandeling/placebo
O: Kwaliteit van leven, psychosociale uitkomsten

1.2 Sociale en praktische ondersteuning

Vraag 2: Welke sociale en praktische ondersteuning wordt als effectief beschouwd door kinderen tussen 0 en 18 jaar in de palliatieve fase en hun familieleden en verzorgers?
P: kinderen tussen 0 en 18 jaar in de palliatieve fase en hun familieleden en verzorgers
I: sociale en praktische ondersteuning
C: -
O: kwaliteit van leven, psychosociale uitkomsten

1.3 Culturele, spirituele en religieuze ondersteuning

Vraag 3: Welke culturele, spirituele en religieuze ondersteuning wordt als effectief beschouwd door kinderen tussen 0 en 18 jaar in de palliatieve fase en hun familieleden en verzorgers?
P: kinderen tussen 0 en 18 jaar in de palliatieve fase en hun familieleden en verzorgers
I: spirituele en religieuze ondersteuning
C: -
O: kwaliteit van leven, psychosociale uitkomsten

2 Resultaten van het literatuuronderzoek

Jaar	Bibliografie	Studie karakteristieken
1A: Wat is de effectiviteit van psychologische interventies voor kinderen tussen de 0 en 18 jaar in de palliatieve fase?*		
2019	***National institute for health and care Excellence (NICE).***The epilepsies, the diagnosis and management in adults and children in primary and secondary care.2019 (previous versions, 2012,2013,2015, 2018)[1]	Richtlijn kinderen en volwassenen
2019	***Rosenberg AR et al.*** Hope and benefit finding: Results from the PRISM randomized controlled trial. Pediatr Blood Cancer 2019 66 (1): e27485	RCT kinderen
2019	***Steineck A et al.*** A Psychosocial Intervention's Impact on Quality of Life in AYAs with Cancer: A Post Hoc Analysis from the Promoting Resilience in Stress Management (PRISM) Randomized Controlled Trial. Children (Basel) 2019 6 (11)	RCT kinderen
2014	***Goldbeck L et al.*** Psychological interventions for individuals with cystic fibrosis and their families. Cochrane Database of Systematic Reviews 2014 6)	SR van RCTs kinderen en ouders
1B: Wat is de effectiviteit van psychologische interventies bij familieleden en verzorgers van kinderen tussen 0 en 18 jaar in de palliatieve fase?*		
2016	***National institute for health and care Excellence (NICE).*** End of life care for infants, children and young people: planning and management. 2016[1]	Richtlijn kinderen
2019	***Rosenberg AR et al.*** Effect of the Promoting Resilience in Stress Management Intervention for Parents of Children With Cancer (PRISM-P): A Randomized Clinical Trial. JAMA Netw Open 2019 2 (9): e1911578	RCT ouders
2015	***Eccleston C et al.*** Psychological interventions for parents of children and adolescents with chronic illness. Cochrane Database of Systematic Reviews 2015 4):	SR van RCTS ouders
2014	***Goldbeck L et al.*** Psychological interventions for individuals with cystic fibrosis and their families. Cochrane Database of Systematic Reviews 2014 6):	SR van RCTs kinderen en ouders
2: Welke sociale en praktische ondersteuning wordt als effectief beschouwd door kinderen tussen 0 en 18 jaar in de palliatieve fase en hun familieleden en verzorgers?*		
2016	***National Institute for Health and Care Excellence (NICE).*** End of life care for infants, children and young people with life-limiting conditions: planning and management. 2016	Richtlijn kinderen
3: Welke culturele, spirituele en religieuze ondersteuning wordt als effectief beschouwd door kinderen tussen 0 en 18 jaar in de palliatieve fase en hun familieleden en verzorgers?*		
2016	***National Institute for Health and Care Excellence (NICE).*** End of life care for infants, children and young people with life-limiting conditions: planning and management. 2016	Richtlijn kinderen
2016	***Borjalilu S et al.*** Spiritual care Training for Mothers of Children with Cancer: Effects on Quality of Care and Mental Health of Caregivers. Asian Pac J Cancer Prev, 17 (2), 545-552, 2016 [1]	RCT ouders
2016	***Beheshtipour N et al.*** The Effect of Educational-spiritual Intervention on The Burnout of The Parents of School Age Children With Cancer: A Randomized Controlled Clinical Trial. IJCBNM January 2016; Vol 4,No 1[1]	RCT ouders

[1]RCT is uit volgend systematische review gehaald: Robert R et al. S Spiritual assessment and spiritual care offerings as a standard of care in pediatric oncology: A recommendation informed by a systematic review of the literature. Pediatr Blood Cancer 2019 66 (9):e27764.

*systematisch gezocht, zie: bijlage 7 zoekverantwoording – search 1

3 Evidence tabellen

3.1 Psychologische interventies

3.1.1 Effectiviteit van psychologische interventies voor kinderen in de palliatieve fase

Effectivity of psychological interventions for children in the palliative phase from 0 to 18 years				
Rosenberg AR et al. Hope and benefit finding: Results from the PRISM randomized controlled trial. Pediatr Blood Cancer 2019 66 (1): e27485				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: Parallel Randomized controlled trial Setting: 1 centre, USA Duration: 6- month follow-up Study years: Jan 2015 – October 2016 Protocol published in register: Protocol registered in clinicaltrials.gov: NCT02340884	Number and type of participants: *A total of 92 Adolescents and Young Adults with cancer receiving systemic chemotherapy.* • Intervention group: 50 – 1 patient who was not fluent in English and 1 patient (2%) who did not complete baseline survey = 48 • Control group: 50 – 6 (12%) patients who did not complete baseline survey = 44 Age at baseline: • Intervention group: Range 12-17 yrs.: 35 (73%) Range 18-25 yrs.: 13 (27%) • Control group: Range 12-17 yrs.: 32 (73%) Range 18-25 yrs.: 12 (27%) Sex at baseline • Intervention group: M: 32 (67%), F: 16 (33%) • Control group: M: 20 (45%), F: 24 (55%) Race at baseline): • Intervention group: Non-white: 15 (31%), White: 33 (69%) • Control group: Non-white: 19 (43%), White: 25 (57%) Diagnosis at baseline: • Intervention: Leukaemia/Lymphoma: 30 (63%)	Type of intervention: Promoting Resilience in Stress Management (PRISM): PRISM targets skills in stress management i.e. breathing, relaxation, awareness of stressors; goal-setting i.e. identifying Specific measurable and actionable goals; cognitive-restructuring i.e. identifying 'negative self-talk; and benefit-finding i.e. finding meaning or benefit from difficult situations. PRISM intervention consists of four 30 to 50 minute 1 on 1 sessions every other week delivered by non-clinical college graduates. An optional fifth session consists of a facilitated family meeting where participants shared skills with family and friends. Type of control: Psychosocial Usual Care (UC): An assigned social worker maintained a relationship with the patient and his or her family throughout the study. Social workers routinely conduct a psychosocial assessment at the time of diagnosis and continue to provide services ranging from behavioural health support to financial support. Patients had access to referral based services e.g. psychologist/psychiatrist etc.	Outcome definitions: **Benefit-finding:** The Benefit Finding Scale for children (adapted by paediatric psychosocial clinicians from the benefit finding scales used among adult patients with cancers). Scale depicts potential benefit of illness (10 items) and potential burdens (10 items). All were answered a 5 point Likert scale. Score range is 12-50, higher score indicate higher benefit-finding. Mean score was 37, suggesting a Mean Clinically Importance Difference (MCID) of 3.9 **Hope finding:** Hope scale measures hopeful patterns of thought. • Pathways; individuals perceived ability to generate a route to his her goals. • Agency: perceived ability and maintain actions necessary to reach a goal. It is scored on an 8 point Likert scale. Score is ranging from 12-48, higher scores indicating greater levels of hopeful thought patterns. Mean score is 25 suggesting a MCID of 1.5 **Goal-setting skills:** Open-ended questions about participant 'goals' i.e. please give an example of a goal you hope to accomplish over the next month. Goals were scored based on how SMART the goals were. Score range 1-9) Results (per outcome) **Benefit-finding scores 6 month follow-up:** Estimated Mean difference $_{\text{intervention – control}}$: 3.1 (95% CI 0.0 to 6.2), p = 0.05, d = 0.4 (effect-size) PRISM participants' benefit-finding score increased an estimated 3.1 points more than UC participant. **Hope-finding scores at 9-month follow-up** *Total scores:* Estimated Mean difference $_{\text{intervention – control}}$: 3.6 (95% CI 0.7 to 6.4)), p = 0.01, d = 0.6 (effect-size) PRISM participant hope scores improved *Subscales:*	Strengths: Limitations: • Result of study outcomes for adolescents (13-17) and young adults (18-25) were not distinguished. • Generalizability is limited as the study was conducted at a large medical centre, with mostly white, English speaking AYAs • Results in abstracts are not in line with result in full-text. Range of age for adolescents is 13-17 in abstract and 12-17 in results. • Lack of power to confirm statistical significance. **Risk of bias** A. Selection bias: low risk Reason: A study statistician constructed the randomizations using permuted blocks of varying sizes, stratified by age. Study staff were blinded prior to the randomization. B. Attrition bias: low risk Reason: Outcomes of all 92 participants were assessed. C. Performance bias High Reason: Unclear whether participants and parents were

	Central Nervous System (CNS): 3 (7%) Non-CNS solid Tumour: 15 (3%) Advanced Cancer: 10 (21%) • Control: Leukaemia/Lymphoma: 27 (61%) Central Nervous System (CNS): 3 (7%) Non-CNS solid Tumour: 14 (32%) Advanced Cancer: 14 (32%)		EMD agency subscale: 1.8 (95% CI 0.1 to 3.5), p = 0.04 and d = 0.5 EMD pathway subscale: 1.8 (95% CI 0.2 to 3.4), p = 0.05, d = 0.5 PRISM participant hope scores improved **Goal-setting skills;** EMD $_{\text{intervention – control}}$: -0.5 points (95% CI, -1.2, 0.3), p = 0.23, d = -0.3 No changes in endorsed qualitative goals in either group, nor appreciable differences in score distributions.	blinded from receiving either intervention or control (seems almost impossible. <u>D. Detection bias</u> low risk Reason: Staff collecting outcome data remained blinded to the assignment.

Effectivity of psychological interventions for children in the palliative phase from 0 to 18 years				
Steineck A et al. A Psychosocial Intervention's Impact on Quality of Life in AYAs with Cancer: A Post Hoc Analysis from the Promoting Resilience in Stress Management (PRISM) Randomized Controlled Trial. Children (Basel) 2019 6 (11) **Same study population as Rosenberg AR et al.**				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: Parallel Randomized controlled trial Setting: 1 centre, USA Duration: 6- month follow-up Study years: Jan 2015 – October 2016 Protocol published in register: Protocol registered in clinicaltrials.gov: NCT02340884	Number and type of participants: *A total of 92 Adolescents and Young Adults with cancer receiving systemic chemotherapy.* • Intervention group: 50 – 1 patient who was not fluent in English and 1 patient (2%) who did not complete baseline survey = 48 • Control group: 50 – 6 (12%) patients who did not complete baseline survey = 44 Age at baseline: • Intervention group: Range 12-17 yrs.: 35 (73%) Range 18-25 yrs.: 13 (27%) • Control group: Range 12-17 yrs.: 32 (73%) Range 18-25 yrs.: 12 (27%) Sex at baseline • Intervention group: M: 32 (67%), F: 16 (33%) • Control group: M: 20 (45%), F: 24 (55%) Race at baseline): • Intervention group: Non-white: 15 (31%), White: 33 (69%)	Type of intervention: Promoting Resilience in Stress Management (PRISM): PRISM targets skills in stress management i.e. breathing, relaxation, awareness of stressors; goal-setting i.e. identifying Specific measurable and actionable goals; cognitive-restructuring i.e. identifying 'negative self-talk; and benefit-finding i.e. finding meaning or benefit from difficult situations. PrISM intervention consists of four 30 to 50 minute 1 on 1 sessions every other week delivered by non-clinical college graduates. An optional fifth session consists of a facilitated family meeting where participants shared skills with family and friends. Type of control: Psychosocial Usual Care (UC): An assigned social worker maintained a relationship with the patient and his or her family throughout the study. Social workers routinely conduct a psychosocial assessment at the time of diagnosis and continue to provide services ranging from behavioural health support to financial support. Patients had access to referral based services e.g. psychologist/psychiatrist etc.	Outcome definitions: *Patient-reported outcomes:* **Health-Related Quality of Life (HRQOL):** Assessed by PedsQL existing from subscales: • **Generic HRQOL:** The PedsQL 4.0 Generic Score Scale is a nonspecific PRO instrument and encompasses subdomains representing core dimensions of health including physical, emotional, social and school well-being. 15 items • **Cancer-related HRQOL** the PEDSQL cancer module is an instruments assessing subdomains specifically related to the cancer experience (pain, nausea, procedural anxiety). Score of PedsQL was ranging from 0 to 100, higher scores representing better quality of life. Mean clinically important difference is estimated to be 4.4 for total scores. MCID for subscale scores is 6.6 – 6.9 Results (per outcome) **Generic Health related Quality of Life (Intervention vs control)** • Mean (SD) PedsQL 4.0 score at baseline: 62 (16) vs 59 (21) • Mean (SD) PedsQL 4.0 score at 6 month follow-up 60 (19) vs 67 (15) *Percentage of positive QoL Trajectories (generic) at 6 month follow up.* Participants who received PRISM had a higher proportion of positive long-term HRQoL trajectories. • Global: PRISM 47% (95% CI 32% to 63%) vs UC 26% (95% CI 15% - 42%), p = 0.06 • Physical: PRISM 36% (95% CI 22% to 52%) vs UC 34% (95% CI 21% - 50%), p = 0.86 • Emotional: PRISM 58% (95% CI 42% to 73%) vs UC 37% (95% CI 23% - 53%), p = 0.06 • Social: PRISM 83% (95% CI 68% to 92%) vs UC 66% (95% CI 50% - 79%), p = 0.08 • School: PRISM 44% (95% CI 30% to 60%) vs UC 34% (95% CI 21% - 50%), p = 0.37 *Percentage of improved QoL trajectories (generic) at 6 month follow up.* More PRISM recipients than UC recipients improved (PRISM: 33% vs UC: 0%). **Cancer-related health related Quality of Life (intervention vs control)** • Mean (SD) Cancer Module Total Score at baseline: 66 (16)) vs 65 (17)	Strengths: Evaluating the intervention impact on HRQOL by subdomain, rather than by total score adds to the understanding of how the intervention impacts specific elements of cancer experience. Study useful for application of PRISM intervention Limitations: • Lack of power to confirm statistical significance. • HRQOL was measured using an abbreviated PedsQL form, this may have limited ability to detect significant differences. • Result of study outcomes for adolescents (13-17) and young adults (18-25) were not distinguished. • Generalizability is limited as the study was conducted at a large medical centre, with mostly white, English speaking AYAs • Results in abstracts are not in line with result in full-text. Range of age for adolescents is 13-17 in abstract and 12-17 in results. **Risk of bias** A. Selection bias: low risk Reason: A study statistician constructed the randomizations using permuted blocks of varying sizes, stratified by age. Study staff

	• Control group: Non-white: 19 (43%), White: 25 (57%) Diagnosis at baseline: • Intervention: Leukaemia/Lymphoma: 30 (63%) Central Nervous System (CNS): 3 (7%) Non-CNS solid Tumour: 15 (3%) Advanced Cancer: 10 (21%) • Control: Leukaemia/Lymphoma: 27 (61%) Central Nervous System (CNS): 3 (7%) Non-CNS solid Tumour: 14 (32%) Advanced Cancer: 14 (32%)		• Mean (SD) Cancer Module Total Score at 6-month follow-up: 64 (20) vs 72 (11) *Percentage of positive QoL Trajectories (generic) at 6 month follow up.* Proportion of participants with positive trajectories was higher for PRISM recipients in the following subdomains Intervention vs control): • Nausea: 64% (95% CI 48% to 78%) vs 39% (95% CI 26% to 55%), p = 0.04 • Treatment anxiety: 72% (95% CI 56% to 84%) vs 61% (95% CI 45% to 74%), p = 0.29 • Worry: 50% (95% CI 34% to 66%) vs 24% (95% CI 13% to 39%), p = 0.02 • Cognitive: 58% (95% CI 42% to 73%) vs 42% (95% CI 28% to 58%), p = 0.16 • Physical appearance: 50% (95% CI 34% to 66%) vs 42%(95% CI 28% to 58%), p = 0.50 • Communication 69% (95% CI 53% to 82%) vs 55%(95% CI 40% to 70%), p = 0.21 Greatest advantage observed in nausea worry and cognitive domains. For following subdomains participants with positive trajectories was lower among PRISM recipients Pain: 36% (95% CI 22% to 52%) vs 39% (95% CI 26% to 55%), p = 0.77 Procedural anxiety: 58% (95% CI 42% to 73%) vs 74% (95% CI 58% to 85%), p = 0.16 At least 50% of PRISM recipients had positive trajectories in seven of the eight subdomains, compared to three out of eight subdomains for UC recipients.	were blinded prior to the randomization. <u>B. Attrition bias:</u> low risk Reason: Outcomes of all 92 participants were assessed. <u>C. Performance bias</u> Unclear Reason: Unclear whether participants and parents were blinded from receiving either intervention or control (seems almost impossible. <u>D. Detection bias</u> low risk Reason: Staff collecting outcome data remained blinded to the assignment.

Effectivity of psychological interventions for children in the palliative phase from 0 to 18 years			
Goldbeck L et al. Psychological interventions for individuals with cystic fibrosis and their families. Cochrane Database of Systematic Reviews 2014 6):			
Study characteristics	**Population and intervention**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: Systematic review of RCTs Included studies 16 RCTs and one CCT(controlled clinical trial) of 33 reports were included Searched databases MEDLINE, CENTRAL, OVID MEDLINE, OVID Embase, OVID PsychINFO. Inclusion criteria *Study type:* All randomised controlled and quasi-randomised controlled studies, published and unpublished *Participant type:* Children, adolescents and adults diagnosed with Cystic Fibrosis, Family members (parents/siblings). *Intervention type:* • Included psychological methods within the scope of psychotherapeutic or psychosomatic intervention. • Was facilitated by psychologists, psychotherapists or other trained professionals under supervision • Main targets for psychological interventions are genetic screening for CF, adherence to treatments, coping or adapting to prescribed treatments, decision making, and transition towards independence	Number and type of participants: A total of 556 participants (Children/adolescents and adults with CF and/or family members (parents/siblings)) from 16 RCTs were included in this review. Age: Not reported Sex: Not reported Type of intervention and control *Intervention* Cognitive behavioural interventions • To improve adherence (5 studies) • To improve psychosocial adjustment (1 study) Cognitive interventions • To improve adherence (2 studies) • Associated with decision making (1 study) *Family systems or systemic* One psychological intervention for parenting a child with chronic illness. *Other interventions (6 studies)* • Self-hypnosis on psychological and physiological functioning in children aged 7 to 18 (1 study) • Effectiveness of respiratory muscle biofeedback technique used with adolescents and adults (1 study). • Effectiveness of massage therapy in school aged children (1 study). • The effectiveness of music therapy in mothers and infants under 2 yrs. of age (1 study). • Effectiveness of dance and movement therapy in adult hospitalised patients (1 study). • Telemedicine sessions (1 study).	Outcome definitions: In this review all RCTs reported on one or more of the following outcomes: • Psychological and psychosocial outcomes: Quality of Life, stress, distress and psychopathology • Adaptation to disease management • Physiological outcomes *Only* psychological and psychosocial outcomes for children are described. Results (per outcome) The studies included in this review were so diverse that pooling results became impossible. A large number of different outcome measures were used and are described for readability and clarity *Cognitive behavioural interventions to improve psychosocial adjustment* *Study:* Christian et al, 2006 *Type of participants:* Children with CF aged 8-12 receiving care from one of four CF centres in North Carolina. *Number of participants:* 116 (58 vs 58) *Intervention vs control:* Educational problem-solving and social skills interventions vs. usual care. *Psychosocial/Psychological outcomes:* • **Child's loneliness** *Outcome measure:* the Children's Loneliness Scale' (16 items) *Results:* No statistically significant differences between the groups at any point in time were observed at: three months, MD -0.76 (95% CI -4.26 to 2.74); six months, MD 0.39 (95% CI -2.78 to 3.56); nine months, MD -2.17 (95% CI -5.73 to 1.39) • **Social support peers** *Outcome measure:* subscale 'Peers' of the 'Social Support Scale for Children' *Results:* No statistically significant differences were found between the two groups at: three months MD 0.75 (95% CI -0.59 to 2.09); at six months MD -0.05 (95% CI -1.13 to 1.03); and at nine months, MD -0.09 (95% CI -1.13 to 0.95) • **Social support classmates** *Outcome measure:* subscale 'Classmates' of the 'Social Support Scale for Children'. *Results: N*o statistically significant differences were found between the two groups at: three months, MD 0.06 (95% CI -1.59 to 1.71); at six months, MD 0.35 (95%CI -1.11 to 1.81); and at nine months, MD 1.33 (95% CI -0.20 to 2.86).	Strengths: Limitations: Studies were so diverse that that pooling results became impossible. Therefor outcome measured were described per study. **Total Risk of bias** Selection bias: Low risk: 8/16 studies High risk: 1/16 studies Unclear: 7/16 studies Detection bias: Low risk: 6/16 studies High risk: 5/16 studies Unclear: 5/16 studies Attrition bias: Low risk: 9/16 studies High risk: 3/16 studies Unclear: 4/16 studies Reporting bias: Low risk: 4/16 studies High risk: 4/16 studies Unclear:8/16 studies *Christian et al 2006.* Selection bias: Low Detection bias: Low

• Aimed at improving, psychological and psychosocial outcomes (QoL, stress, distress, psychopathology etc.) adaptation to disease management or physiological outcomes (or both) • Compared to either no psychological intervention/or alternative psychological intervention, • Individually- or family-oriented or group setting. • Included intervention types: Cognitive behavioural, cognitive, family systems or systemic, psychodynamic, other interventions.			Attrition bias: Low Performance bias: Low Reporting bias: Unclear

3.1.2 *Effectiviteit van psychologische interventies voor ouders en familieleden van kinderen in de palliatieve fase*

Effectivity of psychological interventions for parents and family members of children in the palliative phase from 0 to 18 years				
Rosenberg AR et al. Effect of the Promoting Resilience in Stress Management Intervention for Parents of Children With Cancer (PRISM-P): A Randomized Clinical Trial. JAMA Netw Open 2019 2 (9): e1911578				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: Phase 2 three-arm randomized clinical trial. Setting: 1 centre, USA Duration: 3 month follow-up Study years: *December 2016 – December 2018* Protocol published in register: ClinicalTrials.gov identifier: NCT02998086	Number and type of participants: 94 English-speaking parents or guardians of children (3-14 yrs.) who had received a diagnosis of a new malignant neoplasm 1 to 10 weeks prior to enrolment. • Intervention 1 – One on one sessions: 32 • Intervention 2 – Group sessions: 32 • Control: 30 Age: *(mean, median, range)* • Intervention 1 – One on one sessions: Mean: 35, Range: 31-41 • Intervention 2 – Group sessions Mean: 36, Range 32-44 • Control Mean: 38, range 34-44 Relationship to the patient: *(N (%))* • Intervention 1 – One on one sessions: Mother: 26 (81%), Father: 6 (19%), Other: 0 (0%) • Intervention 2 – Group sessions Mother: 25 (78%), Father: 7 (22%), Other: 0 (0%) • Control Mother: 22 (73%), Father: 7 (23%), Other 1 (3%) Other: *(specify)* • Intervention group 1 – One on one sessions • Intervention group 2 – Group sessions • Control group	Type of intervention: Promoting Resilience in Stress Management, Parent-directed (PRISM-P) Adapted version of the PRISM intervention for Adolescents and young people. PRISM- P targets skills in (1) stress management i.e. breathing, relaxation, awareness of stressors; (2) goal-setting i.e. identifying SMART goals; (3) cognitive reframing i.e. identifying 'negative self-talk; and (4) benefit-finding i.e. finding meaning or benefit from difficult situations. All PRISM-P sessions were delivered by the same psychologist.2 delivery options were explored: *Intervention group 1 – One on one* Separate one on one sessions of maximum 60 minutes were scheduled every other week in conjunction with planned hospital admissions or clinic visits or by telephone. *Intervention group 2 – Group sessions* All 4 sessions were conducted on the same day in which 2 to 5 parents were included. . Type of control: Psychosocial Usual Care (UC): An assigned social worker maintained a	Outcome definitions: Primary outcomes **Resilience** Connor-Davidson Resilience Scale assesses self-perceived resilience. All 10 items were scored on a 5-point Likert Scale. Score ranges from 0 – 40. Higher scores reflecting higher resilience. **Benefit finding:** Benefit Finding Scale assesses personal growth (priorities, activities), Total score is mean of item scores which ranges from 1 – 5. Higher score indicates higher benefit finding Secondary outcomes **Hope:** Hope Scale measures overall perception that one's goals can be met. Score ranges from 8 to 64, higher score suggest higher hope **Social support:** Medical outcomes study social support survey addresses social interaction. Total score is the mean of item scores, ranging from 1 – 5. Higher scores suggesting better perception of support **Health related quality of life.** Medical outcomes study evaluates physical functioning. Domain scores are transformed to a scale of 0 to 100. Higher score suggesting better health-related quality of life. **Perceived stress:** Perceived stress scale. Total scores range from 0 to 40. Higher scores indicating higher stress. **Psychological distress:** Kessler psychological Distress scale. Score ranging from 0 to 24, higher scores reflect greater distress. Results (per outcome) **Resilience, benefit-finding, hope, social support at three month follow-up** *intervention 1 vs control* Resilience: EMD 2.3 (0.1 to 4.6),p = 0.04 Benefit finding: EMD 0.5 (0.2 to 0.8), p=0.001 Hope–total: EMD 1.3 (–1.4 to 4.0), p=0.34 Social support–total: EMD 0.0 (–0.6 to 0.5), p=0.86 *Intervention 2 vs control* Resilience: EMD 0.9 (–3.2 to 1.3), p=0.41	Conclusion: In summary, the PRISM-P intervention showed a positive effect on parent-reported resilience and benefit finding when delivered individually to parents of children with cancer. These findings underscore a critical goal in caregiver support: PRISM-P may help parents feel more resilient, which in turn may facilitate their continued ability to care for their child. Strengths: Effectivity of both one on one and group sessions were tested in this study. Limitations: Small sample size How to operationalize PRISM-P remains unclear. This study was not designed to compare the efficacy of 2 formats against each other. **Risk of bias** A. Selection bias: Low risk Reason: Parents were randomized 1:1:1 to the three study arms, randomization algorithm was constructed using permuted blocks in varying sizes. B. Attrition bias: high risk Reason: Outcome was assessed for 81% of the intervention 1 group, 88% of the intervention 2 group and 29% in the control group

		relationship with the patient and his or her family throughout the study. Social workers routinely conduct a psychosocial assessment at the time of diagnosis and continue to supportive care (financial, housing etcetera). If psychosocial support was needed parents were referred to clinicians outside the hospital.	Benefit finding: EMD 0.1 (–0.3 to 0.4), p=0.66 Hope–total: EMD –0.9 (–3.9 to 2.1), p=0.54 Social support–total: –0.1 (–0.7 to 0.4), p=0.59 **Quality of life** *Intervention 1 vs control* General Health: EMD 3.3 (-3.8 to 10.5), p=0.36 *Intervention 2 vs control* General Health: EMD 2.7 (-5.2 to 10.6), p=0.49 **Perceived stress and psychological distress** *Intervention 1 vs control* Perceived stress: EMD -0.8 (-3.6 to 2.0), p=0.58 Distress: EMD -1.8 (-3.9 to 0.2), p=0.07 *Intervention 2 vs control* Perceived stress: EMD 1.7 (-1.3 to 4.7), p=0.27 Distress: EMD -0.7 (-2.9 to -1.4), p=0.50 Compared with parents who received UC, those who received one-on-one PRISM-P reported improved resilience (β, 2.3; 95%CI, 0.1-4.6; P = .04) and benefit finding (β, 0.5; 95%CI, 0.2-0.8; P = .001)	C. Performance bias high risk Reason: Owing to the nature of the intervention, we were unable to blind participants to randomization status D. Detection bias unclear Reason: Blinding of outcome assessors was not reported

Effectivity of psychological interventions for parents and family members of children in the palliative phase from 0 to 18 years			
Eccleston C et al. Psychological interventions for parents of children and adolescents with chronic illness. Cochrane Database of Systematic Reviews 2015 4):			
Study characteristics	**Patient characteristics**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: Systematic review of RCTs Included studies 47 RCTs Searched databases CENTRAL, MEDLINE, EMBASE, PsychINFO Inclusion criteria *Participants* • Parents had to be referred to in the title or abstract of each study • The parent had to be the primary caregiver of the child • Children had to have one or more of the chronic illnesses: Asthma, Cancer, Diabetes Mellitus, Gynaecological disorder, inflammatory bowel diseases (IBD), Painful condition (i.e. headache), skin diseases, and traumatic brain injury. • Children had to be in the age range: 3 months – 19 yrs. • 10 or more participants in each	Number and type of participants: parents of children with chronic illness (painful conditions; cancer; diabetes; asthma; traumatic brain injury) Age: Not reported Sex: Not reported Type of intervention and control *Intervention:* Four classes of psychological therapies were tested. • Cognitive Behavioural Therapy (CBT) – includes a range of strategies with the goals of modifying social/environmental and behavioural factors that may exacerbate or cause symptoms. • Family Therapy (FT) – focus on altering patterns of interactions between family members • Problem-Solving Therapy – didactic instruction in problem-solving, followed by in-session modelling, behavioural rehearsal and performance feedback. • Multi-systemic Therapy – intensive family-community based intervention based on social ecological model and family systems theory. MST targets the child, their family and the school.	Outcome definitions: Primary outcomes: Parenting behaviour, low scores indicate less adverse behaviour ratings Parent mental health, high scores indicating poor mental health Secondary outcomes: Child behaviour/disability, low scores indicate less adverse behaviour/disability ratings Child mental health, high scores indicate poor mental health Child illness-related symptoms, family function, low scores indicate better family functioning Results (per outcome) Individual conditions across all psychological therapies. *Effect of all psychological interventions on parents of children with cancer.* **Parent behaviour – post treatment** *Included:* 836 (I = 405/C = 431) parents of children from 5 studies *Effect:* Psychological had a small beneficial effect for parenting behaviour. SMD is -0.20, 95% CI -0.36 to -0.04, p = 0.01, z = 2.44 *Consistency:* I^2 = 18% *Risk of bias:* Selection bias: low in 2/5, unclear in 3/5; Attrition bias: low in 2/5, unclear in 2/5, high in 1/5; Performance bias: unknown; Detection bias: low in 1/5, unclear in 4/5; Reporting bias: low in 2/5, unclear in 3/5 **Parent behaviour – Follow-up** Included: 789 (I = 386/C=403) parents of children from 5 studies Effect: Effect was not maintained at follow-up, SMD is -0.12 95%CI -0.29 to 0.05, z = 1.39, p=0.16 *Consistency:* I^2 = 21% *Risk of bias:* Selection bias: low in 2/5, unclear in 3/5; Attrition bias: low in 2/5, unclear in 2/5, high in 1/5; Performance bias: unknown; Detection bias: low in 1/5, unclear in 4/5; Reporting bias: low in 2/5, unclear in 3/5 **Parent mental health – post-treatment** Included: 1010 (I = 494/ C = 516) parents of children from 9 studies Effect: There was no effect of psychological therapies on parent Mental health post-treatment. SMD is -0.22 , 95%CI -0.46 to 0.01, z = 1.86, p = 0.06 *Consistency:* I^2 = 63% *Risk of bias:* Selection bias: low in 4/9, unclear in 5/9; Attrition bias: low in 5/9, unclear in 2/6, high in 2/9; Performance bias: unknown; Detection bias: low in 3/9, unclear in 6/9; Reporting bias: low in 5/9, unclear in 4/9 **Parent mental health – follow-up** *Included:* 819 (I = 399, C = 420) parents of children from 6 studies	Strengths: Large amount of studies included Outcomes are assessed per condition and per psychological therapy Limitations: Definitions of primary and secondary outcomes are not reported **Risk of bias** See outcome/ results for risk of bias per outcome

condition at the end of the treatment assessment. *Intervention* • Intervention had to be psychological in at least 1 treatment arm. • design = RCT, • 1 or more parents had to be treated with the intervention • Parents or child had to complete assessments at baseline and at a point in time after/during intervention *Comparison groups* • Active treatment group • Treatment-as-usual group • Waiting list control	*Control:* • Active treatment group (16 studies) • Treatment-as-usual group (17 studies) • Waiting list control (10 studies) • Three comparator arms (4 studies)	*Effect:* Psychological therapies had a small beneficial effect for improving parent mental health (SMD = -0.18, 95%CI -0.32 to -0.04, Z = 2.58, p = 0.01 *Consistency:* $I^2 = 0.0\%$ *Risk of bias:* Selection bias: low in 2/6, unclear in 4/6; Attrition bias: low in 3/6, unclear in 2/6, high in 1/6; Performance bias: unknown; Detection bias: low in 1/6, unclear in 5/6; Reporting bias: low in 2/6, unclear in 4/6 <u>Individual psychological therapies across all conditions</u> *Cognitive behavioural therapy* **Parent behaviour – Post treatment** *Included:* 166 (I = 86, C = 80) parents of children from 4 studies *Effect:* no effect of CBT on parenting behaviour. SDM is -0.02 (95%CI -0.41 to 0.38) z = 0.08. p = 0.94 *Consistency:* $I^2 = 39.0\%$ *Risk of bias:* Selection bias: low in 1/4, unclear in 3/4; Attrition bias: unclear in 2/4, high in 2/4; Performance bias: unknown; Detection bias: low in 1/4,unclear in 3/4; Reporting bias: low in 2/4, high in 2/4 **Parent behaviour – follow-up** *Included:* 85 (I = 42, C = 43) parents of children from 2 studies *Effect:* no effect of CBT on parenting behaviour. SDM is -0.28 (95%CI -1.26 to 0.70) z = 0.56. p = 0.58 *Consistency:* $I^2 = 80\%$ *Risk of bias*: Selection bias: unclear in 2/2; Attrition bias: unclear in 2/2; Performance bias: unknown; Detection bias: low in 1/2, high in 1/2; Reporting bias: low in 1/2, high in 1/2 **Parent mental health – post treatment** Included: 325 (I = 175, C = 150) parents of children from 7 studies Effect: No effect of CBT on parent mental health was identified SDM is -0.14 95%CI -0.56 to 0.28, z = 0.66. p = 0.51 *Consistency:* $I^2 = 68\ \%$ *Risk of bias:* Selection bias: low in 3/7, unclear in 4/7; Attrition bias: low in 4/7, unclear in 1/7, high in 2/7; Performance bias: unknown; Detection bias: low in 2/7, unclear in 5/7; Reporting bias: low in 4/7, unclear in 2/7, high in 1/7 **Parent mental health – follow-up** Included: 115 (I = 67, C = 48) parents of children from 2 studies Effect: No effect of CBT on parent mental health was identified. SDM is 0.32 95%CI -0.18 to 0.82, z = 1.26. p = 0.21 *Consistency:* $I^2 = 41\%$ *Risk of bias:* Selection bias: low in 1/2, unclear in 1/2; Attrition bias: low in 2/2; Performance bias: unknown; Detection bias: unclear in 2/2; Reporting bias: low in 1/2, unclear in 1/2 **Child behaviour/disability – post-treatment** Included: 487 (I = 247, C = 240) children from 8 studies Effect: No effect of CBT on child behaviour post treatment was identified. SDM is -0.21 (95%CI -0.51 to 0.10), z = 1.34. p = 0.18 *Consistency:* $I^2 = 59\%$ *Risk of bias:* Selection bias: low in 4/8, unclear in 4/8; Attrition bias: low in 3/8, unclear in 4/8, high in 1/8; Performance bias: unknown; Detection bias: low in 5/8, unclear in 3/8; Reporting bias: low in 6/8, unclear in 1/8, high in 1/8 **Child behaviour/disability – follow-up** Included: 289 (I = 150, C = 139) children from 3 studies	

		Effect: No effect of CBT on child behaviour/disability was identified. SDM is -0.17 (95%CI -0.52 to 0.18), z = 0.95, p = 0.34 *Consistency:* I^2 = 49% *Risk of bias:* Selection bias: low in 2/3, unclear in 1/3; Attrition bias: low in 2/3, unclear in 1/3; Performance bias: unknown; Detection bias: low in 2/3, unclear in 1/3; Reporting bias: low in 2/3, unclear in 1/3 **Child mental health – post-treatment** Included: 439 (I = 232, C = 207) children from 5 studies Effect: No effect of CBT was identified. SDM is 0.03 95%CI -0.23 to 0.29, z = 0.21 p = 0.83 *Consistency:* I^2 = 41% *Risk of bias:* Selection bias: low in 5/6, unclear in 1/6; Attrition bias: low in 3/6, unclear in 2/6, high in 1/6; Performance bias: unknown; Detection bias: low in 4/6, unclear in 2/6; Reporting bias: low in 3/6, unclear in 2/6, high in 1/6 **Child mental health – follow-up** Included: 257 (I = 130, C= 127) children from 2 studies Effect: No effect of CBT was identified. SDM is 0.03 95%CI -0.21 to 0.28, z = 0.27. p = 0.78. *Consistency:* I^2 = 0% *Risk of bias:* Selection bias: low in 2/2; Attrition bias: low in 1/2, unclear in 1/2; Performance bias: unknown; Detection bias: low in 2/2; Reporting bias: low in 2/2 **Family functioning – post-treatment** Included: 211 (I = 114, C= 97) children from 3 studies Effect: No effect of CBT was identified. SDM is 0.06 95%CI -0.22 to 0.33, z = 0.40 p = 0.69) *Consistency:* I^2 = 0% *Risk of bias:* Selection bias: low in 1/3, unclear in 2/3; Attrition bias: low in 2/3, high in 1/3; Performance bias: unknown; Detection bias: unclear in 3/3; Reporting bias: low in 1/3, unclear in 1/3, high in 1/3 **Family functioning – follow-up** Included: 107 (I = 60, C = 47) children from 2 studies Effect: No effect of CBT was identified. SDM is -0.16 95%CI -0.66 to 0.35, z = 0.61. p = 0.54. *Consistency:* I^2 = 33% *Risk of bias:* Selection bias: low in 1/2, unclear in 1/2; Attrition bias: low in 2/2; Performance bias: unknown; Detection bias: unclear in 2/2; Reporting bias: unclear in 1/2, low in 1/2 *Family therapy* **Parent mental health – post treatment** Included: 131 (I = 74, C = 57) parents of children from 3 studies Effect: No effect of FT on parent mental health was identified SDM is -0.03 95%CI -0.41 to 0.35, z = 0.16. p = 0.88 *Consistency:* I^2 = 15% *Risk of bias:* Selection bias: unclear in 3/3; Attrition bias: low in 3/3; Performance bias: unknown; Detection bias: low in 1/3, unclear in 2/3; Reporting bias: low in 2/3, unclear in 1/3 **Child behaviour/disability – post-treatment** Included: 107 (I = 53, C = 54) children from 2 studies Effect: No significant effect was found. FT was not beneficial for children with chronic condition. SDM is -0.87 (95%CI -2.05 to 0.31) z = 1.44. p = 0.15) *Consistency:* I^2 = 85%	

		Risk of bias: Selection bias: unclear in 2/2; Attrition bias: unclear in 2/2; Performance bias: unknown; Detection bias: low in 1/2, unclear in 1/2; Reporting bias: low 1/2, high in 1/2 **Family functioning** Included: 132 (I = 63, C = 69) children from 2 studies Effect: No effect of FT was identified. SDM is -0.08 95%CI -0.42 to 0.26, z = 0.45, p = 0.65 *Consistency:* I^2 = 0% *Risk of bias:* Selection bias: unclear in 2/2; Attrition bias: unclear in 2/2; Performance bias: unknown; Detection bias: low in 1/2,unclear in 1/2; Reporting bias: high in 2/2 *Problem solving therapy* **Parent behaviour – Post treatment** *Included:* 832 (I = 405, C = 427) parents of children from 5 studies *Effect*: Small beneficial effect of PST on parenting behaviour SMD is -0.25 (95% CI -0.39 to -0.11), z = 3.59. p <0.01 *Consistency:* I^2 = 0% *Risk of bias:* Selection bias: low in 3/5, unclear in 2/5; Attrition bias: unclear in 4/5, high in 1/5; Performance bias: unknown; Detection bias: low in 2/5, unclear in 3/5; Reporting bias: low in 1/5, unclear in 4/5 **Parent behaviour – follow-up** Included: 748 (I = 366, C = 382) parents of children from 4 studies *Effect*: Effect was not maintained *SDM* is -0.15 (95%CI -0.31 to 0.02) z = 0.1.75. p = 0.08 *Consistency:* I^2 = 18% *Risk of bias:* Selection bias: low in 2/4, unclear in 2/4; Attrition bias: unclear in 3/4, high in 1/4; Performance bias: unknown; Detection bias: low in 1/4, unclear in 3/4; Reporting bias: low in 1/4, unclear in 3/4 **Parent mental health – post treatment** Included: 907 (I = 438, C = 469) parents of children from 7 studies Effect: Small beneficial effect of PST on parent mental health SMD -0.24, 95% CI -0.42 to -0.05,z = 2.50, p = 0.01 *Consistency:* I^2 = 37% *Risk of bias:* Selection bias: low in 2/7, unclear in 5/7; Attrition bias: low in 2/7, unclear in 4/7, high in 1/7; Performance bias: unknown; Detection bias: low in 2/7, unclear in 5/7; Reporting bias: low in 1/7, unclear in 6/7, high in 1/7 **Parent mental health – follow-up** Included: 778 (I = 379, C = 399) parents of children from 5 studies Effect: Small beneficial effect of PST on parent mental health SMD -0.19, 95% CI -0.34 to -0.04, z = 2.55. p = 0.01 *Consistency:* I^2 = 4% *Risk of bias:* selection bias: low in 2/5, unclear in 3/5; Attrition bias: low in 1/5, unclear in 3/5, high in 1/5; Performance bias: unknown; Detection bias: low in 1/5, unclear in 4/5; Reporting bias: low in 1/5, unclear in 4/5 **Child behaviour/disability – post-treatment** Included: 260 (I = 130, C= 130) children from 5 studies Effect: No effect of PST was identified. SDM is -0.17 (95%CI -0.45 to 0.11), z = 1.21. p = 0.22 *Consistency:* I^2 = 18%	

		Risk of bias: selection bias: low in 1/5, unclear in 4/5; Attrition bias: low in 1/5, unclear in 3/5, high in 1/5; Performance bias: unknown; Detection bias: low in 4/5, unclear in 1/5; Reporting bias: low in 1/5, unclear in 4/5 **Family functioning – post-treatment** Included: 183 (I = 90, C = 93) children from 3 studies Effect: No effect of PST was identified. SDM is -0.10 95%CI -0.48 to 0.27, z = 0.54 p = 0.59 *Consistency:* I^2 = 28% *Risk of bias:* Selection bias: low in 1/3, unclear in 2/3; Attrition bias: low in 2/3, unclear 1/3; Performance bias: unknown; Detection bias: low in 2/3, unclear in 1/3; Reporting bias: unclear in 2/3, high in 1/3 *Multisystemic therapy* ***Child behaviour/disability – post-treatment*** Included: 313 (I = 158, C = 155) children from 2 studies Effect: No effect of MST on child behaviour/disability was identified. SDM is -0.17 (95%CI -0.50 to 0.17), z = 0.99, p = 0.32 *Consistency:* I^2 = 56% *Risk of bias:* Selection bias: low in 1/2, unclear in 1/2; Attrition bias: low in 1/2, unclear in 1/2; Performance bias: unknown; Detection bias: low in 2/2; Reporting bias: unclear in 2/2	

Effectivity of psychological interventions for parents and family members of children in the palliative phase from 0 to 18 years			
Goldbeck L et al. Psychological interventions for individuals with cystic fibrosis and their families. Cochrane Database of Systematic Reviews 2014 6):			
Study characteristics	**Population and intervention**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: Systematic review of RCTs Included studies 16 RCTs and one CCT(controlled clinical trial) of 33 reports were included Searched databases MEDLINE, CENTRAL, OVID MEDLINE, OVID Embase, OVID PsychINFO. Inclusion criteria *Study type:* All randomised controlled and quasi-randomised controlled studies, published and unpublished *Participant type:* Children, adolescents and adults diagnosed with Cystic Fibrosis, Family members (parents/siblings). *Intervention type:* • Included psychological methods within the scope of psychotherapeutic or psychosomatic intervention. • Was facilitated by psychologists, psychotherapists or other trained professionals under supervision • Main targets for psychological interventions are genetic screening for CF, adherence to treatments, coping or adapting to prescribed treatments, decision making, and transition towards independence • Aimed at improving, psychological and psychosocial outcomes (QoL, stress, distress, psychopathology etc.) adaptation to disease management or physiological outcomes (or both) • Compared to either no psychological intervention/or alternative psychological intervention, • Individually- or family- oriented or group setting. • Included intervention types: Cognitive behavioural, cognitive, family systems or systemic, psychodynamic, other interventions.	Number and type of participants: A total of 556 participants (Children/adolescents and adults with CF and/or family members (parents/siblings)) from 16 RCTs were included in this review. Age: Not reported Sex: Not reported Type of intervention and control *Intervention* Cognitive behavioural interventions • To improve adherence (5 studies) • To improve psychosocial adjustment (1 study) Cognitive interventions • To improve adherence (2 studies) • Associated with decision making (1 study) *Family systems or systemic* One psychological intervention for parenting a child with chronic illness. *Other interventions (6 studies)* • Self-hypnosis on psychological and physiological functioning in children aged 7 to 18 (1 study) • Effectiveness of respiratory muscle biofeedback technique used with adolescents and adults (1 study). • Effectiveness of massage therapy in school aged children (1 study). • The effectiveness of music therapy in mothers and infants under 2 yrs. of age (1 study). • Effectiveness of dance and movement therapy in adult hospitalised patients (1 study). • Telemedicine sessions (1 study).	Outcome definitions: In this review all RCTs reported on one or more of the following outcomes: • Psychological and psychosocial outcomes: Quality of Life, stress, distress and psychopathology • Adaptation to disease management • Physiological outcomes *For this guideline/uitgangsvraag only* psychological and psychosocial outcomes for parents are described. Results (per outcome) The studies included in this review were so diverse that pooling results became impossible. A large number of different outcome measures were used and are described for readability and clarity Family systems or systemic interventions *Study:* Chernoff et al. (2002), *Type of participants*: Children with Cystic Fibrosis aged 7 to 11 and their mothers *Number of participants:* Children: 13 (7 vs 6); Parents 13 (7 vs 6) *Intervention vs control:* Community-based support program versus contact with telephone number *Psychosocial/psychological outcomes:* **Psychiatric Symptom Index - Anxiety subscale – mothers** *Outcome measure:* anxiety subscale, score range of 0 to 100. The reported effects for the whole group of carers of children with a chronic illness in the source article showed reduced anxiety following the intervention. For the subgroup of carers with a child with CF, no significant difference was found between groups, MD -3.60 (95% CI -18.14 to 10.94) at 12-month post-baseline. This subgroup was small and unlikely to demonstrate a clear effect.	Strengths: Studies were so diverse that that pooling results became impossible. Therefor outcome measured were described per study. Limitations: **Risk of bias** Selection bias: Low risk: 8/16 studies High risk: 1/16 studies Unclear: 7/16 studies Detection bias: Low risk: 6/16 studies High risk: 5/16 studies Unclear: 5/16 studies Attrition bias: Low risk: 9/16 studies High risk: 3/16 studies Unclear: 4/16 studies Reporting bias: Low risk: 4/16 studies High risk: 4/16 studies Unclear:8/16 studies *Chernoff et al 2002* Selection bias: Unclear Detection bias: Low Attrition bias: high Performance bias: Low Reporting bias: High

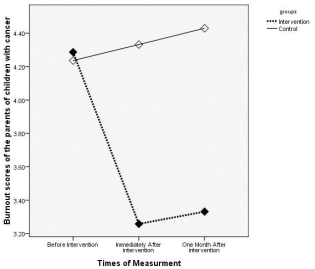
3.2 Sociale en praktische ondersteuning

No studies were found

3.3 Culturele, spirituele en religieuze ondersteuning

Effectivity of cultural, spiritual and religious support for children in the palliative phase from 0 to 18 years and their parents and/or family members				
Borjalilu S et al. Spiritual care Training for Mothers of Children with Cancer: Effects on Quality of Care and Mental Health of Caregivers. Asian Pac J Cancer Prev, 17 (2), 545-552, 2016				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: Quasi experimental study Setting: 1 centre, Iran Duration: Outcomes are measured at baseline, post-treatment and 3 month follow-up Study years: 2014 Protocol published in register: Not reported	Number and type of participants: 42 mothers of children with cancer aged 7 - 15 • Intervention group: 21 • Control group: 21 Age: • Intervention group: Mean: 36.8 years, Range: 21 – 52 years • Control group: Mean: 31.9 years, Range: 21 – 52 years Gender: • Intervention group: F: 21 (100%) • Control group: F: 21 (100%)	Type of intervention: Spiritual training package encompassed seven sessions of 90 minutes offered once a week in groups of 7 mothers. The spiritual training package is based on the ASSET model (Actioning Spirituality and Spiritual Care Education training). According to this model major skills for spiritual care in this model are communication skills, encouragement and offering hope. For this intervention it the package was modified in conformity with local customs, beliefs and accepted norms. The spiritual training package is primarily concerned with psychoeducational therapy which integrates psychotherapeutic and educational interventions.	Outcome definitions: **Stress, Anxiety and Depression:** Measured by Depression, Anxiety and Stress Scale (DASS-21), Set of three self-report scales to assess depression, anxiety, and stress, scale contains 21 items that are rated on a 4-point Likert scale. **Spirituality, religiosity, personalized care, spiritual care** Measured by the Spirituality & Spiritual Care Rating Scale (SSCR), contains 17 items that are rated on a 5-point Likert scale. Results (per outcome) **Stress (Intervention vs Control)** • Baseline: Mean (SD) is 2.71 (0.148) vs 2.67 (0.12) • Post-treatment: Mean (SD) is 2.37 (0.194) vs 2.58 (0.152) Significant, difference between groups and time in pre- and post-test; p < 0.001 • 3 month follow-up: Mean (SD) is 2.18 (0.144) vs 2.45 (0.148), p = 0.114 **Anxiety (Intervention vs Control)** • Baseline: Mean (SD) is 2.7 (0.053) vs 2.68 (0.185) • Post-treatment: Mean (SD) is 2.54 (0.14) vs 2.65 (0.11) Significant, difference between groups and time in pre- and post-test; p < 0.001 • 3 month follow-up: Mean (SD) is 2.42 (0.068) vs 2.65 (0.104); p < 0.001 **Depression (Intervention vs Control)** • Baseline: Mean (SD) is 2.68 (0.0132) vs 2.63 (0.105) • Post-treatment: Mean (SD) is 2.4 (0.116) vs 2.6 (0.086) Significant, difference between groups and time in pre- and post-test; p < 0.001 • 3 month follow-up: Mean (SD) is 2.4 (0.116) vs 2.62 (0.101), p = 0.123 **Spirituality (Intervention vs Control)** • Baseline: Mean (SD) is 3.73 (0.015) vs 3.72(0.013) • Post-treatment: Mean (SD) is 3.93 (0.037) vs 3.75 (0.033) Significant, difference between groups and time in pre- and post-test; p < 0.00 • 3 month follow-up: Mean (SD) is 4.022 (0.034) vs 3.74 (0.03), p < 0.001 **Religiosity (Intervention vs Control)** • Baseline: Mean (SD) is 3.5 (0.007) vs 3.51 (0.046)	Strengths: Limitations: Scores on outcomes like stress/anxiety/depression are very dependent on the situation a parent is in. This might influence the results that are found. **Risk of bias** A. Selection bias: High risk Reason: Parents were randomized, there was no allocation concealment. B. Attrition bias: Low risk Reason: Outcome was assessed for 100% of the intervention group and 100% of the control group. C. Performance bias high risk Reason: Owing to the nature of the intervention, we were unable to blind participants to randomization status D. Detection bias unclear Reason: Blinding of outcome

		Type of control: Wait-list control, control group received the intervention after follow-up was over	• Post-treatment: Mean (SD) is 3.51 (0.006) vs 3.52 (0.01) Significant, difference between groups and time in pre- and post-test; p < 0.001 • 3 month follow-up: Mean (SD) is 3.73 (0.079) vs 3.53 (0.033), p < 0.001 **Personalized care (Intervention vs Control)** • Baseline: Mean (SD) is 2.21 (0.052) vs 2.19 (0.046) • Post-treatment: Mean (SD) is 2.96 (0.079) vs 2.24 (0.07) Significant, difference between groups and time in pre- and post-test; p < 0.001 • 3 month follow-up: Mean (SD) is 3.04 (0.079) vs 2.26 (0.07), p = 0.123 **Spiritual care (Intervention vs Control)** • Baseline: Mean (SD) is 3.49 (0.038) vs 3.5 (0.034) • Post-treatment: Mean (SD) is 4.16 (0.04) vs 3.53 (0.035) Significant, difference between groups and time in pre- and post-test; p < 0.004 • 3 month follow-up: Mean (SD) is 4.22 (0.037) vs 3.53 (0.033), p < 0.004	assessors was not reported

Effectivity of cultural, spiritual and religious support for children in the palliative phase from 0 to 18 years and their parents and/or family members				
Beheshtipour N et al. The Effect of Educational-spiritual Intervention on The Burnout of The Parents of School Age Children With Cancer: A Randomized Controlled Clinical Trial. IJCBNM January 2016; Vol 4, No 1				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: Randomized Controlled Trial Setting: Iran Duration: Outcomes are measured at baseline, post treatment and at 1 month follow-up. Study years: December 2013 – July 2014 Protocol published in register: Trial Registration Number: IRCT 2014061818144N1	Number and type of participants: 135 parents of children aged with cancer aged 6 to 12 years (6 months to 2 years after diagnosis) • Intervention group: 65 • Control group: 70 Age: *(mean, median, range)* • Intervention group: Mean (SD), 34.50 (9.00) • Control group: Mean (SD), 34.30 (6.77) Gender of parents: *N (%)* • Intervention group: M: 27 (41.5%), F: 38 (58.5) • Control group: M: 32 (45.7%), F: 38 (54.3%) Parents' education *N (%)* • Intervention group: Primary school and second degree: 25 (38.4%), High school and diploma 25 (38.4%), College degree: 15 (23.2%) • Control group: Primary school and second degree: 22 (31.4%), High school and diploma 38 (54.3%), College degree: 15 (14.3%) *No significant difference between intervention and control was found at baseline.*	Type of intervention: Educational-spiritual intervention consisted of 6 educational sessions of 45 minutes containing a lecture, question and answer in groups of 7 to 10 people. There was a one week interval was between the sessions. Educational topics included an introduction to cancer disease, diagnosis and treatment of cancer, side effects of various treatments, daily activity, diet and spiritual teaching like philosophy of life and death and life after death, divine fate acceptance, patience and fortitude (held by a religious advisor) Type of control: Not reported	Outcome definitions: **Burnout** Burnout was measured by Shirom and Melamed Burnout Questionnaire (SMBQ) composed of 22 items which are rated on a 7 point Likert scale, 1 (almost never) to 7 (nearly always. Questionnaire contained 4 subdomains of physical fatigue, cognitive weariness, tension and listlessness. For the scale as a whole and each subdomain, the total score is averaged by dividing it by the number of items in the domain/scale. Threshold score is 3.37 Score < 2.75 healthy 2.75 ≥ score ≤ 3.37 represents moderate burnout Score > 3.37 represents high burnout Score ≥ 4.47 pathological condition of burnout Results (per outcome) **Burnout scores baseline (intervention vs control** Mean (SD) is 4.28 (0.61) vs 4.23 (0.50) **Burnout scores post-treatment (intervention vs control** Mean (SD) is 3.25 (0.68) vs 4.33 (0.56), p <0.0001 **Burnout scores at 1 month follow-up (intervention vs control)** Mean (SD) is 3.33 (0.68) vs 4.42 (0.56), p <0.0001  	Strengths: Limitations: Some results are not written down correctly in the article. For example in the article it is said that the majority of both groups were fathers, and it says there is a significant difference between groups at baseline. Which does not seem to be true. **Risk of bias** A. Selection bias: Unclear Reason: Parents were randomly allocated to the intervention or control group. Allocation concealment was unclear. B. Attrition bias: Low risk Reason: Outcome was assessed for 92% of the intervention group and 100% of the control group C. Performance bias high risk Reason: Due to the nature of the intervention it is impossible to blind participants D. Detection bias unclearReason: Blinding of outcome assessors was not reported

4 Samenvatting en gradering van bewijs

4.1 Psychologische interventies

4.1.1 Effectiviteit van psychologische interventies voor kinderen in de palliatieve fase

4.1.1.1 Geïncludeerde uitkomstmaten

Included outcomes
Benefit-finding
Hope-finding
Health-related Quality of Life
Cancer-specific Quality of Life

4.1.1.2 Promoting Resilience in Stress Management (PRISM)

Promoting Resilience in Stress Management (PRISM)				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Benefit-finding, Benefit Finding Scale for children, score ranging from 12- 50, higher score indicates higher benefit-finding.				
Rosenberg, 2019	Children and adolescents with cancer receiving systemic chemotherapy aged 12-25 years (73% are children aged 12-17).	Total of 92 Intervention: 48 • 35 children aged 12-17 • 13 adolescents aged 18-25 Control: 44 • 32 children aged 12-17 • 12 adolescents aged 18-25	Promoting Resilience in Stress Management (PRISM) including following elements: skills in stress management, goal-setting and cognitive restructuring vs. psychosocial usual care (UC).	**Benefit-finding scores at 6 month follow-up:** Estimated Mean difference $_{\text{intervention – control}}$: 3.1 (95% CI 0.0 to 6.2), p = 0.05, d = 0.4 (effect-size) PRISM participants' benefit-finding score increased an estimated 3.1 points more than UC participant.

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-1	Some limitations - Selection bias: Low; Attrition: bias low; Performance bias: high; Detection bias: low
Consistency:	0	No important inconsistency. Only 1 study performed
Directness:	0	Outcomes are direct. Unclear if outcomes are generalizable to children in palliative care as study sample also includes adolescents
Precision:	-2	Some imprecision due to small sample size (n=92). Only 1 study performed
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence that there is no significant effect (p=0.05) of Promoting Resilience in Stress Management on benefit-finding at 6 month follow-up in children and adolescents with cancer as compared to usual care.**

Promoting Resilience in Stress Management (PRISM)				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Hope-finding, Hope scale, score ranging from 12-48, higher score indicating more hopeful patterns of thought				
Rosenberg, 2019	Children and adolescents with cancer receiving systemic chemotherapy aged 12-25 years (73% are children aged 12-17).	Total of 92 Intervention: 48 • 35 children aged 12-17 • 13 adolescents aged 18-25 Control: 44 • 32 children aged 12-17 • 12 adolescents aged 18-25	Promoting Resilience in Stress Management (PRISM) including following elements: skills in stress management, goal-setting and cognitive restructuring vs. psychosocial usual care (UC).	**Hope-finding scores at 6 month follow-up** *Total scores* Estimated Mean difference $_{\text{intervention – control}}$: 3.6 (95% CI 0.7 to 6.4), p = 0.01, d = 0.6 (effect-size) PRISM participant score higher on hope scale (more hopeful patterns of thought).

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-1	Some limitations - Selection bias: Low; Attrition: bias low; Performance bias: high; Detection bias: low
Consistency:	0	No important inconsistency. Only 1 study performed
Directness:	0	Outcomes are direct. Unclear if outcomes are generalizable to children in palliative care as study sample also includes adolescents
Precision:	-2	Some imprecision due to small sample size (n=92). Only 1 study performed
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		**⊕⊖⊖⊖ VERY LOW**
Conclusion:		**There is very low quality of evidence that Promoting Resilience in Stress Management increases hope-finding at 6 month follow-up in children and adolescents with cancer as compared to usual care.**

Promoting Resilience in Stress Management (PRISM)				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Health Related Quality of Life, PedsQL 4.0 Generic Score Scale, score ranging 0 to 100, higher score representing better Quality of Life				
Steineck, 2019	Children and adolescents with cancer receiving systemic chemotherapy aged 12-25 years (73% are children aged 12-17).	Total of 92 Intervention: 48 • 35 children aged 12-17 • 13 adolescents aged 18-25 Control: 44 • 32 children aged 12-17 • 12 adolescents aged 18-25	Promoting Resilience in Stress Management (PRISM) including following elements: skills in stress management, goal-setting and cognitive restructuring vs. psychosocial usual care (UC).	**Generic Health related Quality of Life (Intervention vs control)** • Mean (SD) PedsQL 4.0 score at baseline: 62 (16) vs 59 (21), p = unknown • Mean (SD) PedsQL 4.0 score at 6 month follow-up 60 (19) vs 67 (15), p=unknown **Percentage of positive QoL Trajectories at 6 month follow up.** Participants who received PRISM had a higher proportion of positive long-term HRQoL trajectories. PRISM 47% (95% CI 32% to 63%) vs UC 26% (95% CI 15% - 42%), p = 0.06 Percentage of positive QoL trajectories at 6 month follow up per subdomain: • Physical: PRISM 36% (95% CI 22% to 52%) vs UC 34% (95% CI 21% - 50%), p = 0.86 • Emotional: PRISM 58% (95% CI 42% to 73%) vs UC 37% (95% CI 23% - 53%), p = 0.06 • Social: PRISM 83% (95% CI 68% to 92%) vs UC 66% (95% CI 50% - 79%), p = 0.08 • School: PRISM 44% (95% CI 30% to 60%) vs UC 34% (95% CI 21% - 50%), p = 0.37
Grade assessment				
Study design:	+4	1 Randomized Controlled Trial		
Study limitations	-1	Some limitations - Selection bias: Low; Attrition: bias low; Performance bias: high; Detection bias: low		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Outcomes are direct. Unclear if outcomes are generalizable to children in palliative care as study sample also includes adolescents		
Precision:	-2	Some imprecision due to small sample size (n=92). Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence that there is no significant effect of Promoting Resilience in Stress Management on the percentage of positive Quality of Life trajectories at 6 month follow-up in children and adolescents with cancer as compared to usual care.**		

Promoting Resilience in Stress Management (PRISM)				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Cancer specific Quality of Life, PedsQL cancer module, score ranging 0 to 100, higher score representing better Quality of Life				

Steineck, 2019	Children and adolescents with cancer receiving systemic chemotherapy aged 12-25 years (73% are children aged 12-17).	Total of 92 Intervention: 48 • 35 children aged 12-17 • 13 adolescents aged 18-25 Control: 44 • 32 children aged 12-17 • 12 adolescents aged 18-25	Promoting Resilience in Stress Management (PRISM) including following elements: skills in stress management, goal-setting and cognitive restructuring vs. psychosocial usual care (UC).	**Cancer specific Quality of Life (intervention vs control)** • Mean (SD) Cancer Module Total Score at baseline: 66 (16)) vs 65 (17), p = unknown • Mean (SD) Cancer Module Total Score at 6-month follow-up: 64 (20) vs 72 (11)), p = unknown **Percentage of positive QoL Trajectories at 6 month follow up.** Proportion of participants with positive trajectories was higher for PRISM recipients in the following subdomains Intervention vs control): • Nausea: 64% (95% CI 48% to 78%) vs 39% (95% CI 26% to 55%), p = 0.04 • Treatment anxiety: 72% (95% CI 56% to 84%) vs 61% (95% CI 45% to 74%), p = 0.29 • Worry: 50% (95% CI 34% to 66%) vs 24% (95% CI 13% to 39%), p = 0.02 • Cognitive: 58% (95% CI 42% to 73%) vs 42% (95% CI 28% to 58%), p = 0.16 • Physical appearance: 50% (95% CI 34% to 66%) vs 42%(95% CI 28% to 58%), p = 0.50 • Communication 69% (95% CI 53% to 82%) vs 55%(95% CI 40% to 70%), p = 0.21 For following subdomains participants with positive trajectories was lower among PRISM recipients • Pain: 36% (95% CI 22% to 52%) vs 39% (95% CI 26% to 55%), p = 0.77 • Procedural anxiety: 58% (95% CI 42% to 73%) vs 74% (95% CI 58% to 85%), p = 0.16

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-1	Some limitations - Selection bias: Low; Attrition: bias low; Performance bias: high; Detection bias: low
Consistency:	0	No important inconsistency. Only 1 study performed
Directness:	0	Outcomes are direct. Unclear if outcomes are generalizable to children in palliative care as study sample also includes adolescents
Precision:	-2	Some imprecision due to small sample size (n=92). Only 1 study performed
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence that Promoting Resilience in Stress Management increases the percentage of positive cancer specific Quality of Life trajectories regarding the subdomains nausea and worry at six month follow-up, in children and adolescents with cancer as compared to usual care. There is very low quality of evidence that there is no significant effect of Promoting Resilience in Stress Management on the percentage of cancer specific Quality of Life trajectories regarding the subdomains treatment anxiety, procedural anxiety, cognitive, physical appearance, communication and pain at 6 month follow-up, in children and adolescents with cancer as compared to usual care.**

4.1.1.3 Educatieve, probleem-oplossingsgerichte, sociale vaardigheden interventies

Educational problem-solving and social skills interventions				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Child's loneliness, The children's loneliness scale				
1 RCT extracted from systematic review of RCTs: Goldbeck, 2014 Included RCT: Christian, 2006	Children with Cystic Fibrosis (CF) aged 8 to 12 yrs.	116 (58 vs 58)	Educational problem-solving and social skills interventions vs. usual care	**Child's loneliness at 3 month follow up (intervention vs control)** MD: -0.76 (95%CI -4.26 to 2.74) **Child's loneliness at 6 month follow up (intervention vs control)** MD 0.39 (95% CI -2.78 to 3.56) **Child's loneliness at 9 month follow up (intervention vs control)** MD -2.17 (95% CI -5.73 to 1.39)
Grade assessment				
Study design:	+4	1 Randomized Controlled Trials (results extracted from systematic review of RCTs: Goldbeck, 2014)		
Study limitations	0	No limitations- Selection bias: Low; Attrition bias: Low; Performance bias: Low; Detection bias: Low.		
Consistency:	0	No important inconsistency. Only 1 study performed.		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	-1	No important imprecision. Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊕⊕⊖ **MODERATE**		
Conclusion:		**There is moderate quality of evidence that there is no significant effect of educational problem-solving and social skills interventions on loneliness at 3, 6 and 9 month follow-up in children with Cystic Fibrosis as compared to usual care.**		

Educational problem-solving and social skills interventions				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Social support peers, Social support scale of children, subscale 'peers' **Social support classmates,** Social support scale of children, subscale 'classmates'				
1 RCT extracted from systematic review of RCTs: Goldbeck, 2014 Included RCT: Christian, 2006	Children with Cystic Fibrosis (CF) aged 8 to 12 yrs.	116 (58 vs 58)	Educational problem-solving and social skills interventions vs. usual care	**Social support peers at 3 month follow up (intervention vs control)** MD 0.75 (95% CI -0.59 to 2.09) **Social support peers at 6 month follow up (intervention vs control)** MD -0.05 (95% CI -1.13 to 1.03) **Social support peers at 9 month follow up (intervention vs control)** MD -0.09 (95% CI -1.13 to 0.95) **Social support classmates at 3 month follow up (intervention vs control)** MD 0.06 (95% CI -1.59 to 1.71) **Social support classmates at 6 month follow up (intervention vs control)** MD 0.35 (95%CI -1.11 to 1.81) **Social support classmates at 9 month follow up (intervention vs control)** MD 1.33 (95% CI -0.20 to 2.86).
Grade assessment				
Study design:	+4	1 Randomized Controlled Trials (results extracted from systematic review of RCTs: Goldbeck, 2014)		
Study limitations	0	No limitations- Selection bias: Low; Attrition bias: Low; Performance bias: Low; Detection bias: Low.		
Consistency:	0	No important inconsistency. Only 1 study performed.		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	-1	No important imprecision. Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊕⊕⊖ **MODERATE**		
Conclusion:		**There is moderate quality of evidence that there is no significant effect of educational problem-solving and social skills interventions on perceived social support of peers and classmates at 3, 6 and 9 month follow-up by children with Cystic Fibrosis as compared to usual care.**		

4.1.2 Effectiviteit van psychologische interventies voor ouders en familieleden van kinderen in de palliatieve fase

4.1.2.1 Included outcomes

Included outcomes
Resilience
Benefit-finding
Hope
Social support
Health-Related Quality of Life
Perceived stress
Psychological distress
Parent behaviour
Parent mental health

4.1.2.2 Promoting Resilience in Stress Management, Parent-directed (PRISM-P)

Promoting Resilience in Stress Management Parent-directed (PRISM-P) one on one sessions vs usual care				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Resilience, Connor-Davidson Resilience Scale assesses self-perceived resilience, score ranging from 0 – 50, higher score reflects higher resilience. **Benefit-finding,** Benefit-finding Scale, score ranging from 1 – 5 (total score is mean of item scores), higher score indicating higher benefit-finding **Hope,** Hope scale, score ranging from 8 to 64, higher score suggests more hope **Social support (social interaction),** Social support survey, score ranging from 1 – 5 (total score is mean of item scores), higher score indicating better perception of social support **Health related quality of life,** HR-QoL, score ranging from 0 - 100, higher score suggesting better health-related quality of life **Perceived stress,** Perceived stress scale, score ranging from 0 – 40, higher score indicating higher perceived stress **Psychological distress,** Kessler psychological distress scale, score ranging from 0 – 24, higher score reflects greater distress				
Rosenberg, 2019	94 parents or guardians of children aged 3 - 14 who have received diagnosis of a new malignant neoplasm (1 to 10 weeks prior to enrolment	Total of 62 PRISM-P one on one sessions: 32 Control (usual care): 30	Promoting Resilience in Stress Management, parent-directed (PRISM -P) one on one sessions (targeting skills in stress management, goal-setting and cognitive restructuring) vs psychosocial usual care (UC).	**Resilience at 3 month follow-up** EMD 2.3 (0.1 to 4.6),p = 0.04 **Benefit-finding at 3 month follow-up** EMD 0.5 (0.2 to 0.8), p=0.001 **Hope at 3 month follow-up** EMD 1.3 (–1.4 to 4.0), p=0.34 **Social support at 3 month follow-up** EMD 0.0 (–0.6 to 0.5), p=0.86 **Health-related Quality of Life at 3 month follow-up** EMD 3.3 (-3.8 to 10.5), p=0.36 **Perceived stress at 3 month follow-up** EMD -0.8 (-3.6 to 2.0), p=0.58 **Psychological distress at 3 month follow-up** EMD -1.8 (-3.9 to 0.2), p=0.07
Grade assessment				
Study design:	+4	1 Randomized Controlled Trial		
Study limitations	-2	Serious limitations - Selection bias: Low; Attrition bias: high; Performance bias: high; Detection bias: unclear		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	-2	Some imprecision due to small sample size. Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		**⊕⊖⊖⊖ VERY LOW**		
Conclusion:		**There is very low quality of evidence that PRISM-P one on one sessions increase resilience and benefit-finding at 3 month follow-up in parents/guardians of children with cancer as compared to usual care.** **There is very low quality of evidence that there is no significant effect of PRISM-P one on one sessions on hope, perceived social support, health related quality of life, perceived stress and psychological distress in parents/guardians of children with cancer as compared to usual care.**		

Promoting Resilience in Stress Management Parent-directed (PRISM-P) group sessions vs usual care				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Resilience, Connor-Davidson Resilience Scale assesses self-perceived resilience, score ranging from 0 – 50, higher score reflects higher resilience. **Benefit-finding,** Benefit-finding Scale, score ranging from 1 – 5 (total score is mean of item scores), higher score indicating higher benefit-finding **Hope,** Hope scale, score ranging from 8 to 64, higher score suggests more hope **Social support (social interaction),** Social support survey, score ranging from 1 – 5 (total score is mean of item scores), higher score indicating better perception of social support **Health related quality of life,** HR-QoL, score ranging from 0 - 100, higher score suggesting better health-related quality of life **Perceived stress,** Perceived stress scale, score ranging from 0 – 40, higher score indicating higher perceived stress **Psychological distress,** Kessler psychological distress scale, score ranging from 0 – 24, higher score reflects greater distress				
Rosenberg, 2019	94 parents or guardians of children aged 3- 14 who have received diagnosis of a new malignant neoplasm (1 to 10 weeks prior to enrolment	Total of 62 PRISM-P group sessions: 32 Control (usual care): 30	Promoting Resilience in Stress Management, parent-directed (PRISM -P) group sessions (targeting skills in stress management, goal-setting and cognitive restructuring) v	**Resilience at 3 month follow-up** EMD 0.9 (–3.2 to 1.3), p=0.41 **Benefit-finding at 3 month follow-up** EMD 0.1 (–0.3 to 0.4), p=0.66 **Hope at 3 month follow-up** EMD 1.3 (–1.4 to 4.0), p=0.34 **Social support at 3 month follow-up** –0.1 (–0.7 to 0.4), p=0.59 **Health-related Quality of Life at 3 month follow-up** EMD 2.7 (-5.2 to 10.6), p=0.49 **Perceived stress at 3 month follow-up** EMD 1.7 (-1.3 to 4.7), p=0.27 **Psychological distress at 3 month follow-up** EMD -0.7 (-2.9 to -1.4), p=0.50
Grade assessment				
Study design:	+4	1 Randomized Controlled Trial		
Study limitations	-2	Serious limitations - Selection bias: Low; Attrition: bias high; Performance bias: high; Detection bias: unclear		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	-2	Some imprecision due to small sample size. Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence that there is no significant effect of PRISM-P group sessions on resilience, benefit-finding, hope, perceived social support, health related quality of life, perceived stress and psychological distress at 3 month follow-up in parents/guardians of children with cancer as compared to usual care.**		

4.1.2.3 Community-based ondersteuningsprogramma

Community-based support program vs control (contact with telephone number)

Studies	Type of participants	Total no. of participants	Type of intervention vs control	Outcome and Effect size
Anxiety, Psychiatric Symptom Index, Anxiety subscale				
1 RCT extracted from systematic review of RCTs: Goldbeck, 2014 Included RCT: Chernoff, 2002	Mothers of children with Cystic Fibrosis aged 7 to 11 years	13 (7 vs 6)	Community-based support program vs control (contact with telephone number)	**Anxiety at 12 month follow-up** MD -3.60 (95% CI -18.14 to 10.94)
Grade assessment				
Study design:	+4	1 Randomized Controlled Trials (results extracted from systematic review of RCTs: Goldbeck, 2014)		
Study limitations	-2	Serious limitations- Selection bias: Unclear; Attrition bias: High Performance bias: Low; Detection bias: Low		
Consistency:	0	No important inconsistency. Only 1 study performed.		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	-2	Serious imprecision due to small sample size (n=20). Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence there is no significant effect of a community-based support programme on anxiety at 12 month follow-up in mothers of children with Cystic Fibrosis as compared to control (contact with telephone number)**		

4.1.2.4 *Psychologische interventies waaronder cognitieve gedragstherapie, gezinstherapie, probleem-oplossingsgerichte therapie en multi systemische therapie*

Psychological interventions for parents of children with cancer				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Parent behaviour post-treatment, low scores indicate less adverse behaviour ratings				
5 RCTs extracted from systematic review of RCTs: Eccleston, 2015	Parents of children aged 0 to 19 with cancer	836 (405 vs 431)	Psychological interventions for parents i.e. cognitive behavioural therapy; family therapy; problem-solving therapy; multi-systemic therapy) vs control (active treatment group, treatment-as-usual, waiting list control, three comparator arms)	**Parenting behaviour post-treatment** Psychological therapies had a small beneficial effect for parent behaviour post-treatment SMD is -0.20, 95% CI -0.36 to -0.04, p = 0.01, z = 2.44 **Parenting behaviour at follow-up (follow-up time ranging from 2 to 12 months)** Effect of psychological therapies on parent behaviour was not maintained at follow-up, SMD is -0.12 95%CI -0.29 to 0.05, z = 1.39, p=0.16
Grade assessment				
Study design:	+4	5 Randomized Controlled Trials (results extracted from systematic review of RCTs: Eccleston, 2015)		
Study limitations	-2	Serious limitations - Selection bias: low in 2/5, unclear in 3/5; Attrition bias: low in 2/5, unclear in 2/5, high in 1/5; Performance bias: unknown; Detection bias: low in 1/5, unclear in 4/5		
Consistency:	0	No important inconsistency, I^2 = 18% post-treatment and I^2 = 21% at follow-up		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	0	No important imprecision		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊕⊖⊖ **LOW**		
Conclusion:		**There is low quality of evidence that psychological therapies (cognitive behavioural therapy, family therapy, problem-solving therapy or multi-systemic therapy) for parents of children with cancer improve parenting behaviour post-treatment as compared to treatment as usual, active control or wait-list control. There is low quality of evidence that there is no significant effect of psychological therapies (cognitive behavioural therapy, family therapy, problem-solving therapy or multi-systemic therapy) for parents of children with cancer on parenting behaviour at follow-up (2 to 12 months) as compared to treatment as usual, active control or wait-list control.**		

Psychological interventions for parents of children with cancer				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Parent mental health post-treatment, higher score indicating poor mental health				
9 RCTs extracted from systematic review of RCTs: Eccleston, 2015	Parents of children aged 0 to 19 with cancer	1010 (494 vs 516)	Psychological interventions for parents i.e. cognitive behavioural therapy; family therapy; problem-solving therapy; multi-systemic therapy) vs control (active treatment group, treatment-as-usual, waiting list control, three comparator arms)	**Parent mental health post-treatment** There was no significant effect of psychological therapies on parent mental health post-treatment. SMD is -0.22 , 95%CI -0.46 to 0.01, z = 1.86, p = 0.06

Grade assessment		
Study design:	+4	9 Randomized Controlled Trials (results extracted from systematic review of RCTs: Eccleston, 2015)
Study limitations	-2	Serious limitations - Selection bias: low in 4/9, unclear in 5/9; Attrition bias: low in 5/9, unclear in 2/9, high in 2/9; Performance bias: unknown; Detection bias: low in 3/9, unclear in 6/9.
Consistency:	-1	Some inconsistency, $I^2 = 63\%$
Directness:	0	Results are direct. Outcomes are generalizable.
Precision:	0	No important imprecision
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence that there is no significant effect of psychological therapies (cognitive behavioural therapy, family therapy, problem-solving therapy or multi-systemic therapy) for parents of children with cancer on parent mental health post-treatment as compared to treatment as usual, active control or wait-list control.**

Psychological interventions for parents of children with cancer				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Parent mental health at follow-up, higher score indicating poor mental health				
6 RCTs extracted from systematic review of RCTs: Eccleston, 2015	Parents of children aged 0 to 19 with cancer	819 (399 vs 420)	Psychological interventions for parents i.e. cognitive behavioural therapy; family therapy; problem-solving therapy; multi-systemic therapy) vs control (active treatment group, treatment-as-usual, waiting list control, three comparator arms)	**Parent mental health at follow-up (follow-up time ranging from 2 to 12 months)** Psychological therapies had a small beneficial effect on parent mental health at follow-up SMD = -0.18, 95%CI -0.32 to -0.04, Z = 2.58, p = 0.01
Grade assessment				
Study design:	+4	6 Randomized Controlled Trials (results extracted from systematic review of RCTs: Eccleston, 2015)		
Study limitations	-2	Serious limitations - Selection bias: low in 2/6, unclear in 4/6; Attrition bias: low in 3/6, unclear in 2/6, high in 1/6; Performance bias: unknown; Detection bias: low in 1/6, unclear in 5/6		
Consistency:	0	No important inconsistency, $I^2 = 0\%$		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	0	No important imprecision		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊕⊖⊖ **LOW**		
Conclusion:		**There is low quality of evidence that psychological therapies (cognitive behavioural therapy, family therapy, problem-solving therapy or multi-systemic therapy) for parents of children with cancer improve parent mental health at follow-up (2 to 12 months) as compared to treatment as usual, active control or wait-list control.**		

4.2 Sociale en praktische ondersteuning

No evidence was found

4.3 Culturele, spirituele en religieuze ondersteuning

4.3.1 Geïncludeerde uitkomstmaten

Included outcomes
Stress
Anxiety
Depression
Burnout

4.3.2 *Spiritueel trainingspakket (gericht op communicatievaardigheden en het bieden van hoop)*

Effectivity of cultural, spiritual and religious support for children in the palliative phase and their parents and/or family members				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Stress, Depression, Anxiety and stress scale (DASS-21) – stress subscale, mean item score ranging from 1 to 4, higher score indicating higher level of stress				
Borjalilu, 2016	Iranian mothers of children with cancer aged 7 -15	Total participants 42 (21 vs 21)	Spiritual training (offered in 7 group sessions of 90minutes) which focuses on communication skills, encouragement and offering hope. The spiritual training package is primarily concerned with psychoeducational therapy vs Wait-list control	**Stress at baseline vs post-treatment (intervention vs control)** Baseline: Mean (SD) is 2.71 (0.148) vs 2.67 (0.12) Post-treatment: Mean (SD) is 2.37 (0.194) vs 2.58 (0.152) Mean difference (baseline – post-treatment) was significantly different between intervention and control group, $p < 0.001$ **Stress at 3 month follow-up (intervention vs control)** 3 month follow-up: Mean (SD) is 2.18 (0.144) vs 2.45 (0.148), $p = 0.114$

Grade assessment		
Study design:	+4	Quasi experimental study (randomized study with control group)
Study limitations	-2	Serious limitations - Selection bias: high; Attrition bias: low; Performance bias: high; Detection bias: unclear
Consistency:	0	No important inconsistency. Only 1 study performed
Directness:	0	Outcomes are direct. Unclear if outcomes in Iranian mothers are generalizable to the Dutch population due to expected cultural differences
Precision:	-2	Important imprecision due to small sample size (n = 42). Only 1 study performed.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence that spiritual training for mothers of children with cancer decreases stress post-treatment as compared to wait-list control. Stress at 3 month follow-up maintained decreased, however there was no significant difference as compared to wait-list control.**

Effectivity of cultural, spiritual and religious support for children in the palliative phase and their parents and/or family members				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Anxiety, Depression, Anxiety and stress scale (DASS-21) – Anxiety subscale, mean item score ranging from 1 to 4, higher score indicating higher level of stress				
Borjalilu, 2016	Iranian mothers of children with cancer aged 7 -15	Total participants 42 (21 vs 21)	Spiritual training (offered in 7 group sessions of 90minutes) which focuses on communication skills, encouragement and offering hope. The spiritual training package is primarily concerned with psychoeducational therapy vs Wait-list control	**Anxiety at baseline vs post-treatment (intervention vs control)** Baseline: Mean (SD) is 2.7 (0.053) vs 2.68 (0.185) Post-treatment: Mean (SD) is 2.54 (0.14) vs 2.65 (0.11) Mean difference (baseline – post-treatment) was significantly different between intervention and control group, $p < 0.001$ **Anxiety at 3-month follow-up (intervention vs control)** 3 month follow-up: Mean (SD) is 2.42 (0.068) vs 2.65 (0.104); $p < 0.001$

Grade assessment		
Study design:	+4	1 quasi experimental study (randomized study with control group)
Study limitations	-2	Serious limitations - Selection bias: high; Attrition bias: low; Performance bias: high; Detection bias: unclear
Consistency:	0	No important inconsistency. Only 1 study performed
Directness:	0	Outcomes are direct. Unclear if outcomes in Iranian mothers are generalizable to the Dutch population due to expected cultural differences
Precision:	-2	Important imprecision due to small sample size (n = 42). Only 1 study performed.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence that spiritual training for mothers of children with cancer decreases anxiety post-treatment and at 3 month follow-up as compared to wait-list control.**

Effectivity of cultural, spiritual and religious support for children in the palliative phase and their parents and/or family members				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Depression, Depression, Anxiety and stress scale (DASS-21) – Depression subscale, mean item score ranging from 1 to 4, higher score indicating higher level of stress				
Borjalilu, 2016	Iranian mothers of children with cancer aged 7 -15	Total participants 42 (21 vs 21)	Spiritual training (offered in 7 group sessions of 90minutes) which focuses on communication skills, encouragement and offering hope. The spiritual training package is primarily concerned with psychoeducational therapy vs Wait-list control	**Depression at baseline vs post-treatment (intervention vs control)** Baseline: Mean (SD) is 2.68 (0.0132) vs 2.63 (0.105) Post-treatment: Mean (SD) is 2.4 (0.116) vs 2.6 (0.086) Mean difference (baseline – post-treatment) was significantly different between intervention and control group, $p < 0.001$ **Depression at 3 month follow-up (intervention vs control)** 3 month follow-up: Mean (SD) is 2.4 (0.116) vs 2.62 (0.101), $p = 0.123$
Grade assessment				
Study design:	+4	1 quasi experimental study (randomized study with control group)		
Study limitations	-2	Serious limitations - Selection bias: high; Attrition bias: low; Performance bias: high; Detection bias: unclear		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Outcomes are direct. Unclear if outcomes in Iranian mothers are generalizable to the Dutch population due to expected cultural differences		
Precision:	-2	Important imprecision due to small sample size (n = 42). Only 1 study performed.		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence that spiritual training for mothers of children with cancer decreases depression post-treatment as compared to wait-list control.** **Depression at 3month follow-up maintained decreased, however there was no significant difference as compared to wait-list control.**		

4.3.3 *Educatief spirituele interventie*

Effectivity of cultural, spiritual and religious support for children in the palliative phase and their parents and/or family members				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Burnout, Shirom and Melamed Burnout questionnaire (SMBG), mean item score ranging from 1 to 7, score below 2.75 indicates no burnout, score between 2.75 and 3.37 indicates moderate burnout, score above 3.37 indicates high burnout, score above 4.47 indicates pathological condition of burnout.				
Beheshtipour, 2016	Iranian parents of children with cancer aged 6 to 12 years (6 months to 2 years after diagnosis)	Total participants 135 (64 vs 70)	Educational-spiritual intervention (offered in 6 group sessions of 45 minutes once a week) containing a lecture and question and answer session on educational and spiritual topics (introduction to cancer disease, and philosophy of life and death) vs control group	**Burnout at baseline (intervention vs control)** Mean (SD) is 4.28 (0.61) vs 4.23 (0.50) **Burnout post-treatment (intervention vs control)** Mean (SD) is 3.25 (0.68) vs 4.33 (0.56), p <0.0001 **Burnout at 1 month follow-up (intervention vs control)** Mean (SD) is 3.33 (0.68) vs 4.42 (0.56), p <0.0001

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-2	Serious limitations - Selection bias: unclear; Attrition bias: low; Performance bias: high; Detection bias: unclear
Consistency:	0	No important inconsistency. Only 1 study performed
Directness:	0	Outcomes are direct. Unclear if outcomes in Iranian parents are generalizable to the Dutch population due to expected cultural differences
Precision:	-1	No important imprecision. Only 1 study performed.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence that educational-spiritual intervention for parents of children with cancer decreases burnout scores post-treatment and at 1 month follow-up as compared to the control group.**

5 Conclusies van evidence

5.1 Psychologische interventies

5.1.1 Effectiviteit van psychologische interventies voor kinderen in de palliatieve fase

Effectivity of psychological interventions for children in the palliative phase from 0 to 18 years			
Intervention		**Conclusions of evidence**	**Quality of evidence**
Promoting Resilience in Stress management (PRISM)	*vs. usual care*	No significant effect (p=0.05) on benefit-finding at 6 month follow-up in children and adolescents with cancer after intervention	⊕⊖⊖⊖ VERY LOW (1 RCT)
		↑hope-finding at 6 month follow-up in children and adolescents with cancer after intervention	
		no significant effect on the percentage of positive Health-related Quality of Life trajectories at 6 month follow-up in children and adolescents with cancer	⊕⊖⊖⊖ VERY LOW (1 RCT)
		↑ percentage of positive cancer specific Quality of Life trajectories regarding the subdomains nausea and worry at 6 month follow-up in children and adolescents with cancer after intervention	
		no significant effect on the percentage of cancer specific Quality of Life trajectories regarding the subdomains treatment anxiety, procedural anxiety, cognitive, physical appearance, communication and pain at 6 month follow-up in children and adolescents with cancer	
Educational problem-solving and social skills interventions	*vs. usual care*	no significant effect on loneliness at 3, 6 and 9 month follow-up in children with Cystic Fibrosis after intervention	⊕⊕⊕⊖ MODERATE (1 RCT)
		no significant effect on perceived social support of peers and classmates at 3, 6 and 9 month follow-up by children with Cystic Fibrosis after intervention	

5.1.2 *Effectiviteit van psychologische interventies voor ouders en familieleden van kinderen in de palliatieve fase*

Effectivity of psychological interventions for parents and family members of children in the palliative phase from 0 to 18 years			
Intervention		**Conclusions of evidence**	**Quality of evidence**
Promoting Resilience in stress management, parent-directed (PRISM-P) one on one sessions	*vs. usual care*	↑resilience at 6 month follow-up in parents/guardians of children with cancer after intervention	⊕⊖⊖⊖ VERY LOW (1 RCT)
		↑ benefit-finding at 6 month follow-up in parents/guardians of children with cancer after intervention	
		no significant effect on hope at 6 month follow-up in parents/guardians of children with cancer	
		no significant effect on perceived social support at 6 month follow-up by parents/guardians of children with cancer	
		no significant effect on Health-related Quality of Life at 6 month follow-up in parents/guardians of children with cancer	
		no significant effect on perceived stress at 6 month follow-up by parents/guardians of children with cancer	
		no significant effect on psychological distress at 6 month follow-up in parents/guardians of children with cancer	
Promoting Resilience in stress management, parent-directed (PRISM-P) group sessions	*vs. usual care*	no significant effect on resilience at 6 month follow-up in parents/guardians of children with cancer	⊕⊖⊖⊖ VERY LOW (1 RCT)
		no significant effect on benefit-finding at 6 month follow-up in parents/guardians of children with cancer	
		no significant effect on hope at 6 month follow-up in parents/guardians of children with cancer	
		no significant effect on perceived social support at 6 month follow-up by parents/guardians of children with cancer	
		no significant effect on Health-related Quality of Life at 6 month follow-up in parents/guardians of children with cancer	
		no significant effect on perceived stress at 6 month follow-up by parents/guardians of children with cancer	
		no significant effect on psychological distress at 6 month follow-up in parents/guardians of children with cancer	
Community-based support programme	*vs. control (contact with telephone number)*	no significant effect on anxiety at 12 month follow-up in mothers of children with Cystic Fibrosis	⊕⊖⊖⊖ VERY LOW (1 RCT)
Psychological interventions for parents i.e. cognitive behavioural therapy, family therapy, problem-solving therapy or multi-systemic therapy	*vs. treatment as usual, active control or wait-list control*	↑parent behaviour post-treatment in parents of children with cancer after intervention	⊕⊕⊖⊖ LOW (5 RCTs)
		no significant effect on parent behaviour at follow-up (2 to 12 months) of parents of children with cancer	⊕⊕⊖⊖ LOW (5 RCTs)
		no significant effect on parent mental health post-treatment of parents of children with cancer	⊕⊖⊖⊖ VERY LOW (9 RCTs)
		↑ parent mental health at follow-up (2 to 12 months) of parents of children with cancer after intervention	⊕⊖⊖⊖ VERY LOW (6 RCTs)

5.2 Sociale en praktische ondersteuning

Effectivity of social and practical support for children in the palliative phase from 0 to 18 years and their parents and/or family members		
Intervention	**Conclusions of evidence**	**Quality of evidence**
Social and practical support	Unknown effect	No studies

5.3 Culturele, spirituele en religieuze ondersteuning

Effectivity of cultural, spiritual and religious support for children in the palliative phase from 0 to 18 years and their parents and/or family members			
Intervention		**Conclusions of evidence**	**Quality of evidence**
Spiritual training package for parents	*vs. wait-list control*	↓stress post-treatment in mothers of children with cancer after intervention ↓stress at 3 month follow-up in mothers of children with cancer, however no significant difference as compared to the control group	⊕⊖⊖⊖ VERY LOW (1 RCT)
		↓anxiety post-treatment and at 3 month follow-up in mothers of children with cancer after intervention	
		↓depression post-treatment in mothers of children with cancer after intervention ↓depression 3 month follow-up in mothers of children with cancer, however no significant difference as compared to the control group	
Educational spiritual intervention for parents	*vs. control*	↓burnout scores post-treatment and at 1 month follow-up in parents of children with cancer after intervention	⊕⊖⊖⊖ VERY LOW (1 RCT)
Cultural support *Religious support*		Unknown effect	No studies

6 Aanbevelingen uit Richtlijnen

6.1 Psychologische interventies

Psychological interventions for children	
National Institute for Health and Care Excellence (NICE). End of life care for infants, children and young people with life-limiting conditions: planning and management. 2016	
Recommendation	**Level of evidence[1]**
Emotional and psychological support interventions	
Review questions 1: Are psychological interventions effective for infants, children and young people with life-limiting conditions and what factors influence the attitudes of children and young people and the family's involvement and decisions about choices of those interventions? *Clinical evidence:* A mixed method review was execute conducted. Both quantitative and qualitative studies were not identified. *Review question 2:* Are psychological interventions (including short-term bereavement therapies) effective for family members and carers of infants, children and young people and what factors influence their attitudes about those interventions before and after the death of an infant, child or young person with a life-limiting condition? *Clinical evidence:* A mixed method review was conducted. No quantitative studies were identified. One qualitative study was identified. This study was conducted in Ireland among mothers (n=10) whose child died from a life-limiting condition was included. Participants in this study had received formal and informal bereavement support following the death of their child. The study collected data using unstructured interviews and content analysis was employed to analyse qualitative data. Level of evidence - low	
Be aware that children and young people with life-limiting conditions and their parents or carers may have: • emotional and psychological distress and crises • relationship difficulties • mental health problems.	Level C: low quality evidence /Consensus-based
Be aware that children and young people and their parents or carers may need support, and sometimes expert psychological intervention, to help with distress, coping, and building resilience.	Level C: low quality evidence /Consensus-based
Be aware that siblings will need support to cope with: • their brother's or sister's condition and death • the effects of their parents' or carers' grieving. This may include social, practical, psychological and spiritual support.	Level C: low quality evidence /Consensus-based
Be aware that other family members (for example grandparents) and people important to the child or young person (for example friends, boyfriends or girlfriends) may need support. This may include social, practical, emotional, psychological, and spiritual support.	Level C: low quality evidence /Consensus-based
Be aware that children and young people may experience rapid changes in their condition and so might need emergency interventions and urgent access to psychological services.	Level C: low quality evidence /Consensus-based
Be aware of the specific emotional and psychological difficulties that may affect children and young people who have learning difficulties or problems with communication.	Level C: low quality evidence /Consensus-based
Be aware of the specific emotional and psychological difficulties that may affect children and young people who have learning difficulties or problems with communication.	Level C: low quality evidence /Consensus-based
Regularly discuss emotional and psychological wellbeing with children and young people and their parents or carers, particularly at times of change such as:	Level C: low quality evidence /Consensus-based

[1] Level of evidence adapted from GRADE
A: High; further research is very unlikely to change confidence in the estimate of the clinical effect.
B: Moderate; Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
C: Low or very low; further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain.

6.2 Sociale en praktische ondersteuning

Social and practical support	
National Institute for Health and Care Excellence (NICE). End of life care for infants, children and young people with life-limiting conditions: planning and management. 2016	
Recommendation	**Level of evidence[1]**
Review question: What factors of social and practical support (including care of the body) are effective in end of life care of infants, children and young people with life-limiting conditions and their family members or carers, and what influences attitudes about these before and after death? *Clinical evidence:* a mixed method review was conducted. No quantitative studies were identified. 22 qualitative studies were identified. Majority focused on perspectives of parents had received or was receiving hospice or palliative care, or had passed away. Three studies focused on perspectives of health care professionals. 1 study focused on the perspectives of family members. A number of themes emerged from the interviews with parents or healthcare professionals. They were: • social and practical support: Moderate to low quality evidence from 5 studies conducted among parents showed that parents thought that support to help them access care and resources available, and support from family members and the local community, such as parent-to-parent groups, was helpful. • respite services: Moderate to very low quality evidence from 11 studies in which parents or healthcare professionals were interviewed, suggested that raising the awareness and understanding of respite services would be helpful. Parents also thought that they and their child living with a life-limiting condition benefited from respite services greatly, and this benefit extended to other family members. However, parents and healthcare professionals both pointed out that things could be improved regarding respite services, notably the bureaucratic processes involved, such as the booking system, and the lack of flexibility regarding the timing and frequency of respite services. Some parents also reported that they had financial difficulties in procuring all forms of services. • care pre- and post-death of the child: Moderate quality evidence from 1 study where parents were interviewed about the death of their child reported that they appreciated the continuity of the care and of personnel pre- and post-death of their child. They also appreciated the care provided to other family members at this time. • bereavement support and follow-up. In moderate quality evidence from 6 studies based on interviews with parents and healthcare professionals, they reported that bereavement support from hospital staff, such as follow-up calls and the continuity of relationship, was very helpful for the bereavement process.	
Be aware that continuity of care is important to children and young people and their parents or carers. If possible, avoid frequent changes to the healthcare professionals caring for them.	Level B/C: Moderate to low quality evidence
Be aware that children and young people with life-limiting conditions and their parents or carers have varied social and practical support needs, and that those needs may change during the course of their condition. This may include: • material support, for example housing or adaptations to their home, or equipment for home drug infusions • practical support, such as access to respite care • technical support, such as training and help with administering drug infusions at home • education support, for example from hospital school services • financial support.	Level B/C: Moderate to low quality evidence
Discuss with parents or carers the practical arrangements that will be needed after the death of their child, and provide this information in writing. This should cover matters such as: • the care of the body • relevant legal considerations, including • the involvement of the child death overview panel • the involvement of the coroner • registration of the death • funeral arrangements • post-mortem examination (if this is to be performed).	Level B/C: Moderate to low quality evidence

When a child or young person is approaching the end of life, discuss the bereavement support available with their parents or carers and provide them with written information.	Level B/C: Moderate to low quality evidence
When a child or young person is approaching the end of life, talk to their parents or carers about available psychological bereavement support groups.	Level B/C: Moderate to low quality evidence

When planning bereavement support for parents or carers:
• talk to them about the support that is available and explore with them what they would find helpful and acceptable
• think about what support different professionals could provide, for example:
  ○ their GP
  ○ healthcare professionals who know the child or young person and are involved in their care
• think about the role of individual professionals in providing specific aspects of support
• Inform the multidisciplinary team about the support plan.
	Level B/C: Moderate to low quality evidence

When making a bereavement support plan with parents or carers, discuss possible options with them such as:
• opportunities to talk to the professionals caring for the child or young person, to:
  ○ discuss memories and events
  ○ Answer any concerns or questions they may have
• home visits from the healthcare professionals caring for the child or young person
• bereavement support groups.
	Level B/C: Moderate to low quality evidence

Ensure that arrangements are in place for professionals to talk about their thoughts and feelings with colleagues when a child or young person they are caring for is approaching the end of life or has died.	Level B/C: Moderate to low quality evidence
Following the death of a child or young person, a member of the multidisciplinary team should arrange in a timely manner for all relevant organisations and people to be informed.	Level B/C: Moderate to low quality evidence
Update relevant documents and databases after the death of a child or young person (to avoid, for example, clinical appointments being offered by mistake).	Level B/C: Moderate to low quality evidence

[1] **Level of evidence adapted from GRADE**
A: High; further research is very unlikely to change confidence in the estimate of the clinical effect.
B: Moderate; Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
C: Low or very low; further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain.

6.3 Culturele, spirituele en religieuze ondersteuning

Cultural, spiritual and religious support.	
National Institute for Health and Care Excellence (NICE). End of life care for infants, children and young people with life-limiting conditions: planning and management. 2016	
Recommendation	**Level of evidence[1]**
Religious, spiritual and cultural support	
Review question: What factors of spiritual or religious support (including care of the body) are effective in end of life care of infants, children and young people with life-limiting conditions and their family members or carers and what influences attitudes about these before and after death? *Clinical evidence:* A mixed-methods review was conducted. No quantitative studies were identified. A total of 14 studies were identified. 13 studies focused on the perspective of parents who were caring for a child with a chronic or life-limiting condition or whose child had died due to an acute illness or a life-limiting conditions. 1 Study involved siblings, 2 studies involved healthcare professionals, 1 study involved children hospitalised for an acute illness or exacerbation of a chronic condition *A number of themes occurred in the studies* • Attitude towards religion and spirituality: Very low to low quality evidence from 1 qualitative study with parents of children receiving paediatric palliative care and 1 survey study conducted with parents whose children had died in the intensive care unit (ICU) looked at the attitudes towards religious and spiritual beliefs and support. Participants' responses were divided in 4 categories: (1) having a formal religion; (2) having spirituality, but without a formal religion; (3) having no beliefs; (4)not wanting to discuss their beliefs. It was also raised that each person's personal views should be respected. • Spiritual and religious needs: Very low to low quality evidence from 3 qualitative studies with parents who had lost a child and another qualitative study with social workers working in paediatric palliative care reflected on the importance of acknowledging spiritual and religious needs. Some aspects that were raised were: (1) the role of professionals in identifying when spiritual care might be necessary, as well as acknowledging when support is not needed; (2) facilitating the access to religious support (such as the hospital chaplain or the chapel); (3)taking into account spiritual aspect when managing symptoms (such as pain). • Aphorisms: Low quality evidence from 1 qualitative study with parents of children receiving paediatric palliative care identified a number of aphorisms that could be categorised as overall outlook, goodness, human capacity and the belief that there is a reason for everything. • Practices and rituals: Very low to moderate quality evidence from 7 qualitative studies with parents of children receiving palliative care, bereaved families and social workers and 1 qualitative study with hospitalised children reported on the various practices and rituals used. The most common practice mentioned by both children and parents was praying and talking to God. Parents also mentioned reading the sacred texts, using candles, listening to spiritual music and celebrating. The use of memories and legacies was also discussed. Although most children wanted to be remembered, others preferred not to leave anything behind. Most parents found memories (such pictures or clothing) comforting, but some mothers raised that some practices may be forbidden according to certain religious or cultural rules. • Perceived benefits: Very low to moderate quality evidence from 9 qualitative studies with parents of children receiving palliative care and bereaved parents and 1 qualitative study with hospitalised children looked at the perceived benefits of spiritual and religious support and beliefs. Many parents found their religious beliefs were helpful in the decision-making process. They said that their beliefs gave them peace and comfort, helped them to cope with the situation and to make meaning of their child's illness and their loss. Their beliefs regarding an afterlife were also comforting and reassuring for parents. Some parents also reflected on the social and practical support received as a result of being part of a religious community. Children described God as a protector and comforter, who helped them go through the situation or deal with painful procedures. • Perceived difficulties: Low to moderate quality evidence from 3 qualitative studies and 1 survey conducted with parents of children receiving palliative care and bereaved parents looked at the perceived difficulties in relation to religious beliefs. Parents discussed questioning and even rejecting their faith, and they described feelings of anger at God and the church, and some also blamed God for their child's death. • Care after death: parents of children with life-threatening conditions and bereaved parents reflected on the importance of the care of the body. Continuity of care was identified as an important aspect, and this included treating the dead child as if he/she was still alive. Recognising the spiritual presence of the child was also found to be important. Mothers mentioned that cultural and religious beliefs were to be respected, such as washing and wrapping of the body, burial times and being with the child after death. The autopsy was identified as threatening by some parents, as this practise conflicted with their religious beliefs. Parents also expressed the need for bereavement support after the child's death.	

In all discussions with children and young people and their parents or carers explore with them whether, based on their beliefs and values, there are any aspects of care about which they have particular views or feelings.	Level B/C: Moderate to very low quality of evidence
Ask children and young people with life-limiting conditions and their parents or carers if they want to discuss the beliefs and values (for example religious, spiritual or cultural) that are important to them, and how these should influence their care. Be aware that they may need to discuss their beliefs and values more than once.	Level B/C: Moderate to very low quality of evidence
Take account of the beliefs and values of children and young people and of their parents and carers in all discussions with them and when making decisions about their care.	Level B/C: Moderate to very low quality of evidence
Be aware that: • some children and young people and their parents or carers find discussions about their beliefs and values difficult or upsetting • others find these discussions reassuring and helpful.	Level B/C: Moderate to very low quality of evidence
Be aware that children and young people may feel differently to their parents, carers, or healthcare professionals about how their beliefs and values should influence their care. If there is disagreement, try to make a mutually acceptable care plan, and if necessary involve the chaplaincy service or another facilitator..	Level B/C: Moderate to very low quality of evidence
When thinking about the possibility of treatment withdrawal for a child or young person who is approaching the end of life, take into account their beliefs, values and wishes and those of their parents or carers.	Level B/C: Moderate to very low quality of evidence
Take account of the beliefs and values of children and young people and their parents or carers when thinking about funeral arrangements and the care of the child or young person's body after death.	Level B/C: Moderate to very low quality of evidence
When a child or young person is approaching the end of life, discuss with their parents or carers what would help them, for example: • important rituals • recording or preserving memories (for example with photographs, hair locks or hand prints) • plans for social media content.	Level B/C: Moderate to very low quality of evidence

High; further research is very unlikely to change confidence in the estimate of the clinical effect.
B: Moderate; Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
C: Low or very low; further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain.

4 ZORG BIJ VERLIES EN ROUW

Inhoudsopgave

1 Uitgangsvragen

Vraag 1: Wat is de effectiviteit van rouwzorginterventies kinderen tussen 0 en 18 jaar in de palliatieve fase en familieleden en verzorgers?
P: Kinderen tussen 0 en 18 jaar in de palliatieve fase en hun familieleden en verzorgers?
I: Rouwinterventies
C: Geen behandeling/placebo
O: Kwaliteit van leven, rouw

Vraag 2A: Welke componenten worden gebruikt in rouwzorg interventies?
Vraag 2B: Wat zijn de ervaringen en behoeften met betrekking tot componenten van rouwzorg interventies van ouders of/en zorgverleners?

Vraag 3: Welke communicatieve en affectieve strategieën zijn er bekend om ouders te ondersteunen gedurende het levenseinde en na het overlijden van het kind?

2 Resultaten van het literatuuronderzoek

Jaar	Bibliografie	Studie karakteristieken
2016	***National Institute for Health and Care Excellence (NICE).*** End of life care for infants, children and young people with life-limiting conditions: planning and management. 2016	Richtlijn kinderen
1: Wat is de effectiviteit van rouwzorginterventies kinderen tussen 0 en 18 jaar in de palliatieve fase en familieleden en verzorgers?[*]		
2015	***Raitio K et al.*** Evaluating a bereavement follow-up intervention for grieving mothers after the death of a child. Scand J Caring Sci. 2015 Sep;29(3):510-20 [1]	RCT
2A: Welke componenten worden gebruikt in rouwzorg interventies?[**,*] **2B:** Wat zijn de ervaringen en behoeften met betrekking tot componenten van rouwzorg interventies van ouders of/en zorgverleners?[**] **3:** Welke communicatieve en affectieve strategieën zijn er bekend om ouders te ondersteunen gedurende het levenseinde en na het overlijden van het kind?[**]		
2019	***Dias N et al.*** A Systematic Literature Review of the Current State of Knowledge Related to Interventions for Bereaved Parents. Am J Hosp Palliat Care 2019 36 (12): 1124-1133	Systematic review
2013	***Stevenson M et al.*** Pediatric palliative care in Canada and the United States: a qualitative metasummary of the needs of patients and families. J Palliat Med 2013 16(5):566-77	Systematic review
2019	***Sieg SE et al.*** The Best Interests of Infants and Families During Palliative Care at the End of Life: A Review of the Literature. Adv Neonatal Care 2019 19(2):E9-e14	Systematic review
2019	***Thornton R et al.*** **S**coping Review of Memory Making in Bereavement Care for Parents After the Death of a Newborn. J Obstet Gynecol Neonatal Nurs	Systematic review
2012	***Aschenbrenner AP et al***. Integrative review: parent perspectives on care of their child at the end of life. J Pediatr Nurs 2012 27(5):514-22	Systematic review
2018	***Chong PH et al.*** Perceptions of a Good Death in Children with Life-Shortening Conditions: An Integrative Review. J Palliat Med 2018 22 (6): 714-723	Systematic review
2011	**L*ongdon JV et al***. Parental perceptions of end-of-life care on paediatric intensive care units: a literature review. Nurs Crit Care 2011 16(3):131-9	Systematic review
2014	***Donovan LA et al.*** Hospital-based bereavement services following the death of a child: A mixed study review. Palliative Medicine 2015, Vol. 29(3) 193– 210	Systematic review
2020	***Kochen E et al.*** When a child dies: a systematic review of well-defined parent-focused bereavement interventions and their alignment with grief- and loss theories. BMC Palliative Care (2020) 19:28	Systematic review
2015	***Lichtenhal WG et al.*** Bereavement follow-up after the death of a child as a standard of care in pediatric oncology. Pediatr Blood Cancer 2015; 62;S834-S869.	Systematic review.

[1]RCT is uit de volgend systematic review gehaald: *Dias N et al.* A Systematic Literature Review of the Current State of Knowledge Related to Interventions for Bereaved Parents. Am J Hosp Palliat Care 2019 36 (12): 1124-1133

[*]Systematisch gezocht. zie: bijlage 7 zoekverantwoording – search 1

[**] Gezocht naar extra systematische reviews geselecteerd uit de literatuur gevonden in search 1 (zie: bijlage zoekverantwoording search 1)

3 Evidence tabellen

3.1 Effectiviteit van rouwzorg interventies bij kinderen tussen 0 en 18 jaar in de palliatieve fase en familieleden en verzorgers

Nazorg en Rouw				
Raitio K et al. Evaluating a bereavement follow-up intervention for grieving mothers after the death of a child. Scand J Caring Sci. 2015 Sep;29(3):510-20				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: (*RCT, double-blind, etc.)* RCT, single measure post-test control group design Setting: Finnish University hospitals N = 5 All units in the hospitals where a child could die participated. 2 hospitals were assigned as 'intervention hospitals', where all mothers of deceased patients were offered the intervention. 3 hospitals were assigned as 'control hospitals', where all mothers of deceased patients received care as usual. Duration: Questionnaire was sent 6 months after the child's death Study years: Not reported	Number and type of participants: Grieving mothers, with sufficient Finnish language skills, whose child had died at the age of three years or younger. • Intervention group: N = 86 • Control group: N = 53 Age: • Intervention group: Mean: 33.2, range: 23-43 • Control group: Mean: 32.2, range: 19-47 Sex: Only mothers were included in this study Health status (p>0.05): • Intervention group: Poor: n=6 (7%) Satisfactory: n=25 (29%) Good: n=53 (62%) • Control group: Poor: n=3 (6%) Satisfactory: n=15 (28%) Good: n=35 (66%) Age of deceased child (p>0.05): • Intervention group: 1 hour – 1 day: n=7 (29%) 2 – 7 days: n=10 (42%) 8 days – 3 years: n=7 (29%) • Control group: 1 hour – 1 day: n=5 (17%)	Immediately after the death of a child, mothers were assigned to a treatment condition (intervention or control), depending in which hospital they were. Type of intervention: Three complementary components i. Support package: informational letters, poems and stories about the loss of a child; ii. Peer supporters' contact: first via telephone, later (mutually agreed), in the form of a home visit; iii. Health care personnel's contact: meeting 2-6 weeks following the death of the child, or if this was not possible, telephone contact. Type of control: Normal routine hospital care. Care varied between the control group hospitals.	Outcome definitions: • Mothers grief The Hogan Grief Reaction Checklist (HGRC) was used to report grief reactions, six months following the child's death. HGRC is a 61-item self-report instrument with 6 subscales: a) Despair; b) Panic behaviour; c) Personal growth; d) Blame and anger; e) Detachment; f) Disorganization. • Background variables Background variables were collected via a questionnaire, 6 months after the child's death. Results (per outcome) **Effect of a follow-up intervention on mothers grief** No significant differences in grief reactions between intervention group and control group (p>0.05) **Associations with background variables and mothers' grief** • Association between mothers' age and grief reaction (personal growth) Intervention group: younger mothers reported stronger personal growth than those who were older (p=0.041). • Association between health status and grief reactions Both groups: mothers with a poor health status reported stronger grief reactions, a good health status was associated with less grief reactions (p=0.001-0.041). *Except: personal growth in intervention group (p>0.05), and blame and anger in control group (p>0.05).* • Association between age of deceased child and grief reaction (personal growth) Intervention group: mothers who lost a child older than one week, had more personal growth than mothers who lost their newborn baby (p=0.038) • Association between participation in grief-support groups and grief reactions	**Conclusions** • Intervention had no significant effect on grief reactions; • More personal growth was found in younger mothers, mothers who lost a child older than one week and in mothers who received more social support (from spouse, children or HCP); • Poor health status, participation in grief-support groups and less support from spouse or HCP was associated with stronger grief reactions. Strengths: · RCT with clear design in difficult field of work, given the ethical considerations. Limitations: · Small sample sizes; · No initial measurement, because there was no anticipatory knowledge about parents who would lose a child; · Significant differences between mothers' demographic characteristics; · Only one moment of data-collection, 6 months after the death of the child. **Risk of bias** A. Selection bias: low risk/high risk/**unclear** Reason: Due to ethical considerations, allocation was based on hospital. No allocation sequence was used. Unclear if selection bias was present between hospitals.

Protocol published in register: (*clinicaltrials.gov / WHO register*) Not reported	2 – 7 days: n=8 (26%) 8 days – 3 years: n=17 (57%) Participation in grief-support groups (p=0.002): • Intervention group: Yes: n=45 (52%) No: n=39 (45%) • Control group: Yes: n=14 (26%) No: n=38 (72%)		Both groups: mothers who participated in grief-support groups had stronger grief reactions than mothers who did not participate (p=0.000-0.015). *Except: disorganization in control group (p=0.115)* • Correlation between social networks and grief reactions *Spousal support*: showed no correlations in intervention group. Spousal support correlated negatively with despair, panic behaviour, detachment and disorganization (p=0.000-0.017), and correlated positively with personal growth (0.010). *Support from children*: Positive correlations were found on personal growth and detachment in control group (p=0.000 & 0.005). Negative correlations were found in both groups on blame and anger (p=0.001 & 0.027 *Support from HCP:* Negative correlation with despair, blame and anger, detachment (p = 0.001–0.003) in the intervention group. Personal growth showed positive correlation in both groups (p=0.001 &0.022). *Support from friends:* Intervention group showed positive correlation with personal growth (p = 0.050) and negative with blame and anger (p = 0.040). No significant correlations in control group.	B. Attrition bias: low risk/high risk/**unclear** Reason: Unclear which percentage of total mothers who lost a child answered the questionnaire and were included in the study. C. Performance bias low risk/**high risk**/unclear Reason: participants and personnel were not blinded. Mothers were offered the intervention. D. Detection bias low risk/**high applicable risk/**unclear Reason: outcome assessors were not blinded from knowledge of which intervention was received

3.2 Componenten in rouwzorg interventies, ervaringen en behoeften van ouders of/en zorgverleners en communicatieve strategieën.

Nazorg en Rouw			
Dias N et al. A Systematic Literature Review of the Current State of Knowledge Related to Interventions for Bereaved Parents. Am J Hosp Palliat Care 2019 36 (12): 1124-1133			
Study characteristics	**Population**	**Outcome definitions / Main results**	**Conclusions** **Risk of bias**
Type of study: Systematic review of articles that evaluated bereavement care interventions for bereaved parents of children who died of acute or chronic illness Included studies 9 studies were included • Qualitative: 1/9 • RCT: 2/9 • Quasi-experimental: 5/9 • Case study: 1/9 Searched databases MEDLINE, CINAHL, PsycINFO, Embase Selection criteria Inclusion criteria • English language publications • Fully published empirical study that examined any intervention for bereaved parents after their child's death from acute of chronic illness • Retained: sample including children who died of any cause including accidental deaths as part of their samples Exclusion criteria	Number and type of participants: Parents of children who died of acute or chronic illness Total of 430 intervention participants from the 9 studies reviewed: • 150 fathers (35%) • 268 mothers (62%) • 12 others, such as grandparents and children (3%) Sample size varied from 5 to 136, small sample sizes were common. Age: Not reported Sex: See number and type of participants for mother/father representation	Outcome definitions Five components of the included interventions were discussed: • Types of parent bereavement interventions • Intervention effectiveness • Theoretical frameworks used to guide the interventions • Timing of interventions • Recruitment and sample size Main results **Types of parent bereavement interventions** • Single-modal interventions (6/9, 66,6%): Support groups: 8 biweekly, 1-hour sessions, led by 2 health care professionals. No statistically significant findings were reported. Psychotherapy/cognitive-focused interventions: - Group therapy retreat: 48-hour weekend retreat, 4 formal group therapy sessions. Participating parents showed a significant decrease in depressive symptoms, significant improvement in perceived quality of life and no change in perceived social support. - Mindfulness-based intervention: results of this case study remain unclear. - Cognitive behavioral therapy (CBT): 5 to 6 CBT group sessions over 6 weeks resulted in a significant reduction in overall grief symptoms in the intervention group. Therapeutic intentional touch: sessions delivered for 6-8 weeks over a 14-week frame. Intervention group reported a statistically significant effect on 3-grief related symptoms (despair, depersonalization, somatization) Expressive arts therapy: weekend camp with a variety of expressive arts activities. No statistically significant findings were reported • Multimodal interventions (3/9, 33,3%): Telephone bereavement care intervention: an assigned nurse called the parents at times over 13 months. This resulted in parents who felt supported and appreciated the continued relationship with a health-care team member who cared for their child. Combination of a support package, peer support contact and health-care provider contact (2 studies): resulted in stronger personal growth. Contact with health care professionals was reported as supportive. **Theoretical frameworks used to guide the interventions**	**Conclusions** There are individual differences in needs between bereaved parents. Individual suitable interventions should be offered based on identified needs. Those interventions should be studied when targeted to specific populations; there is no one-size-fits-all bereavement care. RCT's in this field are lacking and flaws in research design hinder the evaluation of the efficacy and generalizability of the interventions. Because of the methodological flaws in studies, authors found the intervention studies not adequate for recommendations of effective bereavement care. More general recommendations were seeing bereavement care as an integral element of pediatric palliative care and the use of an integrative palliative care model. Multimodal bereavement care should be offered to address suitable interventions for each individual. Focus should be on improving bereaved parents health outcomes. **Additional remarks** Strengths: Clear report of study selection and quality assessment with a critical view on quality of included studies. Limitations: Methodical weaknesses of included studies were lack of using a control group, nonrandomization, use of nonstandardized measures, heterogeneous sample size and small sample sizes. By using GRADE, studies were quickly seen as inadequate for

Studies were excluded if specifically focused on: • Traumatic deaths of children; • Interventions for family members outside the family role; • Studies that evaluated bereavement care program; • Reviews, editorials and conference abstracts.		2/9 (22,2%) articles described the use of an theoretical model to guide the design and implementation of a bereavement study. Theory on cognitive behavioral therapy and the ATTEND model were used. **Timing of interventions** Intervention exclusively took place within first year after death in 3/9 (33,3%) studies. The earliest intervention commenced prior to parents leaving the hospital, the earliest conclusion of intervention within 6 weeks. In 6/9 studies (66,6%) , interventions were provided beyond the first year of child's death up to five years after. **Recruitment and sample size** Possible concerns about recruitment were discussed. Support located in the hospital where the child was treated before death can deter participants, since returning to this place could be emotionally difficult.	recommendations of effective bereavement studies. This is a relatively strict tool, given the paucity of high-level evidence in this field. **Risk of bias** GRADE tool was used for evidence ratings, instrument range from very low to high. • Very low: 1/9 (11,1%) • Low: 3/9 (33,3%) • Low to moderate: 5/9 (55,5%)

Nazorg en Rouw			
Stevenson M et al. Pediatric palliative care in Canada and the United States: a qualitative metasummary of the needs of patients and families. J Palliat Med 2013 16(5):566-77			
Study characteristics	**Population**	**Outcome definitions / Main results**	**Conclusions** **Risk of bias**
Type of study: Systematic review of qualitative and survey-based studies on the needs of patients and families in pediatric palliative care. Included studies 21 studies Searched databases MEDLINE, PsycInfo, CINAHL Selection criteria Inclusion criteria • Perspectives of either parents, patients or Health Care Professionals (HCPs) in Canada or United States on aspects of PPC and PEOLC • Study methods include thematic surveys, surveys with open-ended question, qualitative methods, published in an English peer-reviewed journal • Published between 2000 and 2010 No exclusion criteria reported	Number and type of participants: Perspectives of health care professionals, patients and parents are reported Age: Not reported Sex: Not reported	Outcome definitions For all findings the proportional frequency of the finding (PFF) is calculated. This indicates the number of times a finding is reported across all included articles. Main results Needs were grouped into 10 thematic domains **Health care delivery and accessibility (13 studies), PFF = 62%** • Continuity consistency and coordination of care, PFF = 52% • Services outside the hospital, PFF = 24% • Access and availability of services, PFF = 14% **Interaction with staff (13 studies), PFF = 62%** • Honest and straightforward communications, PFF = 43% • Parent & patient involvement, PFF = 33% • Families reported wanting a familiar person to deliver difficult news in a sensitive and caring manner, PFF 24% **Information needs (9 studies), PFF 43%** • Need for more information (5 studies), PFF 24% • Clear and understandable information, PFF 29% • Preparation for illness progression and treatment effects, PFF 19% **Bereavement needs (9 studies), PFF 43%** • Continuity with treating hospital: need for extending care from time to diagnosis through to the bereavement period. Parents reported developing a strong bond with the treating hospital and feeling abandoned if this bond was broken, PFF 29% • Preparation for death and bereavement: PFF 19% • Bereavement services: parents expressed a need for bereavement services to be available after their child's death. PFF 19% • Mementos: parents reported wanting mementos such as a handprint or a hospital bracelet, PFF 14% • Parental networking: parents desire contact with other families that have lost a child, PFF 10% **Psychosocial needs (9 studies), PFF 43%** • Emotional support, PFF 33% • Need for dignity and respect, PFF 14% • Patient need access to peers and other children going through similar experiences. PFF 10% • Parents need access to other families in similar situations • Families need unrestricted access to their child when the child approaches end of life, PFF 19% **Spiritual needs (8 studies), PFF 38%** • Maintaining connection to the child, PFF 29%	**Conclusions** Patient and family needs can be categorized in 10 general domains: health care delivery and accessibility, interactions between staff and families, information needs, bereavement needs, psychosocial needs, spirituality needs, pain and symptom management, cultural needs, decision making and needs of siblings. High PFF of health care delivery and accessibility needs and interaction with staff needs shows that these domains are touched on in many of the articles. However a low PFF does not indicate there is less need in the area, but rather that these domains are less represented. All 10 domains are important in consideration of policies to address patient and family needs. **Additional remarks** Strengths: Concise and comprehensive overview of recent literature in PPC and PEOLC. The study highlights the most frequently reported needs as well as needs that are less frequently mentioned but equally important for clinicians and policy makers.

		• Access to spiritual counselor and clergy, PFF 14% • Religious activities, PFF 10% • Guidance according to one's own values, PFF 19% • Hope: Parents highlighted maintenance of hope while accepting their child's prognosis, PFF 5% **Pain and symptom management (6 studies), 29%** • Consistent pain management, PFF 5% • Effective pain and management: Need to relieve pain and symptoms. PFF 24% • Crucial aspect of pain management is the need for the patient to be comforted and soothed, PFF 10% **Cultural needs (6 studies), PFF 29%** • Cultural sensitive care: Families reported importance of providing care and information that is culturally sensitive and fair, PFF 29% • Fair treatment, PFF 5% • Translators: Need for translators when parents did not speak English and communication was not effective, PFF 10% **Decision-making needs (6 studies), PFF 29%** • Control of treatment decisions, PFF 14% • Adequate information to make decisions, PFF 19% • Support during decision making, PFf14% **Siblings' needs (5 studies), PFF 24%** • Support and counseling, PFF 19% • Specific services for siblings, PFF 14% • Family-oriented care, PFF 14%	<u>Limitations:</u> This review was restricted to published literature and did not include theses or dissertations. Several of the studies examined pediatric palliative care services or the care of seriously ill and dying children more generally. Findings across hospital units or type of illness were not compared. **Risk of bias** Not reported

Nazorg en Rouw			
Sieg SE et al. The Best Interests of Infants and Families During Palliative Care at the End of Life: A Review of the Literature. Adv Neonatal Care 2019 19(2):E9-e14			
Study characteristics	**Population**	**Outcome definitions / Main results**	**Conclusions** **Risk of bias**
Type of study: Systematic review of studies on neonatal palliative care, parental needs during and surrounding loss of the infant, and effective bereavement interventions. Included studies 15 studies were included • Systematic reviews 10/15 • Qualitative studies 5/15 Searched databases PubMed, CINAHL Selection criteria Inclusion criteria • Full-text articles published in English • Published after 2012 • Focus on the best interests of neonates and best practices in neonatal palliative care Exclusion criteria • Focus on palliative care for specific diagnosis	Number and type of participants: Neonates who receive neonatal palliative care on NICU and parents of these infants. Number not reported. Age: Not reported Sex: Not reported	Outcome definitions A thematic analysis of the following areas was discussed • Palliative care for infants • Best interests of infants • Best interests of the parents • Effective bereavement interventions **!!! The findings about 'best interests of the parents' and 'effective bereavement interventions' are most relevant for the research on loss and grief. Other findings are therefore discussed in this column briefly.** Main results **Palliative care for infants** Key concepts of qualitative care for the infant's body, mind and spirit were discussed. **Best interest of infants** Specific components of palliative care were mentioned. Such as, withholding or withdrawing medical interventions, use of opiates and anxiolytics and providing nutrition. **Best interest of the parents** Health care providers can facilitate and affect the bereavement process of the parents by their handling. This starts from the diagnosis of a life-limiting diagnosis until after the death of the infant. Several negative and positive factors were pointed out: Factors that increased parental stress: - Healthcare providers not being competent in dealing with the equipment required to care for the infant; - Healthcare providers who did not comprehend the diagnosis, treatment or complications; - Parents who were not given the opportunity for a private peaceful place and sufficient time to say goodbye found a negative effect on grieving, accepting and coping. Positive experiences from parents included nurses who: - Are experienced and show confidence in caring for the infant; - Learn the infant's individual needs and routines; - Express emotions; - Comfort the parents with a hug, smile or beverage; - Not give up hope until it is clear that there is no other course; - Give explanations in understandable language; - Acknowledge the wishes of the parents, even when these wishes conflict with the recommendations of the healthcare team. Having HCPs attend the funeral may enhance parent's feelings of support from the hospital. Follow-up calls or meetings with parents can help facilitate closure for the parents as well as continue to help them feel supported by the hospital. **Effective bereavement**	**Conclusions** It is important that healthcare providers take steps to reduce stress and facilitate the process of grieving from parents of the child who receives palliative care. For example, providing a private and peaceful place to bid farewell and/or plan follow-up calls or meetings after the bereavement of their child. Health care providers should be trained in understanding and encompassing parents' needs. **Additional remarks** Strengths: High amount of systematic reviews included. Thematic analysis resulted in an extensive narrative of parents' perceptions on neonatal palliative care. Limitations: The method for data-extraction was not mentioned in this article. Statements in results are often based on one article. No quality appraisal of selected studies was conducted. **Risk of bias**

		Three interventions have been identified as helpful for parents in the grieving process: • Allowing parents to have input on where and when the infant dies. When their wish is not possible, a private room with a bed is helpful. • Offering parents the opportunity to bathe and dress the infant in a special outfit and directly ask whether there is anything specific they would like to do for or with the infant before death. • Memory boxes, containing mementos. Especially photographs surrounding the death of the infant.	Not reported

Nazorg en Rouw			
Thornton R et al. Scoping Review of Memory Making in Bereavement Care for Parents After the Death of a Newborn. J Obstet Gynecol Neonatal Nurs			
Study characteristics	**Population**	**Outcome definitions / Main results**	**Conclusions** **Risk of bias**
Type of study: Scoping review of studies focused on parents' perception of memory making in bereavement care after the death of a newborn Included studies 25 studies were included • 20/25 qualitative studies • 5/25 mixed method studies (only the qualitative data was used) Searched databases MEDLINE, CINAHL, Embase, PsychINFO Selection criteria Inclusion criteria • Available in English • Included parents of neonates as research participants • Included one or more memory making intervention as the focus of investigation or as a finding • Contained original data from the perspective of bereaved parents Exclusion criteria • Opinion pieces, news items, editorials, and review articles • Quantitative studies • Studies more than 30 years old (Estimated, published before 1988.)	Number and type of participants: Parents of neonates who experience the death of a newborn. Sample sizes varying from 4 to 181 Age: Not reported Sex: 18/25 studies (72%) included mothers and fathers, although mothers were overrepresented in most of these studies. Intervention: Any intervention or experience that encouraged contact or interaction between parent and newborn and any intervention that resulted in the creation or collection of mementos.	Outcome definitions A narrative analysis of the qualitative content was discussed by the following themes: • Contact with the newborn • Opportunities for caregiving • Bereavement photography • Collection and creating of mementos • Guidance in memory making Main results **Contact with the newborn** See, touch and hold the newborn during after life can enable parents to form important bonds and to create memories that are helpful after their newborns death. Holding their child as he/she died, was valued by and helpful for most parents, but also emotionally difficult. Support and reassurance from hospital staff can be needed. Parents' failure to spend time with, or contribute care for their newborn was associated with regrets. **Opportunities for caregiving** Providing care for their newborns may help individuals develop their identities as parents. Being involved and participating in bedside care was identified as helpful. Parents experienced frustration when staff did not welcome their participation and felt regret when their involvement in care was limited. **Bereavement photography** Photographs can help parents by confirming the newborn's existence and may legitimize the parents' loss. The images can provide the basis for a continuing relationship between parents and child. Finally, they are important cues for memory to help parents process their losses. Parents wanted health providers to offer education and encouragement. Although, parents often feel a range of barriers to bereavement photography, most parents who did not receive photographs wished they had. Health care providers could help with overcoming barriers. **Collection and creation of mementos** The collection and creation of mementos was described meaningful from the perspective of bereaved parents in most studies. Examples of commonly collected mementos are: hand-, or footprints; molds; items of clothing that had been in contact with the newborn; locks of hair. **Guidance in memory making** Many of the studies stated the parents need to be actively supported and guided through all aspects of memory making. Including spending time with the newborn, having physical contact and collecting or creating mementos. Parents felt emotionally unstable and were grateful to staff who actively supported them.	**Conclusions** Parents need active guidance and practical support from health care professionals to engage in memory making with their newborns, suitable to their individual and cultural preferences. This can be put into practice by helping parents in caregiving activities, until they are at ease with spending time with their newborn by themselves. Also, mementos can be offered; varying from photographs to items used in their newborns' care. Staff should store these items when parents' are reluctant in accepting mementos, there is a chance that parents need time, but appreciate them later on. **Additional remarks** Strengths: Broad range in definition of memory making to allow for the identification and review of as many relevant articles as possible. This review has a clear study design. *Arksey and O'Malley (2005)* framework for scoping reviews was used. Limitations: Only articles in English language are included, this can affect the range of represented cultures. Moreover, articles have not been assessed for methodological quality. For evaluation of effectiveness, further research is needed. **Risk of bias** Not reported

Nazorg en Rouw			
Aschenbrenner AP et al. Integrative review: parent perspectives on care of their child at the end of life. J Pediatr Nurs 2012 27(5):514-22			
Study characteristics	**Population**	**Outcome definitions / Main results**	**Conclusions** **Risk of bias**
Type of study: Systematic review on parents' perspectives on end-of-life care for their children Included studies 15 studies were included • Qualitative: 12/15 • Research design not reported: 3/15 Searched databases CINAHL, MEDLINE, PSYCHinfo Selection criteria Inclusion criteria • Research studies about parent or family perspectives on end-of-life care in general Exclusion criteria • Articles with no discussion of parent perceptions of experiences at the end of their child's life included	Number and type of participants: Parents' of children who receive end-of-life care Number not reported Age: Not reported Sex: Not reported Other: • Nursing articles: 6/15 • Palliative care articles: 3/15 • Medical articles: 6/15	Outcome definitions Thematic analysis of recurring themes from review of literature: • Poor communication/Lack of information • Strained relationships/Inadequate emotional support • Parental need to maintain parent/child relationships in life and death • Quality of care continues after the death of the child • Influence of services/Planning on parent/child impacts quality of life • The difficult decision to terminate life support Main results **Poor Communication/Lack of Information** Dissatisfaction from parents regarding communication and information was found in several studies. Problems that were mentioned included perceiving inadequate information and not knowing who to ask for help, difficulties with understanding what was told and receiving emotional information in a public area. Parents felt that they received insufficient information about their child's care, and information was sometimes delivered in an inappropriate way. **Strained Relationships/Inadequate Emotional Support** The overall satisfaction with care was high. However, especially when care shifted from curing to palliative, parents reported that it seemed as nurses had difficulties supporting them emotionally. Emotional support and compassion were aspects of care that parents were missing. No suggestions are given for improvement. **Parental Need to Maintain Parent/Child Relationships in Life and Death** During the end of the child's life, parents desired to maintain relationships with their child. Saving a memento after the death of their child was addressed as an important need. Also, honest communication/information and privacy were reported as important needs. **Quality of Care Continues After the Death of the Child** Follow-up communication from familiar staff members was appreciated by parents. The basis of care quality was built on communication, honesty, respect and anticipation of needs. **Influence of Services/Planning on Parent/Child Impacts Quality of Life** Continuity and coordination of care, shared goals between parents and caregivers, and consistent care were important issues for parents. Communication and providing information was most mentioned as an area for improvement. Priorities on this area were increased sensitivity, empathy and improved physical bereavement care. Parents requested more information about autopsy results, events surrounding death and increased frequency of updates. **The Difficult Decision to Terminate Life Support** Parents' perspectives on decision making were pointed out. Health care providers play a role in providing honest and complete information, support and emotional expression and facilitating ready access to staff.	**Conclusions** The importance of communication is addressed in almost every theme. Health care providers must pay close attention to providing adequate and sufficient information. Moreover, understanding parents' perceptions on their child's care is indispensable for health care providers, including their need for emotional support. Especially when the focus of care shifts from curing to palliative-care, parents' felt a need for more emotional support from health care providers. HCPs expressing emotions and increasing their sensitivity and empathy, could play a positive role in this emotional support. In addition, a care coordinator could facilitate continuity to help ensure quality of care. **Additional remarks** Strengths: Extensive analysis of recurring themes from 15 studies. A broad range of parents' perspectives was discussed by six different themes. Limitations: No method for determination of themes was mentioned. Articles have not been assessed for quality appraisal. Authors stated variation in quality of report and small sample sizes in many studies. Also, a possibility of recall bias was mentioned, given the retrospective nature of studies. In the included articles, there was an overrepresentation of Euro-American participants, which leads to difficulties in generalizing results. **Risk of bias** Not reported

Nazorg en Rouw			
Chong PH et al. Perceptions of a Good Death in Children with Life-Shortening Conditions: An Integrative Review. J Palliat Med 2018 22 (6): 714-723			
Study characteristics	**Population**	**Outcome definitions / Main results**	**Conclusions** **Risk of bias**
Type of study: Systematic review on perspectives of stakeholders on "good death" for children with life-shortening conditions. Included studies 24 studies were included • Qualitative: 19/24 • Mixed-method: 5/24 Searched databases Embase, Web of Science, Medline, CINAHL, PsychINFO Selection criteria Inclusion criteria • Empirical research, published in a peer-reviewed journal • Research on experiences surrounding death and dying in children with life-shortening conditions • Study samples that included patients, family caregivers, and/or health care professionals	Number and type of participants: Perception of death and dying in children with life-limiting diseases (LLD) from: - Patients with LLD (1/24) - Parents of children with LLD (19/24) - Professional caregivers, directly involved in caring for children with LLD (3/24) - Siblings of children with LLD (2/24) Age: Patients' age varying between 1-19 years Sex: Not mentioned	Outcome definitions Narrative about a good death, revolved around three themes: 1. Level of needs 2. The composite experience 3. Control (preservation and letting go) Main results **Level of needs** Needs extracted from the articles were stated and divided in three areas: Wish list or expectations - Actively caring for the dying child - Follow-up after the child's death - Involvement in EOL decisions - Respite care - Bereavement support service - Talk openly with dying children - Special treatment Goals at end of life - Reduce patient's suffering - Doing everything possible to save the child's life - Stay home - Be with patient at point of death - Maintaining hope Unmet needs - Spiritual care - Coordination and continuity of care - Access to respite - No point of reference to guide own experience - Attending to the siblings - Meeting health care providers after the death. Duality and ambivalence in needs was pointed out. Parents needs could change, when faced different challenges. The question was raised in what extend those dichotomous beliefs burden caregivers. Authors assert that mismatch in needs between children with LLD plus their parents, and the care provided from health care professionals, can contribute to the perception of suffering. **The composite experience** Negative and positive experiences from stakeholders about their challenges in the health care system were mentioned. Furthermore, perceptions of suffering were pointed out. Negative experiences - Receiving conflicting information	**Conclusions** Analysis and interpretation of the findings resulted in a tentative model: "the sphere of influence". The sphere refers to the healthcare system in where stakeholders interact. In this sphere, every individual (patient, family or HCP) has their own balance of needs, (composite) experiences and perceived control. The blend of all this factors determines the extent of suffering at any point in time. Suffering is inversely related to the measure of a good death. Since all factors that contribute to suffering are interdependent and fluid, the quality of death itself, at least in and surrounding the dying phase, is never constant. Shifting locus of control back to parental caregivers within a family-centered model of care could mitigate the perception of suffering among stakeholders. Implication for practice: A need for the professional caregiver to be free of assumptions, and to explore in-depth what may appear to be opposing or shifting positions **Additional remarks** Strengths: Strong methodological design with the use of an integrative review design (*Wittemore and Knafl*) and review reporting following ENTREQ statement. A relatively high amount of studies was included. The quality of those included studies was considered as above average. Different

• Reported perceptions from those who were directly involved in caring for dying children • Children referred to in the study were 1-19 years old Exclusion criteria • Language other than English • APRAC quality score below 4 and relevance score below 1 (see risk of bias)		- Unprepared for the child's death - Not given 'time' and 'space' to be with dying child - Suboptimal control of symptoms - Sense of abandonment by health care providers - Loss of parental role and family intimacy in the hospital setting - Inconsistent or change in health care providers near the end of life - Treatment withdrawal; complications related, sudden or unexpected deaths - Altogether a most difficult journey <u>Positive experiences</u> - Relationship between HCP and child that facilitated death conversations - Special qualities of HCP - Given control over how or where child died - Be there with child at point of death - Actively rendering care on their own - Access to HCP day and night - Supported both individually and as a family - See death as "end of suffering" <u>Perceptions of suffering</u> - Loss of function and physical changes in dying child - Caregivers anticipating impending loss during the dying phase - Withdrawal from outside world commonly seen in dying child - Whether "preserving" or "letting go," sense of suffering prevails - Lack of support at home (especially after hours) causing helplessness and distress **Control** The imperative for control and how this affected the stakeholders was mentioned. Provision of informational, emotional and instrumental support enhanced the sense of personal control and authority over the child's death and life with other family members. This helped, particularly parents, with keeping fear and uncertainty within limits of tolerability. Control was seen as a mediating factor in the oscillating passage from "preservation" to "letting go" and a precondition for fulfilling parental tasks.	stakeholders were represented to form a narrative about a good death. Clear needs and perceptions were extracted from the literature. Findings revealed a dynamic and multilayered ecosystem that incorporates different elements and players, within a space bounded by the health care system. <u>Limitations:</u> Risk of recall bias and change of perspective, given the retrospective design of six studies. **Risk of bias** APRAC was used to assess quality Threshold set for quality: 4 Scores ranged from 4-8 Relevance was rated by assessing applicability of findings to the review question. Scores ranged from 1-4 5 studies were excluded from final synthesis based on low quality appraisal.

Nazorg en Rouw			
L*ongden JV et al*. Parental perceptions of end-of-life care on paediatric intensive care units: a literature review. Nurs Crit Care 2011 16(3):131-9			
Study characteristics	**Population**	**Outcome definitions / Main results**	**Conclusions** **Risk of bias**
Type of study: Systematic review of qualitative studies on parental perceptions on end-of-life care for their child in PICU Included studies 13 qualitative studies were included Searched databases Cochrane Library, Medline, CINAHL, PubMed Selection criteria Inclusion criteria • Published in English Exclusion criteria • Published before 2000 Limited selection criteria. Search term included: *pediatric end-of-life care, pediatric intensive care, pediatric palliative care, child death and parental perceptions of need during the death of their child.*	Number and type of participants: Parents of children who died in PICU Sample size varying from 7 to 78 parents Age: Age of PICU non-survivors: • <1 year: 49% • 1-4 years: 19% • 5-10 years: 19% • 11-15 years: 7% • 16+ years: 7% Sex: Not reported Other: Setting: Pediatric Intensive Care Unit (PICU)	Outcome definitions Narrative analysis of the included studies, discussed by the following chapters: • Communication and end-of-life decision-making • The transcendent quality of the parent-child relationship • Spirituality as a concept • Practical considerations during pediatric end-of-life care (ELC) • Bereavement support and follow-up Main results **Communication and end-of-life decision making** Helpful components: • Honest and complete information provided in a timely, compassionate manner in a language parents understand; • Accessibility of medical staff; • Expression of emotions, kindness and compassion from those caring for the child; • Parents being involved in the decision-making process; • Parenting of the child as much as possible. • Interventions focused on improving parents' understanding and individualizing the decision-making process could improve the experience of parents. Negative experiences: • Involvement of a number of health professionals which leads to conflicting information; • Loss of control. **The transcendent quality of the parent-child relationship** Parents felt the need to maintain a connection with their child and to be able to continue to love and care for them in the dying process. Preserving of integrity and sanctity of parent-child relationship should be supported. Helpful components: - Quiet time alone with child and privacy; - Positive environmental memories can have an positive effect on the bereavement process; - Choice in where the child dies; - Acknowledgement for parents' vital role, responsibility and contribution to their child's care. **Spirituality as a concept** Parental religious and spiritual perspectives can affect and influence parents' understanding of, and approach to, illness and end-of-life decision making. Spiritual or religious themes were mentioned as most helpful during the child's last days of life. Helpful spiritual/religious components: - Maintaining a connection with the child; - Religious faith and emotional support from religious leaders; - Support from hospital clergy, parents often rely on an introduction by hospital staff; - Words and actions from critical care staff that demonstrate caring and foster truth. **Practical considerations during pediatric ELC**	**Conclusions** Palliative care should be focused on the needs of the child and their family. Transition of critical to palliative care should be individualized and parents should be given options in their child's end-of-life care. A pediatric care consultant and specialist palliative care nurses play an important role in ensuring this. **Additional remarks** Strengths: Comprehensive analysis of 13 qualitative studies on parental perceptions by five themes. Limitations: Reported statements of parental perceptions were often based on one article. Retrospective design of studies, perceptions of parents could change over time. Information of perceptions was obtained at varying times along the grief process; this could affect the validity of the data since grief could be seen as a

		End-of-life decisions were based on how the level of pain of the child was perceived. Reassuring parents on the fact that their child is not suffering, may have a beneficial effect on long-term adaptive coping. **Bereavement support and follow-up** Components of bereavement support were pointed out: <u>Timing</u>: start at time of death or even before. <u>Interventions and perceptions:</u> - Bereavement services from hospitals were important; - Support groups were beneficial for most parents; - Meeting between HCPs and bereaved parents can offer HCPs a valuable opportunity for learning and receiving feedback. - Follow-up visit with the child's consultant resulted in contradictory experiences for parents. Varying from helpful, to leaving them with unanswered questions. Others felt not ready to return to the hospital. - HCPs should promote a support network that can remain available to parents throughout the bereavement process. - Interventions that built on positive aspects of the relationship between families and HCPs will significantly improve parental experiences and promote better bereavement adjustment.	process. A longitudinal study would be more appropriate. **Risk of bias** CASP appraisal checklist for qualitative research was used. Results were not reported.

Nazorg en Rouw			
Donovan LA et al. Hospital-based bereavement services following the death of a child: A mixed study review. Palliative Medicine 2015, Vol. 29(3) 193– 210			
Study characteristics	**Population**	**Outcome definitions / Main results**	**Conclusions** **Risk of bias**
Type of study: Systematic review on hospital-based bereavement services Included studies 34 articles were included: • Qualitative: 13 • Quantitative: 6 • Mixed Method: 9 • Descriptive article: 6 19 bereavement interventions were identified. **!!! Authors speak of 39 included articles in abstract and of 34 articles in methods section. At first, in the results section authors mention 34 included articles, but later state that 39 articles were included in synthesis This discrepancy remains unclear.** Searched databases MEDLINE, EMBASE, CINAHL, PsychINFO Selection criteria Inclusion criteria • Published between 1980-2014 • Addressing of hospital-based care or outreach services for bereaved parents and/or other family members • Included bereaved parents and/or other family members of neonates, children or adolescents • Published in English	Number and type of participants: Parents, mothers, fathers, grandparents, siblings and health care professionals • Parent 30/34 • Sibling 3/34 • Grandparent 1/34 Age: Not reported Sex: Not reported Other: Settings: • Perinatal/neonatal • Neonatal intensive care unit (NICU) • Pediatric • Pediatric oncology • Pediatric intensive care unit (PICU) • Pediatric palliative care	Outcome definitions Narrative synthesis of the included studies. Starting with a summary of hospital-based services and interventions. Next, psychosocial impact of bereavement interventions was discussed by five themes: i. Feeling cared for and supported ii. Building a new community iii. Helpful relationships iv. Improved coping and personal growth v. Impact on staff Finally, recommendations for best practice were given. Those are stated in the conclusion column on the right. Main results **Summary of hospital-based services and interventions** 19 bereavement interventions for families were identified • Phone calls at key intervals (n=12) • Provision of resource materials (n=10) • Group programs (n=9) • Sibling camp (n=5) • Remembrance program (n=5) • Post bereavement meetings (n=4) • Memory making (n=4) • Mailings at key intervals (n=4) • Referral to community agencies (n=4) • Individual counseling (n=4) • Peer support (n=4) • Sympathy card (n=3) • Home visits (n=3) • Family counseling (n=3) • Educational event (n=3) • Anniversary card (n=2) • Newsletter (n=1) • Financial assistance (n=1) • Photography (n=1) Timeframe: initial contact between families and hospital staff was between 2-6 weeks following the child's death. This was confirmed as an appropriate timeframe for parents. Conclusion of intervention ranged from 6 months to 2 years. **Psychosocial impact of bereavement interventions** i. Feeling cared for and supported	**Conclusions** Qualitative research reports positive effects by hospital-based bereavement services delivered to families bereaved by a child. Those effects were feeling supported, a decreased of sense of isolation and increased coping and personal growth. Quantitative studies report little to no effect on grief, adjustment and coping by parents. A possible beneficial effect from bereavement services on families at risk of developing complex grief was reported. Bereaved parents felt the need for support from health care professional, but also from their informal social network. In those groups, different needs were met. **Recommendations for best practice** ➢ Develop a formal model of care that is theoretically driven and evidence based Suggestions: evidence-based intervention research; funding for formal model of bereavement care; risk screening in bereavement care; more inclusive approach and standard procedures of follow-up and bereavement care after de death of a child, to prevent families dealing with practical items and instead allow them time to grief. ➢ Provide effective communication and continuity of care through diagnosis, treatment, palliative and bereavement care Suggestions: guidance and support early in the care trajectory; relationship building between HCP and family during treatment, which extends beyond the death of the child; transition into community of bereaved parents after death of the child; communication between all parties (especially in transition of care). ➢ Provide a range of interventions for the "whole family" and flexibility in service delivery ➢ Ensure collaboration between family, community, and hospital treatment unit ➢ Provide support, supervision, and education for staff **Additional remarks** Strengths: Comprehensive synthesis of bereavement-services studies with different designs included. Clear study design of the narrative

• Included: Recommendations/a description/an evaluation of a selected intervention aimed at addressing the grief reaction of parents, siblings, or grandparents due to the death of an infant or child • Reflection of experience and recommendation from healthcare professionals working in these settings Exclusion criteria were not mentioned.		<u>Supporting intervention(s):</u> follow-up support (mail/phone/home visits) <u>Findings:</u> Staying connected with deceased child's health care professionals prevented secondary loss and feelings of abandonment. ii. Building a new community <u>Supporting intervention(s):</u> group support <u>Findings:</u> reduction of sense of isolation and development of healing friendships, improvement in emotional status, no significant change in psychosocial functioning and grief reactions. iii. Helpful relationships <u>Supporting intervention(s):</u> offers of (informational) support from healthcare professionals, peer supporters <u>Findings:</u> positive experiences from bereaved families, emotional support and intimacy of similar life experience iv. Improved coping and personal growth <u>Supporting intervention(s):</u> support groups, group intervention, follow-up care, bereavement camp for siblings <u>Findings:</u> qualitatively improving coping and allowing for personal growth v. Impact on staff <u>Findings:</u> meaning and satisfaction from their role in bereavement care. Significantly more suffering by the lack of education, time between patients and staff support. Staff felt ill-equipped to undertake bereavement care.	synthesis, using *Popay et al (2006)*. Overview of large quantity of bereavement interventions. <u>Limitations:</u> Small sample sizes and lack of empirical evidence in quantitative or mixed methods studies. Overrepresentation of western cultures and mothers can cause difficulties in generalizing results. Only hospital-based interventions are included. Community interventions or specialized therapeutic care, with the potential of adding helpful strategies, were not included. A discrepancy in information about included articles was found. Not clear how many articles actually were used for synthesis. **Risk of bias** Mixed Method Appraisal Tool (MMAT) *(Pluye et al., 2009)* was used for quality appraisal. <u>Qualitative studies:</u> QUAL range 0-6, scores varied from 3/6 to 6/6 <u>Quantitative studies:</u> QUAN range 0-3, scores varied from 0/3 to 3/3 <u>Mixed Method studies:</u> MIXED range 0-3, scores varied from 2/3 to 3/3 Descriptive articles were not addressed for quality appraisal.

Nazorg en Rouw			
Kochen E et al. When a child dies: a systematic review of well-defined parent-focused bereavement interventions and their alignment with grief- and loss theories. BMC Palliative Care (2020) 19:28			
Study characteristics	**Population**	**Outcome definitions / Main results**	**Conclusions** **Risk of bias**
Type of study: Systematic review of well-defined parent-focused bereavement interventions Included studies 21 articles were included, describing 15 interventions • Quantitative studies: 4/21 • Qualitative studies: 6/21 • Mixed method studies: 2/21 • Descriptive studies: 9/21 Searched databases MEDLINE, Embase, CINAHL Selection criteria Inclusion criteria • Articles containing bereavement interventions offered by regular HCPs to parents of children who have died or those children in the phase of receiving palliative care. • Interventions aimed at consoling intense feelings of grief during the end-of-life phase or after the loss of a child. Bereavement care may also occur before the death of the child • Studies must address interventions defined as: Intentional acts performed for, with, or on behalf of, a parent or parents. An intervention must consist of well-defined, concrete proceedings. This means it can be replicated by other HCPs and is supported by instructions, a manual,	Number and type of participants: Parents of deceased children or children with a life limiting condition at the end-of-life phase, receiving palliative care. Number not reported Age: Children with the age varying from 0-18 years. Sex: Not reported Other: Interventions were described from parents' or HCPs' viewpoint.	Outcome definitions Intervention characteristics: • Initiation: The bereavement care programs were predominantly (14/15) initiated by hospital staff • Field of work: neonatology (5/15), pediatrics (9/15), or both (1/15) • Timing: start after the child's death (11/15), during end-of-life phase (1/15) or before and after death (3/15) • Intervening person: mostly a nurse (7/15) or a physician (5/15). Other people intervening included clinical social workers, chaplains or peer supporters, photographers, trained counsellors, public health nurses, team members who had the most contact with parents or experienced the lightest workload or, bereavement care team members or not otherwise specified. • Practices described in the interventions: all bereavement interventions could be divided and clustered into five overarching components of intervention: i. Acknowledging parenthood and the child's life ii. Establishing keepsakes iii. Follow-up contact iv. Education and information v. Remembrance activities Main results **Acknowledging parenthood and the child's life** Consist of: washing, holding or dressing the child; giving parents privacy surrounding the death of the child; providing the child with a certificate of life; a blessing ceremony. Implications: These practices can support parents to recognize the unique identity of their child and to adjust gradually to the reality that their child is dying. HCPs can facilitate parents in fulfilling their parental role and acknowledge the identity of their child, before and after death. Supported by theoretical components concerning: anticipatory grief; attachment working models and plans; coping. **Establishing keepsakes** Consist of: safeguarding a lock of hair; hand, foot or face print; pictures; items that belonged to the child such as toys, a blanket, ornaments, a memory stone, clothes, a baby ring or bracelet, memory books, poems or other belongings. Those items were often provided in the form of a comfort basket or memory box. Implications: Keepsakes can help parents by remembering the memories and help processing the loss. Especially in neonatology, keepsakes provide an important way to cherish a part of their child. Over time, keepsakes can serve as a form for expressing the continuation of the bond between parents and child. HCPs can actively support parents in memory making, by handing them options and guide them by, for example, bereavement photography. Supported by theoretical components concerning: attachment working models and plans; coping; continuing bonds. **Follow-up contact** Consist of: follow-up calls; cards; visits; flowers; condolence letters; appointments; facilitating contact with peers. Implications: When parents feel that HCPs have known their child, during follow-up contact, they can see this as an acknowledgement of their child's identity. Follow-up contact gives parents an option to readjust and treasure	**Conclusions** All components of intervention (i-v) were covered by theoretical concepts based on a theoretical synthesis. The interventions all account for fragmented pieces in the grieving process. There are no interventions that emphasize the continuous parental adjustment process as a whole. HCPs could play a significant role in providing this continuous care. **Additional remarks** Strengths: Large amount of included interventions. Although not all interventions did include an empirical or theoretical basis, theoretical synthesis next to the interventions gives insight in theoretical effectiveness. Limitations: Studies containing low appraisal scores are included, due to the explorative nature of the study.

training, a program or other supporting documents • Studies must address regular HCPs defined as: All types of health care professionals who primarily provide care and/or treatment and, therefore, do not specialize in bereavement care • Research in the field of pediatrics and neonatology • Articles published in a peer reviewed journal • Studies published in English Exclusion criteria • Review articles • Articles published before 1998 • Articles containing interventions that focus on complex grief and complex bereavement care • Articles which solely include prenatal death and stillbirth, defined as: No signs of life at or after 28 weeks' gestation. No occurrence of circulation outside of the uterus		memories, address doubt about themselves, or ask questions about the course of treatment, which is important because parents often find themselves being in a haze during the end-of-life phase of their child. Supported by theoretical components concerning: Attachment working models and plans; the appraisal process; coping; continuing bonds. **Education and information** Consist of: folders and booklets with information; financial advice; videos containing information; educational support meetings for peers and relatives; seminars or workshops on coping and grief; information sessions. Implications: In a new, unknown and insecure situation, parents can feel more prepared by help from HCPs on where to find extra (emotional) support when needed. Parents are thus supported by aiding them in regaining some control over the situation. Supported by theoretical components concerning: attachment working models and plans; the appraisal process; coping. **Remembrance activities** Consist of: ceremonies or services; HCPs attending the funeral. Implications: Remembrance activities can make the parents feel connected to the child, in a secure environment. Memories can be recollected and discussing aspects of the proceeded events can help parents to find meaning in the death of their child, which might aid parental coping. Supported by theoretical components concerning: coping; continuing bonds.	Only well-defined interventions were included, resulting in elimination of less defined, although those could potentially contain helpful strategies. **Risk of bias** Quantitative articles: Risk of Bias Cochrane used in 6/21 articles Instrument range 0-7, scores ranged from 2-5 Qualitative articles: QOREQ used in 8/21 articles Instrument range 0-32, scores ranged from 8-21 Not applicable: 9/21 articles

4 Conclusies van evidence

4.1 Effectiviteit van rouwzorg interventies bij kinderen tussen 0 en 18 jaar in de palliatieve fase en familieleden en verzorgers

Bereavement intervention comprising of a support package, peer supporter's contact and health care personnel's contact vs usual care				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Mothers grief, The Hogan Grief Reaction Checklist (HGRC) with following subscales: despair (13 items), panic behaviour (14 items), personal growth (11 items), blame and anger (7 items), detachment (8 items) and disorganisation (8 items). Items were rated on a 5 point Likert scale (1: does not describe me at all) to (4: describes me very well).				
Raitio, 2015	Grieving mothers, with sufficient Finnish language skills, whose child had died at the age of three years or younger.	Total of 139 mothers • Intervention: 86 • Control: 53	Type of intervention: Bereavement intervention consisting of three complementary components v. Support package: informational letters, poems and stories about the loss of a child; v. Peer supporters' contact: first via telephone, later (mutually agreed), in the form of a home visit; vi. Health care personnel's contact: meeting 2-6 weeks following the death of the child, or if this was not possible, telephone contact. Type of control: Normal routine hospital care. Care varied between the control group hospitals.	**Mothers grief reactions at 6 month follow-up (intervention vs control)** *Despair* median (range) score is 2.00 (1.6-2.5) vs 2.00 (1.7-2.9), p = 0.938 *Panic behaviour* median (range) score is 2.07 (1.6-2.6) vs 2.00 (1.5-2.5), p = 0.520 *Personal growth* median (range) score is 2.75 (2.3-3.2) vs 2.75 (2.3-3.2), p = 0.797 *Blame and anger* median (range) score is 1.86 (1.4-2.4) vs 1.86 (1.3-2.4), p = 0.413 *Detachment* median (range) score is 2.29 (1.6-2.9) vs 2.14 (1.4-2.7), p = 0.743 *Disorganisation* median (range) score is 2.29 (1.6-2.9) vs 2.14 (1.4-2.7), p = 0.491

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-2	Serious limitations - Selection bias: unclear; Attrition bias: unclear; Performance bias: high; Detection bias: high
Consistency:	0	No important inconsistency. Only 1 study performed
Directness:	0	Results are direct. Outcomes are generalizable
Precision:	-1	No important imprecision, sample size is n=192. Only 1 study performed
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence that there is no significant effect of bereavement intervention (comprising of a support package, peer supporter's contact and health care personnel's contact) on grief reactions including despair, panic behaviour, personal growth, blame and anger, detachment and disorganisation at 6 month follow-up in mothers of children that had died at age of three years or younger as compared to usual care.**

4.2 Componenten in rouwzorg interventies en ervaringen en behoeften van ouders of/en zorgverleners met betrekking tot componenten van rouwzorg interventies

Components of bereavement interventions and experience and needs of parents and Health Care Professionals regarding components		
Main category	Specific actions per component	Experiences/needs regarding the intervention component as expressed or experienced by parents and health care professionals (HCPs)
Acknowledging the child's life and identity	Providing the child with a certificate of life[1]	• Not reported
	Providing the child with a blessing ceremony[1]	• Not reported
	Acknowledging child's identity[2]	• Learn the infant's individual needs and routines.[2]
	Acknowledging birthdays/holidays/ anniversaries[3,4]	• Not reported
Acknowledging and enabling parenthood	Maintaining relationship between parent and child	• During the end of the child's life, parents desired to maintain their relationship with their child.[5]
	Washing, holding or dressing the child both during the end of life and after death[1,2,6,7]	• See, touch and hold the newborn during after life can enable parents to form important bonds and to create memories that are helpful after their newborns death. Holding their child as he/she died, was valued by and helpful for most parents, but also emotionally difficult. Support and reassurance from hospital staff can be needed. Parents' failure to spend time with, or contribute care for their newborn was associated with regrets.[6] • Providing care for their newborns may help individuals develop their identities as parents. Being involved and participating in bedside care was identified as helpful. Parents experienced frustration when staff did not welcome their participation and felt regret when their involvement in care was limited.[6]
	Giving parents privacy and input surrounding the death of the child[1,2,7]	• Parents wanted to be actively involved in the child's care and talk openly with the dying child. [8] • Acknowledge the wishes of the parents, even when these wishes conflict with the recommendations of the healthcare team.[2] • Parents preferred to be given control over the how and where the child died.[7,8] Some parents preferred to stay home.[8] • Parents expressed the need to be with the child at the time of death. Parents preferred to be provided with intimacy and privacy at the time of death, for example by being offered a private room with as little disturbances as possible.[8] Parents who were not given the opportunity for a private peaceful place and sufficient time to say goodbye found a negative effect on grieving, accepting and coping.[2]
Establishing keepsakes	Safeguarding a lock of hair [1,6]	• Many parents appreciated the opportunity to create mementos with and of their dying child, which was described as meaningful and an important need. Parents expressed a need to be actively supported and guided through all aspects of memory making.[5,6,9]
	Hand, foot or face print [1,6]	
	Basket/memory box: (items that belonged to the child such as toys, a blanket, ornaments, a memory stone, clothes, a baby ring or bracelet, memory books, poems or other belongings) [1,2,4,6]	
	Pictures [1,4,6]	• Photographs can help parents by confirming the newborn's existence and may legitimize the parents' loss. The images can provide the basis for a continuing relationship between parents and child. Finally, they are important cues for memory to help parents process their losses. Parents wanted health providers to offer education and encouragement to ensure that photographs were taken. Although, parents often feel a range of barriers to bereavement photography, most parents who did not receive photographs wished they had.[6]
Establishing follow-up contact with HCPs	Follow-up contact (calls, cards, visits, flowers, condolence letters)[1,3,4,7,10]	• Need for a continuity of care after the child's death by the hospital staff that cared for their child. It was important that the same members of the care team were involved from diagnoses throughout bereavement. The basis of care quality was built on communication, honesty, respect and anticipation of needs.[5] • Parents experienced a strong bond with the hospital staff and felt abandoned if the bond was broken.[3,4,9]

		• Follow-up contact was experienced as supportive and appreciated.[3,5,7,10] Follow-up contact could provide parents with closure, improved coping and facilitated personal growth.[2,4] Some parents felt unable to return to the hospital or that the follow-up meeting left them with unanswered questions.[7]
Providing peer support	Facilitating contact with peers/support groups[1,3,4,7,10]	• Parents value peer support and expressed a desire to have contact with other families that lost a child.[4,9] Peer support reduced a sense of isolation, resulted in development of healing friendships, improved coping and allowed for personal growth.[4] • peer support did not result in a significant change in psychosocial functioning and grief reactions.[4]
	Mindfulness based intervention, cognitive behavioural therapy based and group retreat [10]	• Mindfulness: showed no significant effect.[10] • Cognitive behavioural therapy group: significant reduction in overall grief symptoms in the intervention group.[10] • Group retreat: Participating parents showed a significant decrease in depressive symptoms, significant improvement in perceived quality of life and no change in perceived social support. [10]
Providing education and information	• Information(sessions), videos folders and booklets [1,3,4,10] • Financial advice [1,4] • Educational support meetings for peers and relatives[1] • Seminars or workshops on coping and grief[1] • Being involved in developing training sessions and research	• Parents appreciated being involved in the development and administrating of bereavement education programs and interventions.[3] • Parents expressed a need for more preparation for death and bereavement.[9]
Providing remembrance activities	• Memorial ceremonies or services[1,3,4] • HCPs attending the funeral[1,3]	• Having HCPs attend the funeral may enhance parents' feelings of support from the hospital.[2]
Offering therapies	• Therapeutic intentional touch[10] • Expressive art therapy[10] • Referral for individual counselling [4]	• Parents expressed a need for bereavement mental health support in addition to follow-up.[3]

References

1. Kochen EM, Jenken F, Boelen PA, et al. When a child dies: a systematic review of well-defined parent-focused bereavement interventions and their alignment with grief- and loss theories. *BMC Palliat Care*. 2020;19(1):28. doi:10.1186/s12904-020-0529-z
2. Sieg SE, Bradshaw WT, Blake S, Forsythe PL. The Best Interests of Infants and Families during Palliative Care at the End of Life: A Review of the Literature. *Adv Neonatal Care*. 2019;19(2):E9-E14. doi:10.1097/ANC.0000000000000567
3. Lichtenthal WG, Sweeney CR, Roberts KE, et al. Bereavement follow-up after the death of a child as a standard of care in pediatric oncology. *Pediatr Blood Cancer*. 2015;62:S834-S869. doi:10.1002/pbc.25700
4. Donovan LA, Wakefield CE, Russell V, Cohn RJ. Hospital-based bereavement services following the death of a child: A mixed study review. *Palliat Med*. 2015;29(3):193-210. doi:10.1177/0269216314556851
5. Aschenbrenner AP, Winters JM, Belknap RA. Integrative review: Parent perspectives on care of their child at the end of life. *J Pediatr Nurs*. 2012;27(5):514-522. doi:10.1016/j.pedn.2011.07.008
6. Thornton R, Nicholson P, Harms L. Scoping Review of Memory Making in Bereavement Care for Parents After the Death of a Newborn. *JOGNN - J Obstet Gynecol Neonatal Nurs*. 2019;48(3):351-360. doi:10.1016/j.jogn.2019.02.001
7. Longden J V. Parental perceptions of end-of-life care on paediatric intensive care units: a literature review. *Nurs Crit Care*. 2011;16(3):131-139. doi:10.1111/j.1478-5153.2011.00457.x
8. Chong PH, Walshe C, Hughes S. Perceptions of a Good Death in Children with Life-Shortening Conditions: An Integrative Review. *J Palliat Med*. 2019;22(6):714-723. doi:10.1089/jpm.2018.0335

9. Stevenson M, Achille M, Lugasi T. Pediatric palliative care in Canada and the United States: A qualitative metasummary of the needs of patients and families. *J Palliat Med*. 2013;16(5):566-577. doi:10.1089/jpm.2011.0076
10. Dias N, Hendricks-Ferguson VL, Wei H, Boring E, Sewell K, Haase JE. A Systematic Literature Review of the Current State of Knowledge Related to Interventions for Bereaved Parents. *Am J Hosp Palliat Med*. 2019;36(12):1124-1133. doi:10.1177/1049909119858931

4.3 Communicatieve en affectieve strategieën om ouders te ondersteunen gedurende het levenseinde en na het overlijden van het kind

Communicative and affective strategies to support parents during end of their child's life and after death of their child		
Strategy	Positively labeled	Negative labeled
Provision of communication/information	• Honest and straightforward communication [5,9] • Provision of complete information [5] • Provision of information in understandable language [2,7] • Timely provision of information [2,7] • Facilitating privacy [5]	• Parents receiving inadequate and incomplete information about the child (including autopsy results) [5] • Parents receiving conflicting information[7,8] due to involvement of a number of HCP[7] • Parents receiving emotional information in a public area [5]
Provision of emotional support	• Support, expression of emotions, kindness and compassion by HCPs who care for the child [2,7,9] • Showing dignity and respect [9] • Comforting the parents with a hug, smile or beverage [2] • Delivering difficult news in a sensitive and caring manner [9]	• Lack of sensitivity and empathy [5] • Lack of physical bereavement care [5] • Lack of emotional support and compassion: parents reported that nurses had difficulties supporting them emotionally when care shifted from curing to palliative care. [5]
Provision of hope	• Maintenance of hope while accepting their child's prognosis[8,9] • Not give up hope until it is clear that there is no other course[2]	• Not reported
Provision of knowledge/expertise	• HCPs have experience and show confidence in caring for the child[2]	• Increased parental stress due to incompetence of HCPs, including HCPs not being able to understand the diagnosis, treatment or complications and to deal with equipment required to care for the child.[2]
Provision of consistency and continuity of care (personnel)	• Access to medical staff day/night [7,8] • Coordination and continuity of care [8] • Establishing the relationship between HCP and child facilitated death conversations.[8]	• Inconsistency in HCPs near end of life [8] • Sense of being abandoned by HCPs [8]
Provision of sense of control	• Personal control and authority over the child's death and life, helped parents with keeping fear and uncertainty within limits of tolerability.[8] Provision of informational, emotional and instrumental support enhanced sense of control.[8] Control was seen as a mediating factor in the oscillating passage from "preservation" towards becoming prepared to " let their child go" and a precondition for fulfilling parental tasks.[8]	• Feeling unprepared for child's death [8] • Loss of control [7,8]

References

2. Sieg SE, Bradshaw WT, Blake S, Forsythe PL. The Best Interests of Infants and Families during Palliative Care at the End of Life: A Review of the Literature. *Adv Neonatal Care*. 2019;19(2):E9-E14. doi:10.1097/ANC.0000000000000567
5. Aschenbrenner AP, Winters JM, Belknap RA. Integrative review: Parent perspectives on care of their child at the end of life. *J Pediatr Nurs*. 2012;27(5):514-522. doi:10.1016/j.pedn.2011.07.008
6. Thornton R, Nicholson P, Harms L. Scoping Review of Memory Making in Bereavement Care for Parents After the Death of a Newborn. *JOGNN - J Obstet Gynecol Neonatal Nurs*. 2019;48(3):351-360. doi:10.1016/j.jogn.2019.02.001
7. Longden J V. Parental perceptions of end-of-life care on paediatric intensive care units: a literature review. *Nurs Crit Care*. 2011;16(3):131-139. doi:10.1111/j.1478-5153.2011.00457.x
8. Chong PH, Walshe C, Hughes S. Perceptions of a Good Death in Children with Life-Shortening Conditions: An Integrative Review. *J Palliat Med*. 2019;22(6):714-723. doi:10.1089/jpm.2018.0335
9. Stevenson M, Achille M, Lugasi T. Pediatric palliative care in Canada and the United States: A qualitative metasummary of the needs of patients and families. *J Palliat Med*. 2013;16(5):566-577. doi:10.1089/jpm.2011.0076

5. SYMPTOMEN

A Angst en Depressie

Inhoudsopgave

1 Uitgangsvragen

Vraag 1A: Wat is de meest geschikte diagnostische methode voor het herkennen van angst en depressie bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Diagnostische methode voor het herkennen van angst en depressie
C: -
O: Reproduceerbaarheid en validiteit

Vraag 1B: Wat is de meest effectieve niet-medicamenteuze behandeling van angst en depressie bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Niet-medicamenteuze behandeling van angst en depressie
C: Geen behandeling/placebo
O: Effect op angst en depressie en kwaliteit van leven

Vraag 1C:Wat is de meest effectieve medicamenteuze behandeling van angst en depressie bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Medicamenteuze behandeling van angst en depressie
C: Geen behandeling/placebo
O: Effect op angst en depressie en kwaliteit van leven

2 Resultaten van het literatuuronderzoek

Jaar	Bibliografie	Studie karakteristieken
1A: Wat is de meest geschikte diagnostische methode voor het herkennen van angst en depressie bij kinderen tussen 0 en 18 jaar in de palliatieve fase?[#]		
2016	***Nederlands Centrum Jeugdgezondheid,*** Richtlijn Angst. 2016	Richtlijn kinderen
2016	***Nederlands Centrum Jeugdgezondheid,*** Richtlijn Depressie. 2016	Richtlijn kinderen
2010	***Integraal Kanker Instituut Nederland.*** Depressie. 2010: www.pallialine.nl [1,2]	Richtlijn volwassenen
1B: Wat is de meest effectieve niet-medicamenteuze behandeling van angst en depressie bij kinderen tussen 0 en 18 jaar in de palliatieve fase?[*]		
2016	***Nederlands Centrum Jeugdgezondheid,*** Richtlijn Angst. 2016	Richtlijn kinderen
2016	***Nederlands Centrum Jeugdgezondheid,*** Richtlijn Depressie. 2016	Richtlijn kinderen
2019	***National Institute for Health and Care Excellence (NICE).*** Depression in children and young people: identification and management. 2019 (previous versions 2005 and 2015)[1]	Richtlijn kinderen
2015	***National Institute for Health and Care Excellence (NICE).***Care of dying adults in the last days of life. 2015[1,2]	Richtlijn volwassenen
1C: Wat is de meest effectieve medicamenteuze behandeling van angst en depressie bij kinderen tussen 0 en 18 jaar in de palliatieve fase?[*]		
2016	***Nederlands Centrum Jeugdgezondheid,*** Richtlijn Angst. 2016	Richtlijn kinderen
2016	***Nederlands Centrum Jeugdgezondheid,*** Richtlijn Depressie. 2016	Richtlijn kinderen
2019	***National Institute for Health and Care Excellence (NICE).*** Depression in children and young people: identification and management. 2019 (previous versions 2005 and 2015)[1]	Richtlijn kinderen
2015	***National Institute for Health and Care Excellence (NICE).***Care of dying adults in the last days of life. 2015[1,2]	Richtlijn volwassenen

[1] Aanbevelingen uit de richtlijnen over Angst en Depressie worden gebruikt in de overwegingen.
[2] Aanbevelingen uit richtlijnen over Angst en Depressie bij volwassenen in de palliatieve fase worden gebruikt in de overwegingen wanneer er geen aanbevelingen uit richtlijnen over angst en depressie bij kinderen al dan niet in de palliatieve fase zijn gevonden.
[#] Niet systematisch gezocht
[*] Systematisch gezocht, zie: bijlage 7 zoekverantwoording – search 1

3 Evidence tabellen

Niet van toepassing.

Uit de systematische zoekstrategie resulteerden geen studies over diagnostische methoden voor het herkennen van angst en depressie en geen gerandomiseerde studies over niet-medicamenteuze en medicamenteuze behandeling van angst en depressie.

4 Samenvatting en gradering van bewijs

Niet van toepassing.

Uit de systematische zoekstrategie resulteerden geen studies over diagnostische methoden voor het herkennen van angst en depressie en geen gerandomiseerde studies over niet-medicamenteuze en medicamenteuze behandeling van angst en depressie.

5 Conclusies van evidence

5.1 Diagnostische methoden voor het herkennen van angst en depressie

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5.2 Niet-medicamenteuze behandeling van angst en depressie

Non pharmacological treatment of anxiety and depression		
Intervention	**Conclusions of evidence**	**Quality of evidence**
General interventions for anxiety (cognitive, emotional, behavioural and social) *General interventions for depression (cognitive, emotional, behavioural and social)*	Unknown effect	No studies

5.3 Medicamenteuze behandeling van angst en depressie

Pharmacological treatment of anxiety and depression		
Intervention	**Conclusions of evidence**	**Quality of evidence**
Benzodiazepines *Selective Serotonin Reuptake inhibitor (SSRIs)* *Antidepressants* *Methylphenidate*	Unknown effect	No studies

6 Aanbevelingen uit richtlijnen

6.1 Diagnostische methoden voor het herkennen van angst en depressie

Diagnostic methods for recognizing depression – Adult guideline	
Integraal Kankercentrum Nederland (IKNL). Depressie. 2010	
Recommendation	**Level of evidence**
Overweeg de diagnose depressie bij elke patiënt die zich in de palliatieve fase van de ziekte bevindt.	Expert opinion
Informeer actief naar de gemoedstoestand: 'Bent u somber? Zo ja, herkent u deze reactie van uzelf bij tegenslagen of ervaart u dit als anders en vreemd?	Expert opinion
Gebruik bij twijfel de HADS of de 4DKL.	Expert opinion
Stel de diagnose aan de hand van de DSM-IV-TR-criteria.	Expert opinion
Ga na of de depressie veroorzaakt kan worden door de onderliggende aandoening, de behandeling ervan of medicamenten; sluit een delier uit.	Expert opinion
Raadpleeg een psychiater met ervaring in de palliatieve zorg indien uitgebreide diagnostiek gewenst is of ingestelde initiële behandelingen geen effect hebben.	Expert opinion

6.2 Niet-medicamenteuze behandeling van angst en depressie

Non pharmacological treatment of depression – Child guideline	
National Institute for Health and Care Excellence (NICE). Depression in children and young people: identification and management. 2005 (updated in 2015 en 2019).	
Recommendation	**Level of evidence**
Clinical evidence: *Recommendations were based on 72 RCTs (1986-2018)*	
Treatment for mild depression	
Discuss the choice of psychological therapies with children and young people with mild depression and their family members or carers (as appropriate). Explain: • what the different therapies involve • the evidence for each age group (including the limited evidence for 5- to 11-year-olds) • how the therapies could meet individual needs, preferences and values	Very low to High
Base the choice of psychological therapy on**: • a full assessment of needs, including: o the circumstances of the child or young person and their family members or carers o their clinical and personal/social history and presentation o their maturity and developmental level o the context in which treatment is to be provided o comorbidities, neurodevelopmental disorders, communication needs (language, sensory impairment) and learning disabilities • Patient and carer preferences and values (as appropriate).	Very low to High
For 5- to 11-year-olds with mild depression continuing after 2 weeks of watchful waiting, and without significant comorbid problems or active suicidal ideas or plans, consider the following options adapted to developmental level as needed**: • digital cognitive–behavioural therapy (CBT) • group CBT • group non-directive supportive therapy (NDST) • group interpersonal psychotherapy (IPT). If these options would not meet the child's clinical needs or are unsuitable for their circumstances, consider the following adapted to developmental level as needed**: • attachment-based family therapy • individual CBT.	Very low to High
For 12- to 18-year-olds with mild depression continuing after 2 weeks of watchful waiting, and without significant comorbid problems or active suicidal ideas or plans, offer a choice of the following psychological therapies for a limited period (approximately 2 to 3 months)**: • digital CBT • group CBT • group NDST • group IPT.	Very low to High
Provide psychological therapies in settings such as schools and colleges, primary care, social services and the voluntary sector.	Very low to High
If mild depression in a child or young person has not responded to psychological therapy after 2 to 3 months (recommendations with **), refer the child or young person for review by a CAMHS team.	Very low to High
Follow the recommendations on treating moderate to severe depression for children and young people who have continuing depression after 2 to 3 months of psychological therapy (see section 1.6 on moderate to severe depression)	Very low to High
Treatment for moderate to severe depression	
Children and young people presenting with moderate to severe depression should be reviewed by a CAMHS team.	Very low to High
Discuss the choice of psychological therapies with children and young people with moderate to severe depression and their family members or carers (as appropriate). Explain: • what the different therapies involve	Very low to High

• the evidence for each age group (including the limited evidence for 5- to 11-year-olds) • how the therapies could meet individual needs, preferences and values.	

Base the choice of psychological therapy on:
• a full assessment of needs, including:
  ○ the circumstances of the child or young person and their family members or carers
  ○ their clinical and personal/social history and presentation
  ○ their maturity and developmental level
  ○ the context in which treatment is to be provided
  ○ comorbidities, neurodevelopmental disorders, communication needs (language, sensory impairment) and learning disabilities
• patient and carer preferences and values (as appropriate)
	Very low to High

For 5- to 11-year-olds with moderate to severe depression, consider the following options adapted to developmental level as needed: • family-based IPT • family therapy (family-focused treatment for childhood depression and systems integrative family therapy) • psychodynamic psychotherapy • individual CBT.	Very low to High
For 12- to 18-year-olds with moderate to severe depression, offer individual CBT for at least 3 months	Very low to High
If individual CBT would not meet the clinical needs of a 12- to 18-year-old with moderate to severe depression or is unsuitable for their circumstances, consider the following options: • IPT-A (IPT for adolescents) • family therapy (attachment-based or systemic) • brief psychosocial intervention • psychodynamic psychotherapy.	Very low to High

Non pharmacological treatment of anxiety – Adult guideline	
National Institute for Health and Care Excellence (NICE).Care of dying adults in the last days of life. 2015	
Recommendation	**Level of evidence**
Explore the possible causes of anxiety or delirium, with or without agitation, with the dying person and those important to them. Be aware that agitation in isolation is sometimes associated with other unrelieved symptoms or bodily needs for example, unrelieved pain or a full bladder or rectum.	Expert opinion
Consider non-pharmacological management of agitation, anxiety and delirium in a person in the last days of life.	Expert opinion
Treat any reversible causes of agitation, anxiety or delirium, for example, psychological causes or certain metabolic disorders (for example renal failure or hyponatraemia).	Expert opinion

6.3 Medicamenteuze behandeling van angst en depressie

Pharmacological treatment of depression – Child guideline	
National Institute for Health and Care Excellence (NICE).Depression in children and young people: identification and management. 2019 (previous versions 2005 and 2015)	
Recommendation	**Level of evidence**
Clinical evidence: *Recommendations were based on one systematic review of RCTs*	
Combined treatments for moderate to severe depression	
Consider combined therapy (fluoxetine and psychological therapy) for initial treatment of moderate to severe depression in young people (12–18 years), as an alternative to psychological therapy followed by combined therapy and to recommendations 1.6.8 to 1.6.10	Low to moderate
Following multidisciplinary review, offer fluoxetine if moderate to severe depression in a young person (12–18 years) is unresponsive to a specific psychological therapy after 4 to 6 sessions.	Low to moderate
Following multidisciplinary review, cautiously consider fluoxetine if moderate to severe depression in a child (5–11 years) is unresponsive to a specific psychological therapy after 4 to 6 sessions, although the evidence for fluoxetine's effectiveness in this age group is not established	Low to moderate
How to use antidepressants in children and young people	

Do not offer antidepressant medication to a child or young person with moderate to severe depression except in combination with a concurrent psychological therapy. Specific arrangements must be made for careful monitoring of adverse drug reactions, as well as for reviewing mental state and general progress; for example, weekly contact with the child or young person and their parents or carers for the first 4 weeks of treatment. The precise frequency will need to be decided on an individual basis, and recorded in the notes. In the event that psychological therapies are declined, medication may still be given, but as the young person will not be reviewed at psychological therapy sessions, the prescribing doctor should closely monitor the child or young person's progress on a regular basis and focus particularly on emergent adverse drug reactions.	Low to moderate

Pharmacological treatment of anxiety – Adult guideline	
National Institute for Health and Care Excellence (NICE).Care of dying adults in the last days of life. 2015	
Recommendation	**Level of evidence**
Consider a trial of a benzodiazepine to manage anxiety or agitation.	Expert opinion

7 Overzicht conclusies van evidence en aanbevelingen uit richtlijnen

7.1 Diagnostische methoden voor het herkennen van angst en depressie

Diagnostic methods for recognizing anxiety and depression								
Treatment	Conclusions of evidence (Studies on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children 2013 (2)	Level of evidence
Diagnostic methods for recognizing depression								
Inquiry on the state of mind (are you sad?)	Unknown effect	No studies	Not identified	-	Do	Expert opinion (3;P)	No recommendation	-
HADS questionnaire	Unknown effect	No studies	Not identified	-	Use in case of doubt	Expert opinion (3;P)	No recommendation	-
4DKL questionnaire	Unknown effect	No studies	Not identified	-	Use in case of doubt	Expert opinion (3;P)	No recommendation	-
DSM-IV-TR-criteria	Unknown effect	No studies	Not identified	-	Use for diagnosis	Expert opinion (3;P)	No recommendation	-
Rule out other causes of depression: underlying conditions, its treatment or medication and delirium	Unknown effect	No studies	Not identified	-	Do	Expert opinion (3;P)	No recommendation	-

Legend
P: Palliative context
NP: Non-palliative context
Not identified: No recommendations on specific pharmacological intervention were identified.
Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.

References

2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.
3. Integraal Kankercentrum Nederland. Depressie (2.0). 2010. Available from: www.pallialine.nl/depressie.

7.2 Niet-medicamenteuze behandeling van angst en depressie

Non pharmacological treatment of anxiety and depression								
Treatment	Conclusions of evidence (RCTs on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children 2013 (2)	Level of evidence[1]
Non pharmacological treatments for anxiety								
General interventions for anxiety • *Supporting intakes* • *Cognitive interventions* • *Behavioural interventions* • *Relaxation therapy* • *(self)hypnosis*	Unknown effect	No studies	Not identified	-	Consider	Expert opinion (4;P)	Do (for anxiety); strong recommendation	Level 3 child evidence (5-8); Level 1 adult evidence (8, 9)[2]
Non pharmacological treatments for depression								
General interventions for depression • *Cognitive interventions* • *Emotional interventions* • *behavioural interventions* • *Social interventions*	Unknown effect	No studies	Not identified	-	Not identified	-	Consider (for depression); weak recommendation	Level 1 child evidence (4); Level 1 adult evidence (10-13)[2]
Psychological therapies for mild depression								
• digital cognitive behavioural therapy (CBT) • group cognitive behavioural therapy (CBT) • group non-directive supportive therapy (NDST) group • interpersonal psychotherapy (IPT)	Unknown effect	No studies	Consider for children aged 5 – 11 years with mild depression after 2 weeks of watchful waiting and without significant comorbid problems or suicidal ideas	VERY LOW –HIGH, 72 RCTs (14;NP)	Not applicable	-	No recommendation	-
			Offer a choice of psychological therapies (2-3 months) for children aged 12-18 years with mild depression after 2 weeks of watchful waiting and without comorbid problems or suicidal ideas	VERY LOW –HIGH, 72 RCTs (14;NP)				

Additional: • Attachment-based family therapy • individual cognitive behavioural therapy	Unknown effect	No studies	Consider for children aged 5-11 with mild depression if options above do not meet the child's needs	VERY LOW –HIGH, 72 RCTs(14;NP)	Not applicable	-	No recommendation	-
Psychological therapies for moderate to severe depression								
• family-based Interpersonal psychotherapy • family therapy (family-focused treatment for childhood depression and systems integrative family therapy) • psychodynamic psychotherapy • Individual Cognitive behavioural therapy	Unknown effect	No studies	Consider for children aged 5 – 11 years with moderate to severe depression	VERY LOW –HIGH, 72 RCTs (14;NP)	Not applicable	-	No recommendation	-
Individual cognitive behavioural therapy	Unknown effect	No studies	Offer for children aged 12 – 18 years with moderate to severe depression for at least 3 months.	VERY LOW –HIGH, 72 RCTs(14;NP)	Not applicable	-	No recommendation	-
• Interpersonal psychotherapy for adolescents • family therapy (attachment-based or systemic) • brief psychosocial intervention • Psychodynamic psychotherapy.	Unknown effect	No studies	Consider for children aged 12 – 18 years with moderate to severe depression if options above do not meet child's needs.	VERY LOW –HIGH, 72 RCTs (14;NP)	Not applicable	-	No recommendation	-

Legend
P: Palliative context
NP: Non-palliative context
Not identified: No recommendations on specific pharmacological intervention were identified.
Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified

[1]Level of evidence:
Level 1: Based on a systematic review or at least two randomized controlled trials of good quality
Level 2: Based on one at randomized controlled trial or at least two comparative clinical studies
Level 3: Based on one comparative study or on non-comparative studies
Level 4: Based on expert opinion
[2]Adult evidence is extracted from guidelines of pallialine.nl (3, 15)

References

2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.
3. Integraal Kankercentrum Nederland. Depressie (2.0). 2010. Available from: www.pallialine.nl/depressie.
4. National Institute for Health and Care Excellence. Care of dying adults in the last days of life. [Internet]. London: NICE; 2015 [cited 2021 March, 1]. Available from: www.nice.org.uk/guidance/ng31.
5. Barrera M, Rykov MH, Doyle SL. The effects of interactive music therapy on hospitalized children with cancer: a pilot study. Psycho-oncology. 2002;11(5):379-88.
6. Powers SW. Empirically supported treatments in pediatric psychology: procedure-related pain. Journal of Pediatric Psychology. 1999;24(2):131-45.
7. Robb SL, Ebberts AG. Songwriting and digital video production interventions for pediatric patients undergoing bone marrow transplantation, part I: an analysis of depression and anxiety levels according to phase of treatment. J Pediatr Oncol Nurs. 2003;20(1):2-15.
8. Sheard T, Maguire P. The effect of psychological interventions on anxiety and depression in cancer patients: results of two meta-analyses. Br J Cancer. 1999;80(11):1770-80.
9. Uitterhoeve RJ, Vernooy M, Litjens M, Potting K, Bensing J, De Mulder P, et al. Psychosocial interventions for patients with advanced cancer - a systematic review of the literature. Br J Cancer. 2004;91(6):1050-62.
10. Akechi T, Okuyama T, Onishi J, Morita T, Furukawa TA. Psychotherapy for depression among incurable cancer patients. Cochrane Database Syst Rev. 2008;2008(2):Cd005537.
11. Rodin G, Lloyd N, Katz M, Green E, Mackay JA, Wong RK. The treatment of depression in cancer patients: a systematic review. Support Care Cancer. 2007;15(2):123-36.
12. Stiefel F, Trill M, Berney A, Olarte J, Razavi D. Depression in palliative care: a pragmatic report from the Expert Working Group of the European Association for Palliative Care. Supportive Care in Cancer. 2001;9(7):477-88.
13. Williams S, Dale J. The effectiveness of treatment for depression/depressive symptoms in adults with cancer: a systematic review. Br J Cancer. 2006;94(3):372-90.
14. National Institute for Health Care and Excellence. Depression in Children and Young People: identification and mangement. [Internet]. London: NICE; 2019 [cited 2021 March 1]. Available from: www.nice.org.uk/guidance/ng134.
15. Integraal Kankercentrum Nederland. Angst (1.0) 2009. Available from: https://www.pallialine.nl/angst.

7.3 Medicamenteuze behandeling van angst en depressie

Pharmacological treatment for Anxiety and depression								
Treatment	Conclusions of evidence (RCTs on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children 2013 (2)	Level of evidence[1]
Pharmacological interventions for anxiety								
Benzodiazepines	Unknown effect	No studies	Not identified	-	Consider for anxiety and agitation, and delirium	Expert opinion (4;P)	Consider (for anxiety as adjuvant or until SSRIs are effective); weak recommendation	Level 4 Child evidence (16-18); Level 3 adult evidence (19-21)[2]
Selective Serotonin Reuptake inhibitors (SSRIs)	Unknown effect	No studies	Not identified	-	Not identified	-	Consider (for anxiety); weak recommendation	Level 4 child evidence (22); Level 1 adult evidence(23)[2]
							Consider (for anxiety and depression in children with cancer); weak recommendation	Level 4 child evidence(24-26); Level 1 adult evidence(23)[2]
Pharmacological interventions for depression								
Selective Serotonin Reuptake inhibitor (SSRIs)	Unknown effect	No studies	Not identified	-	Not identified	-	Consider (for depression); weak recommendation	Level 3 child evidence (22, 27, 28); Level 1 adult evidence (11-13, 29, 30)[2]
Fluoxetine and psychological therapy	Unknown effect	No studies	Consider for moderate to severe depression in children aged 12–18 years, as an alternative to psychological therapy followed by combined therapy	LOW – MODERATE, SR of RCTs (14;NP)	Not applicable	-	No recommendation	-
			Offer fluoxetine if moderate to severe depression in children aged 12–18 years is unresponsive to a specific	LOW – MODERATE, SR of RCTs (14;NP)				

			psychological therapy after 4 to 6 sessions.					
			Cautiously consider fluoxetine if moderate to severe depression in children aged 5–11 years is unresponsive to a specific psychological therapy after 4 to 6 sessions	Expert opinion (14;NP)				
Antidepressants	Unknown effect	No studies	Do not offer antidepressant medication to a child or young person with moderate to severe depression except in combination with psychological therapy. Make specific arrangement for monitoring adverse drug reactions.	LOW – MODERATE, SR of RCTs (14;NP)	Not applicable	-	Do not give (for depression); strong recommendation	Controversy in child evidence (31, 32); Level 1 adult evidence (11-13, 30)[2]
Methylphenidate	Unknown effect	No studies	Not identified	-	Not identified	-	Consider (for depression); weak recommendation	Level 4 child evidence (33); Level 3 adult evidence (34, 35)[2]

Legend
P: Palliative context
NP: Non-palliative context
Not identified: No recommendations on specific pharmacological intervention were identified.
Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.

[1]Level of evidence:
Level 1: Based on a systematic review or at least two randomized controlled trials of good quality
Level 2: Based on one at randomized controlled trial or at least two comparative clinical studies
Level 3: Based on one comparative study or on non-comparative studies
Level 4: Based on expert opinion
[2]Adult evidence is extracted from guidelines of pallialine.nl (3, 15)

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2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.
3. Integraal Kankercentrum Nederland. Depressie (2.0). 2010. Available from: www.pallialine.nl/depressie.
4. National Institute for Health and Care Excellence. Care of dying adults in the last days of life. [Internet]. London: NICE; 2015 [cited 2021 March, 1]. Available from: www.nice.org.uk/guidance/ng31.
11. Rodin G, Lloyd N, Katz M, Green E, Mackay JA, Wong RK. The treatment of depression in cancer patients: a systematic review. Support Care Cancer. 2007;15(2):123-36.

12. Stiefel F, Trill M, Berney A, Olarte J, Razavi D. Depression in palliative care: a pragmatic report from the Expert Working Group of the European Association for Palliative Care. Supportive Care in Cancer. 2001;9(7):477-88.
13. Williams S, Dale J. The effectiveness of treatment for depression/depressive symptoms in adults with cancer: a systematic review. Br J Cancer. 2006;94(3):372-90.
14. National Institute for Health Care and Excellence. Depression in Children and Young People: identification and mangement. [Internet]. London: NICE; 2019 [cited 2021 March 1]. Available from: www.nice.org.uk/guidance/ng134.
15. Integraal Kankercentrum Nederland. Angst (1.0) 2009. Available from: https://www.pallialine.nl/angst.
16. Bentley R, Cope M, Jenney M, Hain RDW. Use of intranasal/oral midazolam in paediatric palliative care. Archives of Disease in Childhood. 2002;86:A76.
17. Manassis K. Childhood anxiety disorders: lessons from the literature. Can J Psychiatry. 2000;45(8):724-30.
18. Wolfe J, Hinds P. Textbook of Interdisciplinary Pediatric Palliative Care: Saunders; 2011.
19. Henderson M, MacGregor E, Sykes N, Hotopf M. The use of benzodiazepines in palliative care. Palliat Med. 2006;20(4):407-12.
20. Jackson KC, Lipman AG. Drug therapy for anxiety in palliative care. Cochrane Database Syst Rev. 2004(1):Cd004596.
21. Stiel S, Krumm N, Schroers O, Radbruch L, Elsner F. [Indications and use of benzodiazepinen in a palliative care unit]. Der Schmerz. 2008;22(6):665-71.
22. Goldman A, Hain R, Liben S. Oxford Textbook of Palliative Care for Children: Oxford University Press; 2006.
23. Landelijke Stuurgroep Multidisciplinaire Richtlijnen in de GGZ. Multidisciplinaire richtlijn Angstoornissen 2003. Available from: http://www.med-info.nl/Richtlijnen/Geriatrie/Angststoornissen.pdf.
24. Axelson DA, Birmaher B. Relation between anxiety and depressive disorders in childhood and adolescence. Depress Anxiety. 2001;14(2):67-78.
25. Collins JJ, Byrnes ME, Dunkel IJ, Lapin J, Nadel T, Thaler HT, et al. The Measurement of Symptoms in Children with Cancer. Journal of Pain and Symptom Management. 2000;19(5):363-77.
26. Gurley D, Cohen P, Pine DS, Brook J. Discriminating depression and anxiety in youth: A role for diagnostic criteria. Journal of Affective Disorders. 1996;39(3):191-200.
27. DeJong M, Fombonne E. Citalopram to treat depression in pediatric oncology. J Child Adolesc Psychopharmacol. 2007;17(3):371-7.
28. Gothelf D, Rubinstein M, Shemesh E, Miller O, Farbstein I, Klein A. Pilot study: fluvoxamine treatment for depression and anxiety disorders in children and adolescents with cancer. J Am Acad Child Adolesc Psychiatry. 2005:1258-62.
29. Fisch MJ, Loehrer PJ, Kristeller J, Passik S, Jung SH, Shen J, et al. Fluoxetine versus placebo in advanced cancer outpatients: a double-blinded trial of the Hoosier Oncology Group. J Clin Oncol. 2003;21(10):1937-43.
30. Gill D, Hatcher S. Antidepressants for depression in medical illness. Cochrane Database Syst Rev. 2000(4):CD001312.
31. Maisami M, Sohmer BH, Coyle JT. Combined use of tricyclic antidepressants and neuroleptics in the management of terminally ill children: a report on three cases. J Am Acad Child Psychiatry. 1985;24(4):487-9.
32. Pfefferbaum-Levine B, Kumor K, Cangir A, Choroszy M, Roseberry EA. Tricyclic antidepressants for children with cancer. Am J Psychiatry. 1983;140(8):1074-6.
33. Walling VR, Pfefferbaum B. The use of methylphenidate in a depressed adolescent with AIDS. J Dev Behav Pediatr. 1990;11(4):195-7.
34. Homsi J, Nelson KA, Sarhill N, Rybicki L, LeGrand SB, Davis MP, et al. A phase II study of methylphenidate for depression in advanced cancer. Am J Hosp Palliat Care. 2001;18(6):403-7.
35. Rozans M, Dreisbach A, Lertora JJ, Kahn MJ. Palliative uses of methylphenidate in patients with cancer: a review. J Clin Oncol. 2002;20(1):335-9.

B Delier

Inhoudsopgave

1 Uitgangsvragen

Vraag 2A: Wat is de meest geschikte diagnostische methode voor het herkennen van delier bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Diagnostische methode voor het herkennen van delier
C:
O: Reproduceerbaarheid en validiteit

Vraag 2B: Wat is de meest effectieve niet-medicamenteuze behandeling van delier bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Niet-medicamenteuze behandeling van delier
C: Geen behandeling /placebo
O: Effect op delier en kwaliteit van leven

Vraag 2C: Wat is de meest effectieve medicamenteuze behandeling van delier bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Medicamenteuze behandeling van delier
C: Geen behandeling/placebo
O: Effect op delier en kwaliteit van leven

2 Resultaten van het literatuuronderzoek

Jaar	Bibliografie	Studie karakteristieken
2A: Wat is de meest geschikte diagnostische methode voor het herkennen van delier bij kinderen tussen 0 en 18 jaar in de palliatieve fase?[#]		
2014	***Nederlandse Vereniging voor Psychiatrie (NVvP).*** Multidisciplinaire richtlijn pediatrische delier. 2014[1]	Richtlijn kinderen
2B: Wat is de meest effectieve niet-medicamenteuze behandeling van delier bij kinderen tussen 0 en 18 jaar in de palliatieve fase?[*]		
2016	***National institute for health and care Excellence (NICE).***End of life care for infants, children and young people: planning and management. 2016[1]	Richtlijn kinderen
2014	***Nederlandse Vereniging voor Psychiatrie (NVvP).*** Multidisciplinaire richtlijn pediatrische delier. 2014[1]	Richtlijn kinderen
2C: Wat is de meest effectieve niet-medicamenteuze behandeling van delier bij kinderen tussen 0 en 18 jaar in de palliatieve fase?[*]		
2016	***National institute for health and care Excellence (NICE).***End of life care for infants, children and young people: planning and management. 2016[1]	Richtlijn kinderen
2014	***Nederlandse Vereniging voor Psychiatrie (NVvP).*** Multidisciplinaire richtlijn pediatrische delier. 2014[1]	Richtlijn kinderen

[1] Aanbevelingen uit de richtlijnen over delier bij kinderen in de palliatieve fase en bij kinderen niet in de palliatieve fase worden gebruikt in de overwegingen

[#] Niet systematisch gezocht

[*] Systematisch gezocht, zie: bijlage 7 zoekverantwoording – search 1

3 Evidence tabellen

Niet van toepassing.

Uit de systematische zoekstrategie resulteerden geen studies over diagnostische methoden voor het herkennen van delier en geen gerandomiseerde studies over niet-medicamenteuze en medicamenteuze behandeling van delier.

4 Samenvatting en gradering van bewijs

Niet van toepassing.

Uit de systematische zoekstrategie resulteerden geen studies over diagnostische methoden voor het herkennen van delier en geen gerandomiseerde studies over niet-medicamenteuze en medicamenteuze behandeling van delier.

5 Conclusies van evidence

5.1 Diagnostische methoden voor het herkennen van Delier

Diagnostic methods for recognizing delirium		
Intervention	**Conclusions of evidence**	**Quality of evidence**
DSM-IV criteria *Risk factor screening* *Comfort scale or rass* *Paed* *Sos-PD* *Pcam-icu* *Cap-D + (possibly) parent observation of not recognizing child*	Unknown effect	No studies

5.2 Niet-medicamenteuze behandeling van Delier

Non pharmacological treatment of delirium		
Intervention	**Conclusions of evidence**	**Quality of evidence**
Calm speaking *Reduction of noise and lighting* *Spiritual and religious support*	Unknown effect	No studies

5.3 Medicamenteuze behandeling van Delier

Pharmacological treatment of delirium		
Intervention	**Conclusions of evidence**	**Quality of evidence**
Benzodiazepines (midazolam, diazepam, lorazepam) *Neuroleptics (haloperidol, levomepromazine)* *Antipsychotics* *Risperidone*	Unknown effect	No studies

6 Aanbevelingen uit richtlijnen

6.1 Diagnostische methoden voor het herkennen van Delier

Diagnostic methods for recognizing delirium – Child guideline	
Nederlandse Vereniging voor Psychiatrie (NVvP). Multidisciplinaire richtlijn pediatrische delier. 2014	
Recommendation	**Level of evidence**
Criteria voor pediatrisch delier	
Klinisch bewijs: *1 systematic review over delier op de PICU waarin 1 prospectieve observationele cohortstudie is opgenomen* *Concluderend blijkt er zeer beperkt onderzoek gedaan te zijn naar het pd bij kinderen onder de 5 jaar en bij kritisch zieke kinderen.*	
De diagnose pd wordt gesteld door een deskundig arts (bijvoorbeeld kinder- en jeugdpsychiater).	Level 4
Diagnosticeer een pd bij kinderen vanaf 5 jaar, die niet kritisch ziek, neurologisch beschadigd of geïntubeerd zijn op basis van de criteria zoals genoemd in de DSM-iv of met behulp van de pcam-icu.	Level 4
Stel de diagnose pd bij kinderen van drie maanden tot 5 jaar en/of bij kritisch zieke, neurologisch beschadigde en/of geïntubeerde kinderen met behulp van de cap-d, eventueel aangevuld met de observatie van de ouders dat ze hun kind niet meer herkennen, en bij uitsluiting van andere logische verklaringen.	Level 4
Neem bij kinderen met een neurologische aandoening het eerdere cognitieve en neurologische toestandsbeeld mee in de beoordeling om te bepalen of het kind ook aan een pd lijdt.	Unclear
Risicofactoren	
Klinisch bewijs: *1 systematic review en 1 ongecontroleerd observationele studie.* *Aangezien er maar een beperkt aantal studies bij kinderen werd uitgevoerd, werd ook bestudeerd welke risicofactoren bij volwassenen werden geïdentificeerd en welke risicofactoren daarvan mogelijk een rol kunnen spelen bij het optreden van pd.*	
Een gespecialiseerd kinderverpleegkundige of deskundig arts (bijvoorbeeld kinder- en jeugdpsychiater) screent dagelijks op alle in tabel 5.1 genoemde beïnvloedbare risicofactoren voor pd bij een kritisch ziek kind en bij verhoging van sedativa of opioïden (bij gebruik langer dan vijf dagen).	Level 3
Meetinstrumenten pediatrisch delier	
Klinisch bewijs: *5 artikelen over meetinstrumenten die na 2004 zijn ontwikkeld/gevalideerd* *Aangezien er maar een beperkt aantal studies bij kinderen werd uitgevoerd, werd ook bestudeerd welke risicofactoren bij volwassenen werden geïdentificeerd en welke risicofactoren daarvan mogelijk een rol kunnen spelen bij het optreden van pd.*	
Laat verpleegkundigen drie keer per dag screenen op pd bij patiënten bij die langer dan 48 uur zijn opgenomen op de picu met de paed (gereviseerd, driepuntsschaal), cap-d of sos-pd als screeningsinstrument. Dit als onderdeel van het routinematig meten van (pijn en) discomfort.	Expert opinion
Laat verpleegkundigen op een (medium care) kinderafdeling een screeningsinstrument gebruiken bij kinderen met een hoog risico (bijvoorbeeld post ic, zie Hoofdstuk 5 Risicofactoren) voor screening op pd gedurende 72 uur.	Expert opinion
Gebruik een gevalideerd instrument bij kinderen op een picu (bijvoorbeeld comfort gedragsschaal, en eventueel rass) voor het vaststellen van de mate van sedatie/agitatie/coma, voordat pd kan worden beoordeeld.	Expert opinion
Laat de diagnose pd bevestigen en/of vaststellen door een bekwame arts en consulteer bij twijfel een deskundig arts (bijvoorbeeld kinder- en jeugdpsychiater).	Expert opinion
Vervolg het verloop van een pd en het effect van behandeling bij kinderen met een screeningsinstrument, aangezien er geen valide ernstmeetinstrumenten voor kinderen zijn.	Expert opinion
Gebruik bij wetenschappelijk onderzoek naar pd: de paed, of cap-d of de sos-pd bij kinderen van 0 tot 16 jaar, of de pcam-icu bij kinderen vanaf 5 jaar.	Unclear

6.2 Niet-medicamenteuze behandeling van Delier

Non pharmacological treatment of delirium – Child guideline	
National institute for health and care Excellence (NICE). End of life care for infants, children and young people: planning and management. 2016	
Recommendation	**Level of evidence**
No evidence found after systematic search	
Be aware that as children and young people with life-limiting conditions approach the end of life they may: • become agitated, shown by restlessness, irritability, aggressive behaviour, crying or other distress • show signs of delirium, such as confusion, disrupted attention, disordered speech and hallucinations	Expert opinion
If a child or young person becomes agitated as they are approaching the end of life, look for causes and factors that may be contributing to this, including: • medical disorders and conditions such as pain, hypoxia, anaemia, dehydration, urinary retention or constipation • psychological factors such as fear, anxiety or depression • adverse effects from medication.	Expert opinion
For children and young people with a neurological disability who are approaching the end of life, be aware that the signs and symptoms of agitation or delirium can be mistaken for the signs and symptoms of seizures or dystonia	Expert opinion
If a child or young person who is approaching the end of life needs treatment for agitation: • identify and if possible treat any medical or psychological conditions that may be contributing to it • think about non-pharmacological interventions, such as: o calm speaking, reassurance, distraction, and physical contact such as holding and touch o changes to the environment to make it more comfortable, calm and reassuring, to reduce noise and lighting, to maintain a comfortable room temperature, and to provide familiar objects and people and relaxing music o religious and spiritual support if this is wanted and helpful	Expert opinion, p 370
Nederlandse Vereniging voor Psychiatrie (NVvP). Multidisciplinaire richtlijn pediatrische delier. 2014	
Klinisch bewijs: *2 artikelen werden geïncludeerd waarbij niet-medicamenteuze interventies werden besproken* *Er zijn aanwijzingen dat een combinatie van een aantal niet medicamenteuze interventies (zie tabel 8.1) soms kan voorkomen dat een delier medicamenteus moet worden behandeld.*	
Overweeg veiligheidsgerichte interventies (bedhekken, antislip maatregelen, fysiek toezicht).	Expert opinion
Bied familie voorlichting over delier (mondeling en schriftelijk door middel van een voorlichtingsfolder).	Expert opinion
Pas fixatie, bij voorkeur, niet toe als er alternatieven zijn (met name fysiek toezicht).	Expert opinion
Overweeg de volgende interventies: • bevorder de oriëntatie van het kind (medewerkers noemen naam en functie, foto's, muziek en speelgoed van thuis, kalender, whiteboard, bril, gehoorapparaat, 's nachts gedempt licht op de kamer); • laat het kind zo veel mogelijk door dezelfde verpleegkundigen verzorgen om op deze manier zo veel mogelijk uniformiteit in benadering/behandeling te geven en te zorgen voor vertrouwde gezichten voor zowel kind als ouders. Houd rekening met gestoorde aandachts- en geheugenfuncties (eenvoudige zinnen, informatie herhalen); • voorkom overprikkeling door geluid, tocht, licht, te veel mensen. Oorpluggen kunnen hierbij behulpzaam zijn. Houd geen gesprekken aan het bed. Verplaats het kind eventueel naar een rustiger (hyperactief delier) of meer stimulerende (hypoactief delier) omgeving; • mobiliseer het kind (fysiotherapeut en verpleegkundigen); • houd rekening met het ontwikkelingsniveau bij communicatie; • bied de aanwezigheid van ouders middels rooming-in of de opname van de stem van ouders; • verbeter het dag-nachtritme door onder meer aanbieden van activiteiten, wisselend daglicht; • ondersteun dyspraxie, dysfasie en bij andere factoren die de communicatie bemoeilijken met hulpmiddelen (schrijfblok, aanwijskaart, elektronische middelen).	Level 4

6.3 Medicamenteuze behandeling van Delier

Pharmacological treatment of delirium – Child guideline	
National institute for health and care Excellence (NICE). End of life care for infants, children and young people: planning and management. 2016	
Recommendation	**Level of evidence**
No evidence found after systematic search	
If a child or young person who is approaching the end of life needs treatment for agitation: • identify and if possible treat any medical or psychological conditions that may be contributing to it • think about pharmacological interventions (beginning with low doses and increasing if necessary). Drugs to think about using include: o benzodiazepines, such as midazolam, diazepam or lorazepam o neuroleptics, such as haloperidol or levomepromazine.	Expert opinion, p 370
Nederlandse Vereniging voor Psychiatrie (NVvP). Multidisciplinaire richtlijn pediatrische delier. 2014	
Klinisch bewijs: *5 artikelen* *Alle beschikbare studies uitgevoerd bij kinderen hebben methodologisch forse beperkingen in de zin dat de onderzoeksgroep, de interventie of de uitkomstmaten niet goed zijn omschreven en er geen controlegroep beschikbaar is.*	
Overweeg behandeling van een delier met medicatie bij kinderen indien non-medicamenteuze interventies onvoldoende of onvoldoende snel effect hebben. Dit geldt met name wanneer er sprake is van veel agitatie of onrust, bij wanen of hallucinaties. En ook wanneer het delier leidt tot gevaar voor infuuslijnen of zelfbeschadiging, bij discomfort of stress bij kind en omgeving.	Level 4
Risperidon is de eerste keuze bij lichte tot matige symptomen (matige agitatie) en als er de mogelijkheid is voor per-os-toediening. Dit geldt temeer bij gebleken gevoeligheid voor extrapyramidale bijwerkingen.	Expert opinion
Haloperidol is de eerste keuze bij ernstige symptomen (agitatie, psychotische klachten) of als per-os-toediening niet mogelijk is.	Expert opinion
Bij non-respons of bijwerkingen op het eerste middel is switchen van middel te overwegen.	Expert opinion
Geef bijscholing aan behandelend somatisch artsen en verpleegkundigen over de te verwachten bijwerkingen van antipsychotica, met name extrapyramidale bijwerkingen. Hierin ligt een rol voor de (kinders)psychiater of de arts die regelmatig deze medicatie voorschrijft.	Expert opinion
Weeg het risico op qtc-verlenging bij starten met antipsychotica en gebruik bij de aanwezigheid van risicofactoren en bij risicogroepen monitoring middels ecg.	Expert opinion - level 4

7 Overzicht conclusies van evidence en aanbevelingen uit richtlijnen

7.1 Diagnostische methoden voor het herkennen van Delier

Diagnostic methods for recognizing delirium								
Treatment	Conclusions of evidence (Studies on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children 2013 (2)	Level of evidence
Criteria for diagnosing children with delirium								
DSM-IV criteria/pcam-icu	Unknown effect	No studies	Use for diagnosing children from age 5 (not critically ill, neurologically damaged or intubated	Level 4 (3;NP)	Not applicable	-	No recommendation	-
Cap-D + (possibly) parent observation of not recognizing child	Unknown effect	No studies	Use for diagnosing children aged 3 months to 5 years or for diagnosing critically ill, neurologically damaged or intubated children	Level 4 (3;NP)	Not applicable	-	No recommendation	-
Risk factors for paediatric delirium								
Risk factor screening	Unknown effect	No studies	Screen daily on risk factors for delirium in critically ill children ad in case of increasing dose of sedatives or opioids (tabel 5.1)	Level 3 (3;NP)	Not applicable	-	No recommendation	-
Instruments for assessing paediatric delirium								
Paed (three-point scale); Cap-D; Sos-PD	Unknown effect	No studies	Use to screen children who have been admitted to the PICU for more than 48 hours, 3 times a day. Use in medium care for screening on delirium for 72 hours for children with a high risk on delirium	Expert opinion (3;NP)	Not applicable	-	No recommendation	-
Comfort scale or rass	Unknown effect	No studies	Use for determining the degree of sedation, agitation, coma before assessing delirium	Expert opinion (3;NP)	Not applicable	-	No recommendation	-

Paed *Cap-D* *Sos-PD*	Unknown effect	No studies	Use for scientific research in children aged 0 to 16 years	Expert opinion (3;NP)	Not applicable	-	No recommendation	-
Pcam-icu	Unknown effect	No studies	Use for scientific research in children from 5 years	Expert opinion (3;NP)	Not applicable	-	No recommendation	-

Legend
P: Palliative context
NP: Non-palliative context
Not identified: No recommendations on specific pharmacological intervention were identified.
Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.

References

2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.
3. Nederlandse Vereniging voor Psychiatrie. Multidisciplinaire richtlijn pediatrisch delier. 2014. Available from: www.nvvp.net/stream/richtlijn-pediatrisch-delier-2014.pdf.

7.2 Niet-medicamenteuze behandeling van Delier

Non pharmacological treatment of delirium								
Treatment	Conclusions of evidence (RCTs on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children 2013 (2)	Level of evidence
Safety-oriented interventions: • Side rails • Anti-slip measures • Physical supervision	Unknown effect	No studies	Consider	Expert opinion (3;NP)	Not applicable	-	No recommendation	-
Inform family members on delirium (verbal/written information)	Unknown effect	No studies	Do	Expert opinion (3;NP)	Not applicable	-	No recommendation	-
Improve child's orientation (professionals say their name and function; pictures; music; toys from home; calendar; whiteboard; glasses; hearing aid; reduced light at night)	Unknown effect	No studies	Consider	Level 4 (3;NP)	Not applicable	-	No recommendation	-
Uniformity in approach/ treatment (Care given by same nurses; familiar faces; use simple sentences and repeat sentences)	Unknown effect	No studies	Consider	Level 4 (3;NP)	Not applicable	-	No recommendation	-
Mobilize child	Unknown effect	No studies	Consider	Level 4 (3;NP)	Not applicable	-	No recommendation	-
Improve day-night rhythm by providing activities and changing day light.	Unknown effect	No studies	Consider	Level 4 (3;NP)	Not applicable	-	No recommendation	-
Spiritual and religious support	Unknown effect	No studies	Consider	Expert opinion (4;P)	Not applicable	-	No recommendation	-
Support children with communication difficulties (dyspraxia, dysphasia, other) with aids (writing pad, pointer cards, electronic means)	Unknown effect	No studies	Consider	Level 4 (3;NP)	Not applicable	-	No recommendation	-
Prevention of overstimulation								

Prevent overstimulation by noise, draft, light and many people: use earplugs; do not talk at the bed side; move child to a peaceful (hyperactive delirium) or stimulating (hypoactive delirium) environment.	Unknown effect	No studies	Consider	Level 4 (3;NP)	Not applicable	-	No recommendation	-
Calm speaking, reassurance, distraction, physical content	Unknown effect	No studies	Consider	Expert opinion (4;P)	Not applicable	-	No recommendation	-
Changes to environment: reduction of noise and lighting	Unknown effect	No studies	Consider	Expert opinion (4;P)	Not applicable	-	No recommendation	-

Legend
P: Palliative context
NP: Non-palliative context
Not identified: No recommendations on specific pharmacological intervention were identified.
Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.

References

2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.
3. Nederlandse Vereniging voor Psychiatrie. Multidisciplinaire richtlijn pediatrisch delier. 2014. Available from: www.nvvp.net/stream/richtlijn-pediatrisch-delier-2014.pdf.
4. National Institute for Health and Care Excellence. End of life care for infants, children and young people with life-limiting conditions: planning and management. [Internet]. London: NICE; 2016 [cited 2021 March 1]. Available from: www.nice.org.uk/guidance/ng61.

7.3 Medicamenteuze behandeling van Delier

Pharmacological treatment of delirium								
Treatment	Conclusions of evidence (RCTs on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children 2013 (2)	Level of evidence
• *Benzodiazepines* *Midazolam* • *Diazepam* • *Lorazepam*	Unknown effect	No studies	Consider (for agitation)	Expert opinion (4;P)	Not applicable	-	No recommendation	-
Risperidone	Unknown effect	No studies	First choice for light or mild symptoms (mild agitation)	Expert opinion (3;NP)	Not applicable	-	No recommendation	-
Neuroleptics • *Haloperidol* • *levomepromazine*	Unknown effect	No studies	Consider (for agitation)	Expert opinion (4;P)	Not applicable	-	No recommendation	-
Haloperidol	Unknown effect	No studies	First choice for severe symptoms (agitation or psychotic complaints)	Expert opinion (3;NP)	Not applicable	-	No recommendation	-
Antipsychotics	Unknown effect	No studies	Weigh the risk of QTC prolongation when starting antipsychotics and use in presence of risk factors/risk groups	Expert opinion, Level 4 (3;NP)	Not applicable	-	No recommendation	-

Legend
P: Palliative context
NP: Non-palliative context
Not identified: No recommendations on specific pharmacological intervention were identified.
Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.

References

2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.
3. Nederlandse Vereniging voor Psychiatrie. Multidisciplinaire richtlijn pediatrisch delier. 2014. Available from: www.nvvp.net/stream/richtlijn-pediatrisch-delier-2014.pdf.
4. National Institute for Health and Care Excellence. End of life care for infants, children and young people with life-limiting conditions: planning and management. [Internet]. London: NICE; 2016 [cited 2021 March 1]. Available from: www.nice.org.uk/guidance/ng61.

C Dyspneu

Inhoudsopgave

1 Uitgangsvragen

Vraag 3A: Wat is de meest geschikte diagnostische methode voor het herkennen van dyspneu bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Diagnostische methode voor het herkennen van dyspneu
C: -
O: Reproduceerbaarheid en validiteit

Vraag 3B: Wat is de meest effectieve niet-medicamenteuze behandeling van dyspneu bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Niet-medicamenteuze behandeling van dyspneu
C: Geen behandeling/placebo
O: Effect op dyspneu en kwaliteit van leven

Vraag 3C: Wat is de meest effectieve medicamenteuze behandeling van dyspneu bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Medicamenteuze behandeling van dyspneu
C: Geen behandeling/placebo
O: Effect op dyspneu en kwaliteit van leven

2 Resultaten van het literatuuronderzoek

Jaar	Bibliografie	Studie karakteristieken
3A: Wat is de meest geschikte diagnostische methode voor het herkennen van dyspneu bij kinderen tussen 0 en 18 jaar in de palliatieve fase?[#]		
2015	***Integraal Kankerinstituut Nederland.*** Dyspneu in de palliatieve fase.2015[1]	Richtlijn volwassenen
2018	***Pieper L et al.*** Dyspnea in Children with Life-Threatening and Life-Limiting Complex Chronic Conditions. J Palliat Med 2018 21(4):552-564	Systematic review kinderen
3B: Wat is de meest effectieve niet-medicamenteuze behandeling van dyspneu bij kinderen tussen 0 en 18 jaar in de palliatieve fase?[*]		
2015	***National institute for health and care (NICE).*** Care of dying adults in the last days of life. 2015[1]	Richtlijn volwassenen
2015	***Integraal Kankerinstituut Nederland.*** Dyspneu in de palliatieve fase.2015[1]	Richtlijn volwassenen
2014	***Lima C et al.*** Effects of noninvasive ventilation on treadmill 6-min walk distance and regional chest wall volumes in cystic fibrosis: Randomized controlled trial. Respir Med 2014; 108:1460–1468[2]	RCT kinderen
2001	***De jong W et al.*** Inspiratory muscle training in patients with cystic fibrosis. RESPIRATORY MEDICINE (2001) 95, 31–36[2]	RCT kinderen
3C: Wat is de meest effectieve medicamenteuze behandeling van dyspneu bij kinderen tussen 0 en 18 jaar in de palliatieve fase?[*]		
2015	***National institute for health and care (NICE).*** Care of dying adults in the last days of life. 2015[1]	Richtlijn volwassenen
2015	***Integraal Kankerinstituut Nederland.*** Dyspneu in de palliatieve fase.2015[1]	Richtlijn volwassenen

[1]Aanbevelingen uit richtlijnen over dyspneu bij volwassenen in de palliatieve fase worden gebruikt in de overwegingen omdat er geen aanbevelingen uit richtlijnen over dyspneu bij kinderen in de palliatieve fase zijn gevonden.
[2]RCT is uit de volgende systematic review gehaald: *Pieper L et al.* Dyspnea in Children with Life-Threatening and Life-Limiting Complex Chronic Conditions. J Palliat Med 2018 21(4):552-564
[#] Niet systematisch gezocht
[*] Systematisch gezocht, zie: bijlage 7 zoekverantwoording – search 1

3 Evidence tabellen

3.1 *Diagnostische methoden voor het herkennen van dyspneu*

Diagnostic methods for recognizing dyspnoea			
Pieper L et al. Dyspnoea in Children with Life-Threatening and Life-Limiting Complex Chronic Conditions. J Palliat Med 2018 21(4):552-564			
Study characteristics	**Population**	**Main results**	**Conclusions** **Risk of bias**
Type of study: Systematic review Included studies 45 studies included • 23 retrospective studies • 14 prospective studies • 2 RCT's • 7 Case-series studies Searched databases PubMed Inclusion criteria • dyspnoea • Complex Chronic Conditions (CCC) that are Life Threatening (LT) or Life Limiting (LL) • Age 0-25 yrs. • Original data • In case series, the number of patients is ≥ 3 • English or German language	Number and type of participants: Children and young people with CCC (LT or LL) Age: 0-25 yrs. Sex: All	Measurement and assessment of dyspnoea: 14 studies reported on the measurement of dyspnoea, 8 tools were identified. Subjective self-rating tools: • *Dalhousie dyspnoea scales, validated for children ≥8 yrs. with CF or asthma:* Visualization of severity of dyspnoea sensations, i.e. effort, chest tightness, throat closing (mentioned in 1 study) • *Modified Borg Scale, validated for children ≥9 yrs. with CF:* Assessment of effort to breath and discomfort during exercise, score ranging from 0 to 10 (mentioned in 4 studies) • *Visual analogue Scale, not validated: assessment of* the severity of breathlessness, score ranging from 0 to 10 (mentioned in 3 studies) • *Medical Research Council dyspnoea Scale/numeric rating scale, not validated*: assessment of impairment due to dyspnoea (1 study). • *Memorial Symptom Assessment Scales, not validated for rating of dyspnoea alone*: Rating of shortness of breath, frequency, severity and distress with regard to this symptom was measured using a 4 or 5-point Likert Scale (mentioned in 2 studies) Subjective proxy-rating tools • *Liverpool Respiratory Symptom Questionnaire, validated for healthy children and children with CF (6-12)*: Assessment of chronic respiratory symptoms across different domains, including shortness of breath. Parents documented their observations of the child over a period of 3 moths (mentioned in 1 study). Objective parameters *Fifteen-Count breathless Score, validated for children with CF aged 6 to 18 yrs.:* Distinguishes different degrees of breathlessness by measuring the number of breaths taken to count up to 15.	**Main conclusions** There's a lack of an adequate assessment tool. Many children are unable to self-report. Symptoms must be interpreted by the caregiver. Only four of the analysed studies provide validation of self-assessment A combination of the subjective BS or the VAS with an objective tool as the 15-count score can improve reliability and accuracy of the measurement. The Dalhousie dyspnoea scales provide an accurate means to assess the sensation of dyspnoea. There is no gold standard for the assessment of dyspnoea in children. **Additional remarks** Strengths: Limitations: Study may not capture all nonmedical interventions **Risk of bias** Publication bias?

3.2 *Niet-medicamenteuze behandeling van dyspneu*

Non pharmacological treatment of dyspnoea				
Lima C et al. Effects of non-invasive ventilation on treadmill 6-min walk distance and regional chest wall volumes in cystic fibrosis: Randomized controlled trial. Respir Med 2014;108:1460–1468				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: open randomized controlled crossover clinical trial Setting: 1Centre, Brazil Duration: No follow-up. All outcomes are measured 30 minutes before TWT and directly after TWT. Study years: Not reported Protocol published in register: (*clinicaltrials.gov / WHO register*) Not reported	Number and type of participants: *An open randomized controlled cross-over trial was conducted. Participants acted as their own control* 13 children and adolescents with Cystic Fibrosis (clinically stable, with no history of hospitalization for respiratory failure in last 3 months. • Intervention group: 13 Start: Assessment of CF with NIV, N = 6 Start: Assessment of CF without NIV, N = 7 • Control group: 13 Start: Assessment of CF with NIV, N = 6 Start: Assessment of CF without NIV, N = 7 Age: • Intervention group: Mean: 10,7, Range 7-15 yrs. • Control group: Mean: 10,7, Range 7-15 yrs. Sex: • Intervention group: Start: Assessment of CF with NIV M: n = 3; F: n = 3 Start: Assessment of CF without NIV M: n =5, F: n = 2 • Control group: Start: Assessment of CF with NIV M: n = 3; F: n = 3 Start: Assessment of CF without NIV M: n =5, F: n = 2	*Open randomized controlled cross-over trial* Procedure: 1.Baseline Optoelectronic plethysmography (OEP) which assesses variations in compartmental chest wall volume and ventilator pattern – duration = 3 min 2. Baseline Spirometry which assesses pulmonary function – duration = 5 min 3. Resting time – 30 min 4. Treadmill Walking Test (TWT) with or without Non-invasive Ventilation (depending on randomization) 5. OEP after, duration = 3 min 6. Spirometry after, duration = 5 min 24/48 rest Same procedure, only the treadmill walking test will be without or with ventilation (depends on start procedure) Type of intervention: Non-invasive ventilation (NIV) in walk distance (WD) in the treadmill walking test (TWT) Before the test patients are submitted to NIV on a BiLevel mode for 30 minutes. Treadmill test initiated with a speed of 2.5km/h every 30s the patient was asked if the speed could be increased, maintained or decreased.	Outcome definitions: **Primary outcome** • Walk distance (WD) in the treadmill walking test (TWT), meter **secondary outcomes** *Cardiorespiratory variables* • peripheral O2 saturation (SpO2) • heart rate (HR) • respiratory rate (RR), • Score on the Borg dyspnoea scale (BDS), score ranging from 0 (none) to 10 (maximum), higher score indicating higher level of dyspnoea. *pulmonary function variables* • forced expiratory volume in the first second (FEV1), • forced vital capacity (FVC) • forced expiratory flow of 25%e75% of FVC (FEF 25e75) *Variables resulting from OEP analysis* • minute volume (MV) • tidal volume (Vt), • pulmonary rib cage volume (Vrcp), • abdominal rib cage volume (Vrca) • abdominal volume (Vab), • inspiratory time (Ti), • expiratory time (Te), • total ventilatory cycle time (Ttot) • duty cycle (Ti/Ttot) • frequency/tidal volume ratio (RR/Vt) Results (per outcome) **Walking distance (intervention vs control)** Mean (SD) 415.38m (77.52) vs 386.92m (84.89), P = 0.039. *Cardiorespiratory variables* There was no significant difference between intervention and control group immediately after the TWT for all cardio respiratory outcomes (SpO2, HR, RR and BS) *Pulmonary function variables* Intervention vs Control • no significant difference in FEV1 (%)/FVC (ml/%)/ FEF25-75 (ml/% between groups Before vs After TWT	Strengths: Well performed study Limitations: No conflict of interest Only for CF during activities **Risk of bias** A. Selection bias: low risk Reason: A randomized plan was compiled using the website randomization.com, applying a generator of random-permuted blocks to define the order in wich patients would execute the treadmill walking test (with or without NIV). Allocation concealment very likely because of use computer B. Attrition bias: Low risk Reason: No loss to follow-up C. Performance bias High risk Reason: Researchers and patient were not blinded (not possible) D. Detection bias Unclear Reason: Blinding of outcome assesors was not reported

		Speed could not exceed 7 km/h. <u>Type of control:</u> No use of Noninvasive ventilation (NIV) in walk distance (WD) in the treadmill walking test (TWT)	Intervention group: • Significant increase in FEV1 (ml) after TWT, p = 0.036 • no significant difference FEV1 (%)/FVC (ml/%)/ FEF25-75 (ml/%) before and after TWT Control group: • no significant difference in pulmonary function variables FEV1 (ml/%)/FVC (ml/%)/ FEF25-75 (ml/%) before and after TWT Variables resulting from OEP analysis (MV, Vt, Vrcp, vrca, vab, ti, te, Ttot, Ti/Ttot, RR/VT) <u>Intervention vs control</u> • no significant difference in MV, Vt, Vrcp, vrca, vab, ti, te, Ttot, Ti/Ttot, RR/VT between groups <u>Before and after TWT</u> Intervention group: • Significant increase in MV after TWT, p =0.013 • Significant increase in Vt after TWT, p = 0.005 • Significant increase in Vrcp after TWT, p =, 0,011 • no significant difference in vrca, vab, ti, te, Ttot, Ti/Ttot, RR/VT before and after TWT Control group: • no significant difference in MV, Vt, Vrcp, vrca, vab, ti, te, Ttot, Ti/Ttot, RR/VT	**Main conclusions** The pulmonary impairment in cystic fibrosis patients can increase the ventilatory demand even in performing their Activities of daily living.

No evidence table is available for the study of ‘De jong W et al. Inspiratory muscle training in patients with cystic fibrosis. RESPIRATORY MEDICINE (2001) 95, 31–362’.

4 Samenvatting en gradering van bewijs

4.1 *Diagnostische methoden voor het herkennen van dyspneu*

Diagnostic methods for recognizing dyspnoea		
Studies	Type and number of studies	Conclusions
Pieper, 2018	14 observational studies	8 tools to assess dyspnoea in three categories were identified: Subjective self-rating tools: • *Dalhousie dyspnoea scales, validated for children ≥8 years with CF or asthma:* Visualization of severity of dyspnoea sensations, i.e. effort, chest tightness, throat closing (mentioned in 1 study) • *Modified Borg Scale, validated for children ≥9 years with CF:* Assessment of effort to breath and discomfort during exercise, score ranging from 0 to 10 (mentioned in 4 studies) • *Visual analogue Scale, not validated: assessment of* the severity of breathlessness, score ranging from 0 to 10 (mentioned in 3 studies) • *Medical Research Council Dyspnoea Scale, not validated:* Assessment of impairment due to dyspnoea • *Numeric rating scale, not validated*: assessment of impairment due to dyspnoea (1 study). • *Memorial Symptom Assessment Scales, not validated for rating of dyspnoea alone*: Rating of shortness of breath, frequency, severity and distress with regard to this symptom was measured using a 4 or 5-point Likert Scale (mentioned in 2 studies) Subjective proxy-rating tools • *Liverpool Respiratory Symptom Questionnaire, validated for healthy children and children with CF (6-12)*: Assessment of chronic respiratory symptoms across different domains, including shortness of breath. Parents documented their observations of the child over a period of 3 moths (mentioned in 1 study). Objective parameters • *Fifteen-Count breathless Score, validated for children with CF aged 6 to 18 years:* Distinguishes different degrees of breathlessness by measuring the number of breaths taken to count up to 15.
Conclusion:	**This systematic review identified 8 tools to assess dyspnoea: Dalhousie dyspnoea scales (validated), modified Borg scale (validated), visual analogue scale, medical research council dyspnoea scale, numeric rating scale, Memorial symptom assessment scales, Liverpool respiratory symptom questionnaire (validated) and the fifteen-count breathless score (validated).** **No gold standard for the assessment of dyspnoea in children with advanced disease can be identified. The main problem concerning assessment of dyspnoea in children is that many children with life threatening or life limiting complex chronic conditions that experience dyspnoea are unable to self-report, therefore symptoms must be frequently be interpreted by the caregiver. Due to the subjective nature of these interpretations, it is likely that symptom intensity and child suffering are under evaluated. Additionally, only 4 of the 8 identified assessment tools are validated for children from 6 years old. None of the assessment tools have been validated for pre-school children.** **A combination of Modified Borg Scale or Visual Analogue Scale with the objective Fifteen-count breathless Score could improve the reliability and accuracy of the measurement of dyspnoea.** **The Dalhousie dyspnoea scales can be used to accurately assess the sensation of dyspnoea. It is yet unclear how the scales can be used in a clinical setting to assess a dyspnoea attack.**	

4.2 *Niet-medicamenteuze behandeling van dyspneu*

4.2.1 Geïncludeerde uitkomstmaten

Included outcomes
Degree of Dyspnoea
Exercise capacity
Pulmonary function

4.2.2 Effect van non-invasieve beademing

Non-invasive ventilation				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Degree of dyspnoea, measured by modified Borg Scale or Medical Research Council (MRC) Dyspnoea Scale, higher score indicating higher degree of dyspnoea				
1) Lima, 2014	1) children and young adolescents with CF aged 7-15 years	1) 13 (13 vs 13) Open randomized controlled cross-over trial. Participants acted as their own control.	1) 6-min Treadmill Walking Test (TWT) with non-invasive Ventilation vs 6-min Treadmill Walking test without non-invasive ventilation	**1) Modified Borg Scale score** No significant difference in scores between intervention and control group was found.

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-1	Some limitations - Selection bias: Low; Attrition: bias low; Performance bias: high; Detection bias: unclear
Consistency:	0	No important inconsistency. Only 1 study performed.
Directness:	0	Results are direct. Outcomes generalizable.
Precision:	-2	Some imprecision due to small sample size. Only 1 study performed
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship.
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence there is no significant effect of walking with non-invasive ventilation in children with Cystic Fibrosis on degree of dyspnoea as compared to walking without non-invasive ventilation.**

Non-invasive ventilation				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Exercise capacity				
1) Lima, 2014	1) children and young adolescents with CF aged 7-15 years	1) 13 (13 vs 13) Open randomized controlled cross-over trial. Participants acted as their own control.	1) 6-min Treadmill Walking Test (TWT) with non-invasive Ventilation vs 6-min Treadmill Walking test without non-invasive ventilation	**Walking distance (intervention vs control)** Mean (SD) 415.38m (77.52) vs 386.92m (84.89), p = 0.039. **Exercise capacity (cardiorespiratory variables)** • Peripheral oxygen saturation (SpO_2): No significant difference between groups • Heart Rate (HR): No significant difference between groups • Respiratory rate (RR): No significant difference between groups

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-1	Some limitations - Selection bias: Low; Attrition: bias low; Performance bias: high; Detection bias: unclear
Consistency:	0	No important inconsistency. Only 1 study performed.
Directness:	0	Results are direct. Outcomes generalizable.
Precision:	-2	Some imprecision due to small sample size. Only 1 study performed
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship.
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence that walking with non-invasive ventilation during 6-min TWT in children with Cystic Fibrosis increases exercise capacity (walking distance) as compared to walking without non-invasive ventilation (no significant effect on peripheral oxygen saturation, heart rate, respiratory rate)**

Non-invasive ventilation				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Pulmonary function				
1) Lima, 2014	1) children and young adolescents with CF aged 7-15 years	1) 13 (13 vs 13) Open randomized controlled cross-over trial. Participants acted as their own control.	1) 6-min Treadmill Walking Test (TWT) with non-invasive Ventilation vs 6-min Treadmill Walking test without non-invasive ventilation	**Pulmonary function variables** • Forced expiratory volume in the first second (FEV1 in ml): Significant increase after TWT in the intervention group, p = 0.036 • Minute Volume (MV in L): Significant increase after TWT in the intervention group, p=0.013 • Tidal volume (Vt in L): Significant increase after TWT in the intervention group, p=0.005 • Pulmonary rib cage volume (Vrcp in %): Significant increase after TWT in the intervention group, p = 0.011 • Forced expiratory volume in the first second (FEV1 in %); Forced vital capacity (FVC in l and %); forced expiratory flow of FVC (FEF 25-75 in ml/s); abdominal rib cage volume (Vrca in %); abdominal volume (Vab in %); inspiratory time (Ti in s); expiratory time (Te in s) Total ventilatory cycle time (Ttot in s); duty cycle (Ttot/Ti in %) No significant difference before and after TWT in both intervention and control group

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-1	Some limitations - Selection bias: Low; Attrition: bias low; Performance bias: high; Detection bias: unclear
Consistency:	0	No important inconsistency. Only 1 study performed.
Directness:	0	Results are direct. Outcomes generalizable.
Precision:	-2	Some imprecision due to small sample size. Only 1 study performed
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship.
Plausible confounding:	0	No plausible confounding
Quality of evidence:		**⊕⊖⊖⊖ VERY LOW**
Conclusion:		**There is very low quality of evidence that walking with non-invasive ventilation in children with Cystic Fibrosis increases pulmonary function (forced expiratory volume in the first second, minute volume, tidal volume and pulmonary ribcage volume) as compared to walking without non-invasive ventilation (no significant effect on FEV1 %, FVC in ml and %, FEF25e75, Vrca, Vab, Ti, Te, Ttot, Ti/tot, RR/vT[1]).**

[1]FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; FEF 25e75,forced expiratory flow of 25%e75% of FVC; Vrca, abdominal rib cage volume; Vab, abdominal volume; Ti, inspiratory time; Te, expiratory time; Ttot, total ventilatory cycle time; Ti/Ttot, duty cycle; RR/vt, Frequency/tidal volume ratio

4.2.3 Effect van hoog intensieve training

high intensity training

Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Degree of dyspnoea, measured by modified Borg Scale or Medical Research Council (MRC) Dyspnoea Scale, higher score indicating higher degree of dyspnoea				
1) de Jong, 2001[1]	1) children with CF aged 10-25 years • Intervention: Mean (SD): 19 (5.5) years • Control: Mean (SD): 17 (5.2) years	1) 16 (8 vs 8)	1) High intensity training, trained up to 40% maximal static inspiratory pressure during 6 weeks vs low intensity training, trained up to 10% maximal static inspiratory pressure during 6 weeks	**1) Change in degree of dyspnoea from baseline to post-treatment (intervention vs control)** • Borg $_{max}$, endurance (score at maximal work load during inspiratory muscle endurance test): Mean(SD)$_{Post\text{-}treatment - baseline}$ 1.3 (1.3) -1.4 (1.3) vs 1.0 (1.8) – 1.0 (1.8), p = 0.603 • Borg $_{max}$, bicycle: Borg (score at maximal work load during bicycle test) Mean(SD)$_{Post\text{-}treatment - baseline}$ 4.3 (3.5)- 5.3(2.7) vs 4.5 (3.3) - 4.2 (3.3), p = 0.603 • MRC Dyspnoea scale: Mean(SD)$_{Post\text{-}treatment - baseline}$ 0,33 (0.82) – 0.43 (0.79) vs 0.50 (0.76) – 0.63 (1.06), p = 0.351

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-2	Serious limitations - Selection bias: unclear; Attrition bias: high; Performance bias: unclear; Detection bias: unclear
Consistency:	0	No important inconsistency. Only 1 study performed.
Directness:	0	Results are direct. Outcomes generalizable.
Precision:	-2	Some imprecision due to small sample size. Only 1 study performed.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship.
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence there is no significant effect of high intensity training in children with Cystic Fibrosis on degree of dyspnoea as compared to low intensity training.**

[1] Selection bias unclear: Patients are randomized, allocation concealment was not reported. Attrition bias = high, 12.5% (n = 1) loss to follow-up in both study arms, performance bias: unclear if researchers and participants were blinded from allocation to study arm. Detection bias: unclear, blinding of outcome assessors was not

High intensity training				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Exercise capacity				
1) de Jong, 2001[1]	1) children with CF aged 10-25 years • Intervention: Mean, 19 (5.5) years • Control: Mean, 17 (5.2) years	1) 16 (8 vs 8)	1) High intensity training, trained up to 40% maximal static inspiratory pressure during 6 weeks vs low intensity training, trained up to 10% maximal static inspiratory pressure during 6 weeks	**Change in exercise capacity from baseline to post-treatment (intervention vs control)** • Maximal Exercise capacity (Wmax in W): No significant difference between groups, p = 0.166 • Maximal volume uptake (VO_2 Max in ml $kg^{-1}min^{-1}$): No significant difference between groups, p = 0.995 • Maximum ventilation (VEmax in L/min): No significant difference between groups, p = 0.347 • Maximal static inspiratory pressure (Pimax in % pred.): No significant difference between groups, p = 0.401 • Inspiratory muscle endurance (IME in %Pimax): Significant increase of IME (%PIMAX) in the intervention group Mean(SD)$_{\text{Post-treatment – baseline}}$: 66 (14) - 49 (12) vs 54 (7) – 50 (5), p = 0.012
Grade assessment				
Study design:	+4	1 Randomized Controlled Trial		
Study limitations	-2	Serious limitations - Selection bias: unclear; Attrition bias: high; Performance bias: unclear; Detection bias: unclear		
Consistency:	0	No important inconsistency. Only 1 study performed.		
Directness:	0	Results are direct. Outcomes generalizable.		
Precision:	-2	Some imprecision due to small sample size. Only 1 study performed.		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship.		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence that high intensity training in children with Cystic Fibrosis increases exercise capacity (inspiratory muscle endurance) as compared to low intensity training (no significant effect on Wmax, VO_2max, VEmax, PiMax)[2].**		

[1] Selection bias unclear: Patients are randomized, allocation concealment was not reported. Attrition bias = high, 12.5% (n = 1) loss to follow-up in both study arms, performance bias: unclear if researchers and participants were blinded from allocation to study arm. Detection bias: unclear, blinding of outcome assessors was not

[2] Wmax, Maximal exercise capacity; VO_2max, maximal volume uptake; VEmax, Maximum ventilation; Pimax, Maximum static inspiratory pressure

High intensity training				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Pulmonary function				
2) de Jong, 2001[1]	2) children with CF aged 10-25 years • Intervention: Mean (SD): 19 (5.5) years Control: Mean (SD): 17 (5.2) years	2) 16 (8 vs 8)	2) High intensity training, trained up to 40% maximal static inspiratory pressure during 6 weeks vs low intensity training, trained up to 10% maximal static inspiratory pressure during 6 weeks	**Change in pulmonary function from baseline to post-treatment (intervention vs control)** • Forced expiratory volume in the first second (FEV1 in L): No significant difference between groups, p = 0.822 • Forced expiratory volume in the first second (FEV1 % pred.): No significant difference between groups, p = 0.460 • Forced vital capacity (FVC in l): No significant difference in between groups, p = 0.999 • Forced vital capacity (FVC in % pred.): No significant difference between groups, p = 0.789

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-2	Serious limitations - Selection bias: unclear; Attrition bias: high; Performance bias: unclear; Detection bias: unclear
Consistency:	0	No important inconsistency. Only 1 study performed.
Directness:	0	Results are direct. Outcomes generalizable.
Precision:	-2	Some imprecision due to small sample size. Only 1 study performed.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship.
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence there is no significant effect of high intensity training in children with Cystic Fibrosis on pulmonary function (FEV1 in L and %, FVC in L and %) as compared to low intensity training**

[1] Selection bias unclear: Patients are randomized, allocation concealment was not reported. Attrition bias = high, 12.5% (n = 1) loss to follow-up in both study arms, performance bias: unclear if researchers and participants were blinded from allocation to study arm. Detection bias: unclear, blinding of outcome assessors was not reported.

5 Conclusies van evidence

5.1 *Diagnostische methoden voor het herkennen van dyspneu*

Diagnostic methods for recognizing dyspnoea		
Diagnostic method	**Conclusions of evidence**	**Quality of evidence**
Dalhousie dyspnoea scales	Validated for children ≥8 yrs. with CF or asthma This scale can be used to accurately assess the sensation of dyspnoea.	Systematic review of observational studies
Modified Borg Scale	Validated for children ≥ 9 yrs. with CF, use of this scale in combination with the Fifteen-Count breathless score could improve reliability and accuracy of the measurement of dyspnoea	
Visual analogue Scale	Not validated, use of this scale in combination with the Fifteen-Count breathless score could improve reliability and accuracy of the measurement of dyspnoea	
Medical Research Council Dyspnoea Scale	Not validated	
Numeric rating scale	Not validated	
Memorial Symptom Assessment Scales	Not validated for rating of dyspnoea alone	
Liverpool Respiratory Symptom Questionnaire	Validated for healthy children and children with CF (6-12)	
Fifteen-Count breathless Score	Validated for children with CF aged 6 to 18	
General conclusion	**No gold standard for the assessment of dyspnoea in children with advanced disease can be identified, due to the following reasons:** - **Symptom intensity and child suffering are likely to be underestimated. These must be reported by the caregiver as most children with dyspnoea are often unable to self-report.** - **Only 4 out of 8 diagnostic methods are validated for children with advanced disease** - **None of the tools diagnostic methods are validated for preschool children (< 6)**	Systematic review of observational studies

5.2 *Niet-medicamenteuze behandeling van dyspneu*

Non Pharmacological treatment of dyspnoea		
Intervention	**Conclusions of evidence**	**Quality of evidence**
Physical therapy (neuro electrical muscle stimulation and chest wall vibration) *Counselling + breathing exercise* *Acupuncture* *Cooling* *Self-hypnosis* *Quiet environment - sensory stimulation ('snoezelen', music and light patterns)* *Nebulization of physiological or hypertonic saline* *Mechanical ventilation*	Unknown effect	No studies
Walking with non-invasive ventilation *vs. walking with non-invasive ventilation*	No significant effect on degree of dyspnoea in children with Cystic Fibrosis	⊕⊖⊖⊖ VERY LOW (1RCT)
	↑ exercise capacity (walking distance) in children with Cystic Fibrosis after intervention (no significant effect on peripheral oxygen saturation, heart rate, respiratory rate).	
	↑ pulmonary function (forced expiratory volume in the first second, minute volume, tidal volume and pulmonary ribcage volume) in children with Cystic Fibrosis after intervention (no significant effect of FEV1 in %, FVC in ml and %, FEF25e75, Vrcp, vrca, Vab, Ti, Te, Ttot, Ti/tot)[1].	
high intensity training *vs. low intensity training*	No significant effect on degree of dyspnoea in children with Cystic Fibrosis	⊕⊖⊖⊖ VERY LOW (1RCT)
	↑ exercise capacity (inspirational muscle endurance) in children with Cystic Fibrosis after intervention (no significant effect on Wmax, VO2max, VEmax, PiMax)[2]	
	No significant effect on pulmonary function (forced expiratory volume in the first second and forced vital capacity) in children with Cystic fibrosis.	

[1]FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; FEF 25e75, forced expiratory flow of 25%e75% of FVC; MV, minute volume; Vt, tidal volume; Vrcp, pulmonary rib cage volume; Vrca, abdominal rib cage volume; Vab, abdominal volume; Ti, inspiratory time; Te, expiratory time; Ttot, total ventilatory cycle time; Ti/Ttot, duty cycle; RR/vt, Frequency/tidal volume ratio
[2] Wmax, Maximal exercise capacity; VO_2max, maximal volume uptake; VEmax, Maximum ventilation; Pimax, Maximum static inspiratory pressure

5.3 *Medicamenteuze behandeling van dyspneu*

Pharmacological treatment of dyspnoea		
Intervention	**Conclusions of evidence**	**Quality of evidence**
Morphine (oral, parental) *Morphine (inhaled)* *Bronchodilators* *Benzodiazepines* *Corticosteroids* *Oxygen*	Unknown effect	No studies
New pharmacological interventions (added in for guideline 2020)		
Morphine sulphate (buccal) *Fentanyl (intranasal)* *Methotrimeprazine + Fentanyl or Morphine sulphate*	Unknown effect	No studies

6 Aanbevelingen uit richtlijnen

6.1 *Diagnostische methoden voor het herkennen van dyspneu*

Diagnostic methods for recognizing dyspnoea – Adult guideline	
Integraal Kankerinstituut Nederland. Dyspneu in de palliatieve fase.2015	
Recommendation	**Level of evidence**
Doe altijd een volledige anamnese, gericht op de dyspneu, de begeleidende symptomen, de mogelijke oorza(a)k(en), de impact voor het dagelijks functioneren en de emotionele, cognitieve, existentiële en gedragsmatige dimensies ervan.	1 Systematic review 1 qualitative study
Doe altijd een lichamelijk onderzoek.	1 Systematic review
Overweeg het gebruik van meetinstrumenten: • een symptoomscore met behulp van een numeric rating scale, vooral om de mate van dyspneu te vervolgen in de loop van de tijd en om het effect van behandeling te evalueren • een multidimensioneel instrument (zoals de Chronic Respiratory Disease Questionnaire (CRQ) bij COPD) om alle dimensies van dyspneu in beeld te brengen en te vervolgen • het Utrecht Symptoom Dagboek (bij patiënten met kanker) om zowel dyspneu als een aantal andere veel voorkomende symptomen (die ook met de dyspneu kunnen samenhangen) in kaart te brengen en te vervolgen	4 Systematic reviews 1 observational study
Doe op indicatie aanvullend onderzoek: • meting van de zuurstofsaturatie met een pulse-oxymeter • laboratoriumonderzoek: Hb, BNP, D-dimeer, glucose, arterieel bloedgas • kweken van sputum en/of bloed • beeldvormend onderzoek: X-thorax, CT-thorax, CT-angiografie, echocardiografie • longfunctieonderzoek • ECG • bronchoscopie	1 observational study
Maak bij de keuze voor aanvullende diagnostiek een afweging van haalbaarheid en therapeutische consequenties, mede in het licht van de wens van de patiënt, zijn of haar verblijfplaats en de levensverwachting.	

6.2 *Niet-medicamenteuze behandeling van dyspneu*

Non pharmacological treatment of dyspnoea – Adult guideline	
National Clinical Guideline Centre (NICE). Care of dying adults in the last days of life. 2015	
Recommendation	**Level of evidence**
Clinical evidence: *Three studies were included in the review, 2 RCTs and 1 non-randomised comparative study.* *Evidence was not meta-analysed as it was inappropriate to pool the data given the difference in study design and outcomes reported. No evidence was found for the quality of life or time-to-death outcomes. The most commonly reported outcome was control of breathlessness, while nausea and vomiting were reported as adverse effects.*	
Identify and treat reversible causes of breathlessness in the dying person, for example pulmonary oedema or pleural effusion.	Expert opinion
Consider non-pharmacological management of breathlessness in a person in the last days of life. Do not routinely start oxygen to manage breathlessness. Only offer oxygen therapy to people known or clinically suspected to have symptomatic hypoxaemia.	Expert opinion
Integraal Kankerinstituut Nederland. Dyspneu in de palliatieve fase.2015	
Geef adviezen ten aanzien van: • ademhalingsoefeningen c.q. -technieken (vooral pursed lip breathing bij patiënten met COPD) • houding • doseren van inspanning Schakel hiervoor, indien nodig en beschikbaar, een gespecialiseerd verpleegkundige, gespecialiseerd fysiotherapeut en/of ergotherapeut in.	18 systematic reviews waarvan 6 van goede kwaliteit 8 RCT's(hoog risico op basis: geen intention-to-treat analyse)
Overweeg de toepassing van ontspanningsoefeningen, vooral wanneer angst en spanning een rol spelen. Schakel hiervoor, indien nodig en beschikbaar, een gespecialiseerd verpleegkundige of gespecialiseerd fysiotherapeut in.	
Overweeg het gebruik van een ventilator.	
Over de rol van niet-invasieve beademing kan geen aanbeveling worden gedaan.	
De volgende interventies worden niet aanbevolen: • acupunctuur/acupressuur • vibratie thoraxwand • neurostimulatie • luchtbevochtiging	

6.3 *Medicamenteuze behandeling van dyspneu*

Pharmacological treatment of dyspnoea – Adult guideline	
National Clinical Guideline Centre (NICE). Care of dying adults in the last days of life. 2015	
Recommendation	**Level of evidence**
Clinical evidence: *Three studies were included in the review, 2 RCTs and 1 non-randomised comparative study.* *Evidence was not meta-analysed as it was inappropriate to pool the data given the difference in study design and outcomes reported. No evidence was found for the quality of life or time-to-death outcomes. The most commonly reported outcome was control of breathlessness, while nausea and vomiting were reported as adverse effects.*	
Identify and treat reversible causes of breathlessness in the dying person, for example pulmonary oedema or pleural effusion.	Very low, expert opinion
Consider managing breathlessness with: • an opioid or • a benzodiazepine or • a combination of an opioid and benzodiazepine.	Very low, expert opinion
Consider non-pharmacological management of breathlessness in a person in the last days of life. Do not routinely start oxygen to manage breathlessness. Only offer oxygen therapy to people known or clinically suspected to have symptomatic hypoxaemia.	Expert opinion
Integraal Kankerinstituut Nederland. Dyspneu in de palliatieve fase.2015	
• Gebruik rescue medicatie alleen voor aanvalsgewijze dyspneu, die naar verwachting langer dan 30 minuten zal aanhouden. • Gebruik voor conversies naar ander opioïd en/of andere toedieningsweg de omrekentabel in richtlijn Pijn in de palliatieve fase. Kies bij een gestoorde nierfunctie (klaring <50 ml/min) voor intermitterende toediening van morfine (zo nodig, op geleide van de klachten) of voor onderhoudsbehandeling met fentanyl of hydromorfon.	9 systematic reviews, 4 RCT's
Overweeg bij onvoldoende effect van morfine, zeker als angst en spanning een rol lijken te spelen, toevoeging van een benzodiazepine: ◦oxazepam 3dd 10 mg of lorazepam 2dd 0,5 mg p.o. (bij een levensverwachting van weken tot maanden), of midazolam 10-30 mg/24 uur s.c. (bij een levensverwachting van dagen tot een week).	9 systematic reviews, 4 RCT's
Start met 1dd 4-8 mg dexamethason of 1dd 30-60 mg prednis(ol)on p.o., s.c. of i.v. bij: • Exacerbatie van COPD • Pneumonitis door radiotherapie of medicamenten • Lymphangitis carcinomatosa • V. cava superior-syndroom • Obstructie van de luchtwegen Beoordeel het effect na een week.	9 systematic reviews, 4 RCT's
Zet palliatieve sedatie in bij refractaire dyspneu. Bij continue en diepe sedatie dient de levensverwachting <1-2 weken te zijn. Bij dreigende verstikking wordt acute sedatie toegepast. Gebruik de middelen en doseringen die vermeld worden in de KNMG-richtlijn Palliatieve sedatie.	9 systematic reviews, 4 RCT's

7 Overzicht conclusies van evidence en aanbevelingen uit richtlijnen

7.1 *Diagnostische methoden voor het herkennen van dyspneu*

Diagnostic methods for recognizing dyspnoea								
Treatment	Conclusions of evidence (studies on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children 2013 (2)	Level of evidence[1]
General diagnostics								
Full medical history focusing on dyspnoea, accompanying symptoms, causes, impact on daily functioning (cognitive, emotional, existential, behavioural)	Unknown effect	No studies	Not identified	-	Do	1 Systematic review and 1 qualitative study (3;P)	No recommendation	-
Physical examination	Unknown effect	No studies	Not identified	-	Do	1 systematic review (3;P)	No recommendation	-
Additional assessments • *Measurement of respiratory rate* • *Oxygen saturation using a pulse oximeter* • *Number of words said in one sentence* • *Laboratory tests (Hb, blood gas parameters)* • *Medical imaging: x-ray* • *Pulmonary function test* *Bronchoscopy*	Unknown effect	No studies	Not identified	-	Consider	1 observational study (3;P)	Consider; weak recommendation	-
Diagnostic methods for recognizing dyspnoea								
Dalhousie dyspnoea scales	Validated for children ≥8 yrs. with CF or asthma This scale can be used to accurately assess the sensation of dyspnoea.	Systematic review of observational studies (4;P)	Not identified	-	Not identified	-	Consider use of instruments (VAS) to assess degree of dyspnoea in children; weak recommendation	-
Modified Borg Scale	Validated for children ≥ 9 yrs. with CF, use of this scale in combination with the Fifteen-Count breathless score could improve reliability and accuracy of the measurement of dyspnoea							-
Visual analogue Scale	Not validated, use of this scale in combination with the Fifteen-Count breathless score could							Level 4 child evidence (5)

	improve reliability and accuracy of the measurement of dyspnoea							
Medical Research Council Dyspnoea Scale	Not validated							-
Numeric rating scale	Not validated	Systematic review of observational studies (4;P)	Not identified	-	Consider (to measure degree of dyspnoea over time)	4 systematic reviews and 1 observational study (3;P)	Consider use of instruments to assess degree of dyspnoea in children; weak recommendation	Level 4 child evidence (5)
Memorial Symptom Assessment Scales	Not validated for rating of dyspnoea alone	Systematic review of observational studies (4;P)	Not identified	-	Not identified	-	Consider use of instruments to assess degree of dyspnoea in children; weak recommendation	-
Liverpool Respiratory Symptom Questionnaire	Validated for healthy children and children with CF (6-12)							-
Fifteen-Count breathless Score	Validated for children with CF aged 6 to 18							-

Legend
P: Palliative context
NP: Non-palliative context
Not identified: No recommendations on specific pharmacological intervention were identified.
Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.

[1]Level of evidence:
Level 1: Based on a systematic review or at least two randomized controlled trials of good quality
Level 2: Based on one at randomized controlled trial or at least two comparative clinical studies
Level 3: Based on one comparative study or on non-comparative studies
Level 4: Based on expert opinion

References

2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.
3. Integraal Kankercentrum Nederland. Dyspneu in de palliatieve fase (3.0). 2015. Available from: www.pallialine.nl/dyspneu-in-de-palliatieve-fase.
4. Pieper L, Zernikow B, Drake R, Frosch M, Printz M, Wager J. Dyspnea in Children with Life-Threatening and Life-Limiting Complex Chronic Conditions. J Palliat Med. 2018;21(4):552-64.
5. Wolfe J, Hinds P. Textbook of Interdisciplinary Pediatric Palliative Care: Saunders; 2011.

7.2 *Niet-medicamenteuze behandeling van dyspneu*

Non pharmacological treatment of dyspnoea								
Treatment	Conclusions of evidence (RCTs on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children 2013 (2)	Level of evidence[1]
Physical therapy: neuro electrical muscle stimulation and chest wall vibration)	Unknown effect	No studies	Not identified	-	Do not give (neuro electrical muscle stimulation and chest wall vibration are not recommended)	18 systematic reviews and 8 RCTs (3;P)	Consider; weak recommendation	Expert opinion; Level 1 adult evidence (6)[2]
Counselling + breathing exercise	Unknown effect	No studies	Not identified	-	Give counselling on breathing exercise, posture and dosing of exercise	18 systematic reviews and 8 RCTs(3;P)	Do; strong recommendation	Level 2 adult evidence (6-12)[2]
Acupuncture	Unknown effect	No studies	Not identified	-	Do not give (Acupuncture is not recommended	18 systematic reviews and 8 RCTs (3;P)	No recommendation can be given	Controversy in adult evidence (6)[2]
Ventilation and cooling	Unknown effect	No studies	Not identified	-	Consider using a ventilator	18 systematic reviews and 8 RCTs (3;P)	Consider; weak recommendation	Level 4 adult evidence (6, 13-15)[2]
Relaxation	Unknown effect	No studies	Not identified	-	Consider relaxation exercises (for dyspnoea in combination with anxiety)	18 systematic reviews and 8 RCTs (3;P)	No recommendation	
Self-hypnosis	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 child evidence (16)
Quiet environment - sensory stimulation ('snoezelen', music and light patterns)	Unknown effect	No studies	Not identified	-	Not identified	-	Do; strong recommendation	Expert opinion; Level 4 child evidence (5)
Nebulization of physiological or hypertonic saline	Unknown effect	No studies	Not identified	-	Do not give (humidification is not recommended)	18 systematic reviews and 8 RCTs (3;P)	Consider; weak recommendation	Level 4 adult evidence (17)[2]
Walking with non-invasive ventilation vs walking without non-invasive ventilation	No significant effect on degree of dyspnoea in children with Cystic Fibrosis ↑ exercise capacity (walking distance) in	VERY LOW, 1 RCT (18;P)	Not identified	-	No recommendation on non-invasive ventilation can be given	18 systematic reviews and 8 RCTs (3;P)	No recommendation	-

	children with Cystic Fibrosis after intervention ↑ pulmonary function (forced expiratory volume in the first second, minute volume, tidal volume and pulmonary ribcage volume) in children with Cystic Fibrosis after intervention							
high intensity training vs low intensity training	No significant effect on degree of dyspnoea in children with Cystic Fibrosis ↑ exercise capacity (inspirational muscle endurance) in children with Cystic Fibrosis after intervention No significant effect on pulmonary function (forced expiratory volume in the first second and forced vital capacity) in children with Cystic fibrosis.	VERY LOW, 1 RCT (19;P)	Not identified	-	Not identified	-	No recommendation	-
Oxygen	Unknown effect	No studies	Not identified	-	Consider (in case of hypoxaemia)	Very low, expert opinion (20;P)	Consider (in case of hypoxaemia); weak recommendation	Controversy in adult evidence (7, 11, 21-25)[2] Level 1 adult evidence for COPD (26)

Legend
P: Palliative context
NP: Non-palliative context
Not identified: No recommendations on specific pharmacological intervention were identified.
Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.

[1]Level of evidence:
Level 1: Based on a systematic review or at least two randomized controlled trials of good quality
Level 2: Based on one at randomized controlled trial or at least two comparative clinical studies
Level 3: Based on one comparative study or on non-comparative studies
Level 4: Based on expert opinion
[2]Adult evidence is extracted from guidelines of pallialine.nl

References

2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.
3. Integraal Kankercentrum Nederland. Dyspneu in de palliatieve fase (3.0). 2015. Available from: www.pallialine.nl/dyspneu-in-de-palliatieve-fase.
5. Wolfe J, Hinds P. Textbook of Interdisciplinary Pediatric Palliative Care: Saunders; 2011.

6. Bausewein C, Booth S, Gysels M, Higginson I. Non-pharmacological interventions for breathlessness in advanced stages of malignant and non-malignant diseases. Cochrane Database Syst Rev. 2008(2):CD005623.
7. Ben-Aharon I, Gafter-Gvili A, Paul M, Leibovici L, Stemmer SM. Interventions for alleviating cancer-related dyspnea: a systematic review. J Clin Oncol. 2008;26(14):2396-404.
8. Bredin M, Corner J, Krishnasamy M, Plant H, Bailey C, A'Hern R. Multicentre randomised controlled trial of nursing intervention for breathlessness in patients with lung cancer. BMJ. 1999;318(7188):901-4.
9. Connors S, Graham S, Peel T. An evaluation of a physiotherapy led non-pharmacological breathlessness programme for patients with intrathoracic malignancy. Palliat Med. 2007;21(4):285-7.
10. Corner J, Plant H, A'Hern R, Bailey C. Non-pharmacological intervention for breathlessness in lung cancer. Palliat Med. 1996;10(4):299-305.
11. DiSalvo WM, Joyce MM, Tyson LB, Culkin AE, Mackay K. Putting evidence into practice: evidence-based interventions for cancer-related dyspnea. Clin J Oncol Nurs. 2008;12(2):341-52.
12. Hately J, Laurence V, Scott A, Baker R, Thomas P. Breathlessness clinics within specialist palliative care settings can improve the quality of life and functional capacity of patients with lung cancer. Palliat Med. 2003;17(5):410-7.
13. Booth S, Moosavi SH, Higginson IJ. The etiology and management of intractable breathlessness in patients with advanced cancer: a systematic review of pharmacological therapy. Nat Clin Pract Oncol. 2008;5(2):90-100.
14. Freedman S. Facial cooling and perception of dyspnoea. Lancet. 1987;2(8569):1215.
15. Schwartzstein RM, Lahive K, Pope A, Weinberger SE, Weiss JW. Cold facial stimulation reduces breathlessness induced in normal subjects. Am Rev Respir Dis. 1987;136(1):58-61.
16. Mize WL. Clinical training in self-regulation and practical pediatric hypnosis: what pediatricians want pediatricians to know. J Dev Behav Pediatr. 1996;17(5):317-22.
17. Ahmedzai S, Davis C. Nebulised drugs in palliative care. Thorax. 1997;52 Suppl 2:S75-7.
18. Lima CA, Andrade Ade F, Campos SL, Brandao DC, Fregonezi G, Mourato IP, et al. Effects of noninvasive ventilation on treadmill 6-min walk distance and regional chest wall volumes in cystic fibrosis: randomized controlled trial. Respir Med. 2014;108(10):1460-8.
19. de Jong W, van Aalderen WM, Kraan J, Koeter GH, van der Schans CP. Inspiratory muscle training in patients with cystic fibrosis. Respir Med. 2001;95(1):31-6.
20. National Institute for Health and Care Excellence. Care of dying adults in the last days of life. [Internet]. London: NICE; 2015 [cited 2021 March, 1]. Available from: www.nice.org.uk/guidance/ng31.
21. Booth S, Wade R, Johnson M, Kite S, Swannick M, Anderson H. The use of oxygen in the palliation of breathlessness. A report of the expert working group of the Scientific Committee of the Association of Palliative Medicine. Respir Med. 2004;98(1):66-77.
22. Bruera E, Schoeller T, MacEachern T. Symptomatic benefit of supplemental oxygen in hypoxemic patients with terminal cancer: the use of the N of 1 randomized controlled trial. J Pain Symptom Manage. 1992;7(6):365-8.
23. Clemens KE, Quednau I, Klaschik E. Use of oxygen and opioids in the palliation of dyspnoea in hypoxic and non-hypoxic palliative care patients: a prospective study. Support Care Cancer. 2009;17(4):367-77.
24. Cranston JM, Crockett AJ, Moss JR, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2005(4):CD001744.
25. Uronis HE, Currow DC, McCrory DC, Samsa GP, Abernethy AP. Oxygen for relief of dyspnoea in mildly- or non-hypoxaemic patients with cancer: a systematic review and meta-analysis. Br J Cancer. 2008;98(2):294-9.
26. Lorenz KA, Lynn J, Dy SM, Shugarman LR, Wilkinson A, Mularski RA, et al. Evidence for improving palliative care at the end of life: a systematic review. Ann Intern Med. 2008;148(2):147-59.

7.3 *Medicamenteuze behandeling van dyspneu*

Pharmacological treatment of dyspnoea								
Treatment	Conclusions of evidence (RCTs on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children 2013 (2)	Level of evidence[1, 2]
Morphine (oral, parental)	Unknown effect	No studies	Not identified	-	Consider an opioid	Very low, expert opinion (20); 4 systematic reviews, 9 RCTs (3;P)	Do; strong recommendation	Level 1 adult evidence (7, 11, 13, 23, 27, 28)[2]
Morphine sulphate (buccal)							No recommendation	-
Fentanyl (intranasal)							No recommendation	-
Morphine (inhaled)	Unknown effect	No studies	Not identified	-	Not identified	-	Do not give; strong recommendation	Level 1 adult evidence (29, 30)
Benzodiazepines	Unknown effect	No studies	Not identified	-	Consider a benzodiazepine	Very low, expert opinion (20;P)	Consider (for dyspnoea in combination with anxiety); weak recommendation	Level 2 adult evidence (31)[2]
					Consider (for dyspnoea in combination with anxiety) - oxazepam, lorazepam, midazolam	4 systematic reviews, 9 RCTs (3;P)		
					Consider (for refractory dyspnoea)	4 systematic reviews, 9 RCTs (3;P)		
Opioid + Benzodiazepine	Unknown effect	No studies	Not identified	-	Consider a combination of an opioid and benzodiazepine	Very low, expert opinion (20;P)	No recommendation	-
Corticosteroids (oral)	Unknown effect	No studies	Not identified	-	Consider prednis(ol)on (for COPD exacerbation, central obstruction, lymphangitis or pneumonitis from radiotherapy or chemotherapy and superior vena cava syndrome)	4 systematic reviews, 9 RCTs (3;P)	Consider (for central obstruction, lymphangitis or pneumonitis from radiotherapy or chemotherapy and superior vena cava syndrome); weak recommendation	Level 4 adult evidence (28)[2], (32)
Bronchodilators	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 adult evidence (32)

Legend
P: Palliative context
NP: Non-palliative context
Not identified: No recommendations on specific pharmacological intervention were identified.
Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.

[1]Level of evidence:

Level 1: Based on a systematic review or at least two randomized controlled trials of good quality
Level 2: Based on one at randomized controlled trial or at least two comparative clinical studies
Level 3: Based on one comparative study or on non-comparative studies
Level 4: Based on expert opinion
[2]For access to full literature references, we refer to the corresponding reference numbers in reference list of *'Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013'*.
[3]Adult evidence is extracted from guidelines of pallialine.nl

References

2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.
3. Integraal Kankercentrum Nederland. Dyspneu in de palliatieve fase (3.0). 2015. Available from: www.pallialine.nl/dyspneu-in-de-palliatieve-fase.
7. Ben-Aharon I, Gafter-Gvili A, Paul M, Leibovici L, Stemmer SM. Interventions for alleviating cancer-related dyspnea: a systematic review. J Clin Oncol. 2008;26(14):2396-404.
11. DiSalvo WM, Joyce MM, Tyson LB, Culkin AE, Mackay K. Putting evidence into practice: evidence-based interventions for cancer-related dyspnea. Clin J Oncol Nurs. 2008;12(2):341-52.
13. Booth S, Moosavi SH, Higginson IJ. The etiology and management of intractable breathlessness in patients with advanced cancer: a systematic review of pharmacological therapy. Nat Clin Pract Oncol. 2008;5(2):90-100.
20. National Institute for Health and Care Excellence. Care of dying adults in the last days of life. [Internet]. London: NICE; 2015 [cited 2021 March, 1]. Available from: www.nice.org.uk/guidance/ng31.
23. Clemens KE, Quednau I, Klaschik E. Use of oxygen and opioids in the palliation of dyspnoea in hypoxic and non-hypoxic palliative care patients: a prospective study. Support Care Cancer. 2009;17(4):367-77.
27. Jennings AL, Davies AN, Higgins JP, Gibbs JS, Broadley KE. A systematic review of the use of opioids in the management of dyspnoea. Thorax. 2002;57(11):939-44.
28. Viola R, Kiteley C, Lloyd NS, Mackay JA, Wilson J, Wong RK, et al. The management of dyspnea in cancer patients: a systematic review. Support Care Cancer. 2008;16(4):329-37.
29. Jennings AL, Davies AN, Higgins JP, Broadley K. Opioids for the palliation of breathlessness in terminal illness. Cochrane Database Syst Rev. 2001(4):CD002066.
30. Polosa R, Blackburn MR. Adenosine receptors as targets for therapeutic intervention in asthma and chronic obstructive pulmonary disease. Trends Pharmacol Sci. 2009;30(10):528-35.
31. Navigante AH, Cerchietti LC, Castro MA, Lutteral MA, Cabalar ME. Midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in patients with advanced cancer. J Pain Symptom Manage. 2006;31(1):38-47.
32. Twycross R. The terminal phase. In: Hanks G, Cherny N, Kaasa S, Christakis NA, Portenoy RK, Fallon M, editors. Oxford textbook of palliative medicine. 4 ed. New York: Oxford University Press; 2009.

D Hematologische verschijnselen

Inhoudsopgave_Toc102114731

1 Uitgangsvragen

Vraag 4A: Wat is de meest effectieve medicamenteuze behandeling van anemie bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Medicamenteuze behandeling van anemie (o.a. erytropoëtine, vitamines & ijzer, erytrocyten transfusie)
C: Geen behandeling/ placebo
O: Effect op vermoeidheid, complicaties, morbiditeit, mortaliteit, ziekenhuis admissies kwaliteit van leven

Vraag 4B: Wat is de meest effectieve medicamenteuze behandeling van trombocytopenie bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase.
I: Medicamenteuze behandeling van trombocytopenie (o.a. trombocytentransfusie)
C: Geen behandeling/placebo
O: Effect op bloedingsneiging, complicaties, morbiditeit, mortaliteit, ziekenhuis admissies en kwaliteit van leven

Vraag 4C: Wat is de meest effectieve medicamenteuze behandeling van bloedingen bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase.
I: Medicamenteuze behandeling van bloedingen
C: Geen behandeling/ placebo
O: Effect op bloeding(sneiging) en kwaliteit van leven

Vraag 4D: Wat is de meest effectieve medicamenteuze behandeling van trombose bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase.
I: Medicamenteuze behandeling van trombose
C: Geen behandeling/ placebo
O: Effect op trombose en kwaliteit van leven

2 Resultaten van het literatuuronderzoek

Jaar	Bibliografie	Studie karakteristieken
4A: Wat is de meest effectieve medicamenteuze behandeling van anemie bij kinderen tussen 0 en 18 jaar in de palliatieve fase?*		
2019	***Federation of Medical Specialists***. (2019). Bloedtransfusiebeleid. Federation of Medical Specialists.[1]	Richtlijn kinderen en volwassenen
2002	***Buyukpamukcu M et al.*** Is Epoetin Alfa a treatment option for chemotherapy-related anaemia in children? Med Pediatr Oncol 2002;29 (4):455-8	RCT kinderen
2006	***Razouk BI et al.*** Double-Blind, Placebo-Controlled Study of Quality of Life, Hematologic End Points, and Safety of Weekly Epoetin Alfa in Children With Cancer Receiving Myelosuppressive Chemotherapy. J Clin Oncol 2006; 24:3583-3589.	RCT kinderen
4B: Wat is de meest effectieve medicamenteuze behandeling van trombocytopenie bij kinderen tussen 0 en 18 jaar in de palliatieve fase?*		
2019	***Federation of Medical Specialists***. (2019). Bloedtransfusiebeleid. Federation of Medical Specialists.[1]	Richtlijn kinderen en volwassenen
4C: Wat is de meest effectieve medicamenteuze behandeling van bloedingen bij kinderen tussen 0 en 18 jaar in de palliatieve fase?*		
Geen literatuur		
4D: Wat is de meest effectieve medicamenteuze behandeling van trombose bij kinderen tussen 0 en 18 jaar in de palliatieve fase?*		
Geen literatuur		

[1]Aanbevelingen uit de richtlijnen over hematologische verschijnselen bij kinderen en volwassenen worden gebruikt in de overwegingen

* Systematisch gezocht, zie: bijlage 7 zoekverantwoording – search 1

3 Evidence tabellen

3.1 Medicamenteuze behandeling van Anemie

Pharmacological treatment for Anaemia				
Buyukpamukcu M et al. Is Epoetin Alfa a treatment option for chemotherapy-related anaemia in children? Med Pediatr Oncol 2002;29 (4):455-8				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: RCT Setting: 1 centre, Turkey Duration: Intervention duration was 2 months Study years: Not reported Protocol published in register: Not reported	Number and type of participants: Total of 34 children with cancer- or chemotherapy related anaemia. • *Intervention group:* N = 17 • *Control group:* N = 17 Age: Median: 5yr, Range 1-16 yr. Sex: M: 20 (58,8%), F: 14 (41,2%) Other: Number and percentage of Cancer Treatments included in the study. • Platinum-based chemotherapy: N = 15, 44,1% • Nonplatinum-based chemotherapy: N = 19, 55,9% • Local regional radiotherapy: N = 13, 38,2% • Cranial and/or spinal radiotherapy: N = 7, 20,6%	All patients Intervention duration was 8 weeks Physical examinations, blood counts and blood pressure measurement were performed weekly. Transfusions were administered if Hb levels dropped below 6g/dL. No Iron supplementation or granulocyte colony-stimulating factor was given to the patients during the study period Type of intervention: Serum erythropoietin was measured at the beginning and end of the study. Epoetin Alfa was administered at a dose of 150IU/kg, 3 times a week subcutaneously for 8 weeks Type of control: Serum erythropoietin (EPO) was measured at the beginning of the study	Outcome definitions: **Hematologic parameters:** Neutrophil counts, thrombocyte counts, serum EPO levels **Haemoglobin level:** Mean Hb levels g/dL **Red Blood Cell (RBC) transfusion requirements:** Number of transfusions required **Safety:** Occurrence of complications (hypertension) Results (per outcome) **Hematologic parameters:** • *Neutrophil counts:* no significant difference in comparison to control group • *Thrombocyte counts*; no significant difference in comparison to control group • *Serum EPO levels:* No significant difference between the Epoetin Alfa and control groups regarding serum EPO levels **Haemoglobin levels (g/dL):** *Mean haemoglobin level at study entry (intervention vs. control):* 8.5 g/dL vs 8.48 g/dL, P = NS *Mean haemoglobin level at Study end (intervention vs. control):* 10.21 g/dL vs 8.41 g/dL, p = 0.027 *Mean Hb over the course of the study* • *Intervention group:* Significant increase in the Epoetin Alfa group from 8.50 to 10.21 g/dL, p = 0.086 • *Control group::* No significant increase in the Epoetin Alfa group from 8.48 to 8.41 g/dL **RBC transfusion requirements** *Number of transfusions required (intervention vs. control):* 1 (5.9%) vs 8 (47.0%), p = 0.08 **Safety** 1 patient in the intervention developed hypertension after 2 weeks of Epoetin Alfa treatment. Epoetin alfa was continued after 1 week without further complications.	Strengths: - Limitations: Small group size **Risk of bias** A. Selection bias: Unclear Reason: patients were randomly assigned to either the Epoetin Alfa group or control group. Allocation concealment was not reported in the study B. Attrition bias: Unclear Reason: Loss of follow-up/dropout was not reported in the study C. Performance bias Unclear Reason: Blinding of patients and personnel was not reported in the study D. Detection bias Unclear Reason: Blinding of outcome assessors was not reported in the study

Pharmacological treatment for Anaemia: Epoetin Alfa				
Razouk BI et al. Double-Blind, Placebo-Controlled Study of Quality of Life, Hematologic End Points, and Safety of Weekly Epoetin Alfa in Children With Cancer Receiving Myelosuppressive Chemotherapy. J Clin Oncol 2006; 24:3583-3589.				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: Double-Blind Placebo-Controlled RCT Setting: 27 sites, USA Duration: Study visits occurred ever 3 / 4 weeks. Final follow-up 4 months after the beginning of intervention. Study years: 2000-2003 Protocol published in register: Protocol published in ClinicaltTrials.gov	Number and type of participants: Total of 224 anaemic paediatric patients who received myelosupressive chemotherapy for nonmyeloid malignancies (excluding brain tumours). • *Intervention group:* n = 111 • *Control group:* n = 111 Age: • *Intervention group:* Mean (SD): 12.4 (3.6), Range 5-18 • *Control group:* Mean (SD): 10.8 (4.0), Range 5-18 Sex: • *Intervention group:* M: 63 (56.8%), F: 48 (43.2%) • *Control group:* M: 58 (52.3%), F: 53 (47.7%) Other: Tumour Type: • *Intervention group:* Solid Tumour: 41 (36.9%) Hodgkin's disease 16 (14.4%) ALL: 40 (36.0%) Non-Hodgkin's lymphoma 14 (12.6%) • *Control group:* Solid Tumour: 57 (51.4%) Hodgkin's disease 11 (9.9%)	Type of intervention: EPO was administered intravenously once per week, starting a dose of 600 units/kg and was increased to 900 units/kg if Hb had not increased by 1 g/dL or more from baseline by first follow-up visit. Red Blood Cell (RBC) transfusion was suggested when Hb was 7 g/dL or less. Type of control: Placebo was administered intravenously once per week. RBC transfusion was suggested when Hb was 7 g/dL or less.	Outcome definitions: **HRQOL – Health related quality of life** • PedsQL- GCS: QoL was measured using a 100-point scale by assessing physical, emotional, social and school functioning. Higher scores indicate higher QoL • PEDsQL3.0 Cancer Module: was measured using a 100-point scale assessing pain/hurt, nausea, procedural anxiety, treatment anxiety, worry, cognitive problems and communication. Higher scores indicate higher QoL • Parent QoL was measured using parent versions of PedsQL- GCS and PEDsQL3.0 Cancer Module. 100-point scale. Higher scores indicate higher QoL **Haemoglobin level:** Mean Hb change from baseline to end/study in g/dL **Blood transfusion:** Number of patients who required blood transfusions; Median time first transfusion **Safety:** Occurrence of adverse events (hypertension) Results (per outcome) **HRQOL – Health related quality of life** *Total PedsQL-GCS scores at final visit (intervention vs control):* • Mean (SD) :74.9 (15.22) vs. 75.5 (15.74 • Group difference: -0.61 (95%CI -4.62 – 3.39), p = 0.823 *Mean (SD) of PEDsQL3.0 Cancer Modules at final visit (intervention vs control):* Pain/hurt: • Mean (SD): 73.1 (23.71) vs 75.7 (24.70); • Group difference: -2.64 (95%CI, -8.87 – 3.58), p = 0.215 Nausea: • Mean (SD) 68.8 (20.11) vs. 72.0 (20.96); • Group difference: -3.19 (95%CI -8.51 – 2.13), p = 502 Procedural anxiety: • Mean (SD): 75.2 (23.94) vs 76.4 (24.87); • Group difference: -1.16 (95%CI -7.47 – 5.15), p =0.940 Treatment anxiety: • Mean (SD): 87.0 (15.07) vs 89.4 (15.66); • Group difference: -2.35 (95%CI -6.31 – 1.62), p=0.673 Worry: • Mean (SD): 74.7 (22.21) vs 77.8 (23.18); • Group difference: -3.09 (95%CI -8.93 – 2.76), p = 0.360 Cognitive problems: • Mean (SD) 81.8 (16.60) vs 80.4 (17.40); • Group difference 1.38 (95%CI -3.05 – 5.82), p=0.476 Perceived physical appearance: • Mean (SD): 84.9 (16.82) vs 84.2 (17.46); • Group difference: 0.79 (95%CI -3.69 – 5.26), p=0.977	Strengths: Large-scale placebo-controlled study. Limitations: Inadequate utilization of iron supplementation in this study may have impaired the response to Epoetin Alfa. Investigators used clinical judgment to identify patients with iron-deficiency anaemia and exclude them from the study, but patients with a low iron level could enrol if the investigator thought it did not contribute to the anaemia. **Risk of bias** A. Selection bias: Unclear Reason: patients were randomly assigned to either intervention or control group. Patients were randomly assigned in a 1:1 ratio in groups of four patients. Allocation concealment was not reported. B. Attrition bias: Low risk Reason: Loss of follow-up/dropout was less than 10% C. Performance bias Unclear Reason: Blinding of patients and personnel was not reported in the study

	ALL: 35 (31.5%) Non-Hodgkin's lymphoma 8 (7.2%)		Communication: • Mean (SD): 86.6 (16.58) vs 85.5 (17.30; • Group difference: 1.13 (95%CI -3.24 – 5.50), p=0.359 **Haemoglobin level** Hb change from baseline to end/study (intervention vs control) • Mean (SD): 1.3 (2.38) vs 1.0 (1.90) • Group difference; 0.37 (95%CI -0.11 – 0.84), p = 0.002 **Blood transfusions** Number (%) of patients (intervention vs control): 72 (64.9%) vs 86 (77.5%) Median time first transfusion (intervention vs control): 15 vs 14.5 days, p=0.254). After 4 weeks patients were more likely to remain transfusion-free. **Haemoglobin levels and quality of life** A significant correlation was found between change in Hb level and change in quality of life score in the intervention group (r = 0.242; p = 0.018. In the placebo group the correlation was not significant (r = 0.86, p = 0.430). **Safety** Hypertension was reported in 2 (1.8%) patients in the intervention group and 1 (0.9%) patient in the placebo group. At least one thrombotic vascular event (intervention vs control): 22.3% vs 22.7%) Serious adverse event rates were similar in intervention and control (68.8% vs. 74.5%) Serious adverse events in intervention group (experienced by more than 5% of the patients) included fever (11.6%), infection (6.3%), Serious adverse events in control group (experienced by more than 5% of the patients) included infection (12.7%), fever (10.0%) and mucositis (5.5%). Four patients died during the study but no deaths were considered related to the study treatment.	<u>D. Detection bias</u> Unclear Reason: Blinding of outcome assessors was not reported in the study

4 Samenvatting en gradering van bewijs

4.1 Medicamenteuze behandeling van anemie

4.1.1 Geïncludeerde uitkomstmaten

Included outcomes
Haemoglobin level
Number of required red blood cell transfusions
Adverse events
Health Related Quality of life

4.1.2 Erytropoëtine (Epoetin Alfa)

Epoetin Alfa				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Mean haemoglobin levels, g/dL				
1) Buyukpamukcu, 2002	1) Children with cancer- or chemotherapy-related anaemia aged 1 to 16 yrs.	1) 34 (17 vs 17)	1) Epoetin Alfa dose of 150units /kg, administered 3 times per week for 8 weeks vs no intervention	1) **Mean Haemoglobin level (g/dL) – intervention vs control** *Study entry:* 8.5 g/dL vs 8.48 g/dL, P = NS *Study end:* 10.21 g/dL vs 8.41 g/dL, p = 0.027 *Over the course of the study (from study entry to study end):* Intervention group*:* 8.50 to 10.21 g/dL, p = 0.086 Control group: 8.48 to 8.41 g/dL, p = NS
2) Razouk, 2006	2) Anaemic paediatric patients who received myelosupressive chemotherapy for nonmyeloid malignancies aged 5 to 18 yrs.	2) 222 (111 vs 111)	2) Epoetin Alfa dose of 600units/kg to 900units/kg (if Hb had not increased by 1g/dL or more from baseline), administered intravenously 1 time per week for 16 months vs placebo administered intravenously 1 time per week for 16 months	2) **Mean (SD) change in Haemoglobin level (g/dL) – intervention vs control** 1.3 (2.38) vs 1.0 (1.90); EMD $_{\text{intervention - control}}$ = 0.37 (95%CI -0.11 to 0.84), p=0.129
Grade assessment				
Study design:	+4	2 Randomized Controlled Trials		
Study limitations	-2	Serious limitations - Selection bias: Unclear in 2/2; Attrition bias: Low in 1/2 and unclear in 1/2; Performance bias: unclear in 2/2; Detection bias: unclear in 2/2		
Consistency:	0	No important inconsistency. All studies show that haemoglobin levels are higher in children receiving Epoetin Alfa		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	0	No important imprecision, large sample size		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊕⊖⊖ **LOW**		
Conclusion:		**There is low quality of evidence that there is no significant effect of Epoetin Alfa (dose starting from 450units/kg per week) on haemoglobin levels of children with cancer- or chemotherapy related anaemia as compared to no treatment or placebo. However, in one study haemoglobin levels did increase in the intervention group (no significant effect).**		

Epoetin Alfa				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Red Blood Cell Transfusion, Number of patients that required Red Blood Cell transfusions				
1) Buyukpamukcu, 2002	1) Children with cancer- or chemotherapy-related anaemia aged 1 to 16 yrs.	1) 34 (17 vs 17)	1) Epoetin Alfa dose of 15units /kg, administered 3 times per week for 8 weeks vs no intervention	1) **N(%) of patients with Red Blood Cell Transfusion - intervention vs control** 1 (5.9%) vs 8 (47%), p = 0.08
2) Razouk, 2006	2) Anaemic paediatric patients who received myelosupressive chemotherapy for nonmyeloid malignancies aged 5 to 18 yrs.	2) 222 (111 vs 111)	2) Epoetin Alfa dose of 600units/kg to 900units/kg (if Hb had not increased by 1g/dL or more from baseline), administered intravenously 1 time per week for 16 months vs placebo administered intravenously 1 time per week for 16 months	2) **N(%) of patients with Red Blood Cell Transfusion - intervention vs control** *Over the course of the study:* 72 (64.9%) vs 86 (77.5%) *After week 4:* 38.7% (intervention) vs 22.5% (control), p = 0.10 (patients were more likely to remain transfusion free)
Grade assessment				
Study design:	+4	2 Randomized Controlled Trials		
Study limitations	-2	Serious limitations - Selection bias: Unclear in 2/2; Attrition bias: Low in 1/2 and unclear in 1/2; Performance bias: unclear in 2/2; Detection bias: unclear in 2/2		
Consistency:	0	No important inconsistency. All studies show that number of patients who required blood transfusions is lower in the Epoetin Alfa group		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	0	No important imprecision, large sample size		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊕⊖⊖ **LOW**		
Conclusion:		**There is low quality of evidence that there is no significant effect of Epoetin Alfa (dose starting from 450units/kg per week) on the number of required blood cell transfusions in children with cancer- or chemotherapy-related anaemia as compared to no treatment or placebo.**		

Epoetin Alfa				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Safety, adverse effect and adverse events				
1) Buyukpamukcu, 2002	1) Children with cancer- or chemotherapy-related anaemia aged 1 to 16 yrs.	1) 34 (17 vs 17)	1) Epoetin Alfa dose of 15units /kg, administered 3 times per week for 8 weeks vs no intervention	1) **N(%) of patients with adverse events (intervention vs control)** Hypertension: 1 (5.8%) vs 0 (0%), p-value unknown
2) Razouk, 2006	2) Anaemic paediatric patients who received myelosupressive chemotherapy for nonmyeloid malignancies aged 5 to 18 yrs.	2) 222 (111 vs 111)	2) Epoetin Alfa dose of 600units/kg to 900units/kg (if Hb had not increased by 1g/dL or more from baseline), administered intravenously 1 time per week for 16 months vs placebo administered intravenously 1 time per week for 16 months	2) **N(%) of patients with adverse events (intervention vs control)** Serious adverse events rate: (68.8%) vs (74.5%) • Most-common serious adverse events in intervention group: fever (11.6%) and infection (6.3%) • Most-common serious adverse events in control group: fever (10.0%), infection (12.7%) and mucositis (5.5%) Hypertension: 2 (1.8%) vs 1 (0.9%) Thrombotic vascular event ≥ 1: (22.3%) vs (22.7%) P-values unknown, unclear whether events were related to the intervention
Grade assessment				
Study design:	+4	2 Randomized Controlled Trials		
Study limitations	-2	Serious limitations - Selection bias: Unclear in 2/2; Attrition bias: Low in 1/2 and unclear in 1/2; Performance bias: unclear in 2/2; Detection bias: unclear in 2/2		
Consistency:	0	No important inconsistency. All studies report adverse events		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	0	No important imprecision, large sample size		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊕⊖⊖ **LOW**		
Conclusion:		**There is low quality of evidence that adverse effects occured in both intervention and control group. Most common adverse effects were hypertension, fever, infection and mucositis.**		

Epoetin Alfa				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Health Related Quality of life PedsQL – GCS, Range of score 0-100, Higher score indicates higher Quality of Life				
1) Razouk, 2006	1) Children with anaemia who received myelosupressive chemotherapy for nonmyeloid malignancies aged 5 to 18 yrs.	1) 222 (111 vs 111)	1) Epoetin Alfa dose of 600units/kg to 900units/kg (if Hb had not increased by 1g/dL or more from baseline), administered intravenously 1 time per week for 16 months vs placebo administered intravenously 1 time per week for 16 months	**Total mean PedsQL-GCS scores at final visit (intervention vs control):** 74.9 (15.22) vs. 75.5 (15.74); EMD $_{\text{intervention - control}}$ = -0.61 (95%CI -4.62 to 3.39), p = 0.823 **Haemoglobin levels and quality of life** A significant correlation was found between change in Hb level and change in quality of life score in the intervention group (r = 0.242, p = 0.018). In the placebo group the correlation was not significant (r = 0.86, p = 0.430)
Grade assessment				
Study design:	+ 4	1 Randomized Controlled Trials		
Study limitations	-1	Serious limitations – Selection bias: unclear; Attrition bias: Low; Performance bias: Unclear; Detection bias: Unclear		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Results are direct. Outcomes generalizable.		
Precision:	-1	No important imprecision. Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship.		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊕⊖⊖ **LOW**		
Conclusion:		**There is low quality evidence there is no significant effect of Epoetin Alfa (dose starting from 600 units/kg per week) on quality of life scores in children with cancer- or chemotherapy induced anaemia as compared to placebo**		

5 Conclusies van evidence

5.1 Medicamenteuze behandeling van hematologische verschijnselen

Pharmacological treatment of haematological symptoms,			
Intervention		**Conclusions of evidence**	**Quality of evidence**
Anaemia			
Erythropoietin (Epoetin Alfa) dose starting from 450 units/kg per week	*vs. no treatment or placebo*	No significant effect on haemoglobin levels in children with cancer- or chemotherapy related anaemia. In one study, haemoglobin levels did increase in the intervention group (no significant effect).	⊕⊕⊖⊖⊖ LOW (2 RCTs)
		no significant effect on the number of required blood cell transfusions in children with cancer- or chemotherapy-related anaemia	
		Adverse effects in both intervention and control group. Most common adverse effects were hypertension, fever, infection and mucositis.	
Erythropoietin (Epoetin Alfa) dose starting from 600 units/kg per week	*vs. placebo*	no significant effect on quality of life scores in children with cancer- or chemotherapy-related anaemia	⊕⊕⊖⊖⊖ LOW (1RCT)
Vitamins		Unknown effect	No studies
Iron			
Erythrocyte transfusion			
Thrombocytopenia			
Platelet transfusion		Unknown effect	No studies
Bleeding			
Desmopressin		Unknown effect	No studies
Tranexamic acid			
Vitamin K			
Recombinant factor VII			
Adrenalin			
Xylometazoline			
FFP			
Thrombosis			
Heparin		Unknown effect	No studies
Low Molecular Heparin			
DOAC		Unknown effect	

6 Aanbevelingen uit richtlijnen

6.1 Medicamenteuze behandeling van hematologische verschijnselen

6.1.1 Anemie

Erythrocyte transfusion – Child and Adult guideline	
Federation of Medical Specialists. (2019). Startpagina - Bloedtransfusiebeleid - Richtlijn - Richtlijnendatabase. Federation of Medical Specialists	
Recommendation	**Level of evidence**
Transfusiebeleid voor IC-patienten: • Transfundeer 1 unit rode bloedcellen bij IC patiënten bij Hb van 4,3 mmol/L of lager. • Overweeg transfusie van 1 unit rode bloedcellen bij IC patiënten met een acuut coronair syndroom bij Hb 5,0 mmol/L of lager. • Monitor de Hb-waarde voor een volgende transfusieorder. • Stem bij overplaatsing naar de afdeling af of bij de patiënt hetzelfde restrictief beleid gehandhaafd kan worden.	High
Transfusiebeleid bij anemie op basis van beenmergfalen • Overweeg bij klinische hematologische patiënten met anemie een restrictief transfusiebeleid op individuele basis een trigger te hanteren tussen 4,3-5,0 mmol/L of symptomen. • Bij klinische hematologische patiënten is op basis van observationeel onderzoek zogenaamd single-unit transfusiebeleid in het kader van een restrictief transfusiebeleid verdedigbaar ten opzichte van multi-unit transfusie beleid. • Hanteer bij langdurig bestaande anemie bij poliklinische patiënten (bijvoorbeeld bij MDS) een individueel transfusiebeleid op basis van gepercipieerde kwaliteit van leven.	Laag - moderate
Transfusiebeleid bij beenmerg-en stamceltransplantatie • Er wordt aanbevolen om ter preventie van hemolyse bij toediening van een majo ABO-incompatibbel stamcel-/beenmerg transplantaat aan een volwassen ontvanger en bij IgG en/of IgM titer > 16 te streven naar: o < 15 ml erytrocyten in het transplantaat en bij kinderen < 10 ml. o de toedieningssnelheid aan te passen aan de titer. • Overweeg voor preventie van minor ABO-incompatibele hemolyse plasmareductie van het transplantaat bij titers > 32. • Overweeg aan ABO-incompabiliteit gelijkwaardige maatregelen bij hoge titers pre-existente major (in patiënt) / minor (in donor) incompatibele non-AB-irregulaire antistoffen. • Er wordt aanbevolen om voor a. goede analyse van de immuungenese (donor vs. patiënt immuunrespons) van posttransplantatie ontstane c.q. geboosterde irregulaire antistoffen en b. juiste behandeling van gerelateerde hemolyse en/of achterblijvende hematopoëse, pretransplantatie volledige bloedgroeptyperingen van patiënt en donor na te streven. • Bloedproducten voor stamceltransplantatiepatiënten dienen te worden bestraald (zie ook module Indicatie voor bestralen van bloedproducten). • Stamceltransplantatiecentra dienen richtlijnen te hebben voor het beleid bij ABO-incompatibiliteit tussen donor en ontvanger • Landelijke afstemming van meer specifieke aanbevelingen bijvoorbeeld ten aanzien van resus-incompatibiliteit is gewenst.	Level 3
Bloedtransfusiebeleid bij anemie en ACS • Overweeg één unit rode bloedcellen bij patiënten met een acuut coronair syndroom met een Hb van 5,0 mmol/L of lager. • Overweeg één unit rode bloedcellen bij patiënten met stabiel coronair lijden en klachten (verlaagde bloeddruk en verhoogde hartslag) met een Hb van 5,0 mmol/L of lager • Transfundeer 1 unit rode bloedcellen per keer • Monitor de Hb-waarde voor een volgende transfusieorder	Zeer laag - moderate
Preventie en behandeling hemolytische ziekte van de foetus en pasgeborene • Foetus o De opsporing en controle van irregulaire antistoffen in de zwangerschap dienen volgens protocol te geschieden. o Ernstig bloedgroepantagonisme leidend tot hydrops is een absolute indicatie voor intra-uteriene transfusies (IUT); ter beperking van complicaties dienen foetale transfusies in een centrum met maximale ervaring te worden uitgevoerd. o Vrouwen die intra-uteriene transfusies ondergaan, hebben een sterk verhoogd risico op bloedgroepimmunisatie. Het wordt aanbevolen de compatibiliteitstest na voorafgaande intra-uteriene transfusies (IUT) met een zo vers mogelijk (< 24 uur oud) monster uit te voeren. • Pasgeborene o Intensieve fototherapie en zo nodig wisseltransfusie(s) dienen overwogen worden te worden bij een pasgeborene met hyperbilirubinemie door hemolytische ziekte van de pasgeborene om hersenschade te voorkomen. o Indien het bilirubine ondanks adequate fototherapie sneller stijgt dan 20 µmol/L/uur is er een indicatie voor wisseltransfusie.	Level 2 - 4

○ Bij wisseltransfusie is permanente ECG-bewaking en periodieke controle nodig van elektrolyten, glucose en trombocyten. ○ Routinematige toediening van intraveneuze immunoglobuline (IVIG) bij behandeling van hemolytische ziekte van de pasgeborene wordt niet aanbevolen.	
Erytrocytentransfusiebeleid bij neonaten met anemie Doelgroep: pasgeborenen, ongeacht zwangerschapsduur en gewicht, jonger dan 1 maand post-terme leeftijd • Voor very low birth-weight infants (geboortegewicht <1500 gram) worden de onderstaande restrictieve transfusiegrenzen geadviseerd (zie tabel: https://richtlijnendatabase.nl/richtlijn/bloedtransfusiebeleid/transfusiebeleid_bij_de_niet_acuut_bloedende_patient/erytrocytentransfusiebeleid_bij_neonaten_met_anemie.html) • Bij het ontbreken van studie met betrekking tot à terme neonaten en late-prematuren (zwangerschapsduur ≥32 weken) worden deze grenzen ook voor deze groepen gehanteerd. • Een transfusietrigger onder de aangeven grenswaarden moet, uit oogpunt van patiëntveiligheid, voorkomen worden bij het ontbreken van studies hiernaar. • Transfundeer met 15 ml/kg met een transfusiesnelheid van 5 ml/kg/uur. • Selecteer bij massale transfusies (>80 mL/kg/ <24 uur of toedieningssnelheid > 5mL/kg/uur) aan neonaten erytrocyten ≤5 dagen oud.	Moderate
Transfusiebeleid bij homozygote beta-thalassemie • De klinische symptomen van anemie en beenmergexpansie vormen de basis voor de beslissing om met een chronisch transfusiebeleid te starten bij patiënten met homozygote bèta-thalassemie of thalassemie intermedia. • Bij chronische transfusietherapie voor bèta-thalassemie patiënten wordt een streef-Hb 5,4 tot 6,2 mmol/L aanbevolen • Een chronisch transfusiebeleid bij bèta-thalassemie patiënten dient te worden gecomplementeerd met adequate chelatietherapie met als target een gemiddeld ferritine van < 2500 µg/L. Dit voorkomt hartfalen en orgaanschade als gevolg van ijzerstapeling.	

6.1.2 Trombocytopenie

Platelet transfusion – Child and Adult guideline	
Federation of Medical Specialists. (2019). Startpagina - Bloedtransfusiebeleid - Richtlijn - Richtlijnendatabase. Federation of Medical Specialists	
Recommendation	**Level of evidence**
Door de hele module wordt een standaarddosis trombocytenconcentraat bij trombocytentransfusie (TT) gedefinieerd als 1 volledige eenheid TROMBOCYTEN, samengevoegd in PAS-E/plasma (kinderen 15-20ml/kg trombocyten tot maximaal 1 volledige samengevoegde eenheid) of een equivalent gedoseerd single donor aferese product. Voor aanvullende specificaties wordt verwezen naar de bloedwijzer van de stichting Sanquin Bloedvoorziening	
Oorzaken trombocytopenie en contra-indiciaties voor trombocytentransfusies • Bij de indicatiestelling voor de transfusie dient de oorzaak van de trombocytopenie te worden betrokken. • Preventie van spontane bloedingen, preventie van bloedingen bij ingrepen of behandeling van manifeste (ernstige) bloedingen > graad 2 zijn mogelijke doelen van trombocytentransfusies bij trombocytopenie. Voor meer informatie wordt naar de andere modules binnen dit thema verwezen.	
Beleid bij trombocytopenie door tijdelijke aanmaakstoornis Geef kinderen met een trombocytengetal van lager dan 10*109 per liter als gevolg van een tijdelijke aanmaakstoornis door een hemato-oncologische aandoening dan wel de behandeling daarvan een profylactische trombocyten transfusie met 15-20ml/kg tot maximum 1 standaarddosis trombocytenconcentraat per keer gevolgd door een opbrengstmeting (na 1 uur en/of zo mogelijk ook na 24 uur).	Zeer laag – moderate
Afkapwaarde profylactische Trombocytentransfusie bij TARs of antistolling Overweeg bij patiënten met een tijdelijke chemotherapie of ziekte geïnduceerde trombocytopenie lager dan 30*109/L die therapeutische antistolling of TAR's gebruiken het onderstaande stappenplan te volgen (zie ook het Stroomdiagram bij de aanverwante producten). Doorloop dit stappenplan/stroomdiagram dagelijks (zie: https://richtlijnendatabase.nl/richtlijn/bloedtransfusiebeleid/trombocytentransfusies/afkapwaarde_profylactische_tt_bij_tars_of_antistolling.html)	No studies
Trombocytenwaarde voor profylactische trombocytentransfusie Overweeg een pre-interventie trombocytentransfusie in de volgende gevallen (zie tabel 1). https://richtlijnendatabase.nl/richtlijn/bloedtransfusiebeleid/trombocytentransfusies/trombocytenwaarde_voor_profylactische_trombocytentransfusie.html	No studies
Onvoldoende opbrengst na trombocytentransfusie • Indien bij een patiënt, zonder klinisch verklarende factoren, de 1 uurs Corrected Count Increment (CCI) van verse ABO compatibele trombocytentransfusie tweemaal < 7,5 is (er is dan sprake van trombocyten refractairiteit), wordt screening op HLA-antistoffen aanbevolen. • Indien ABO en HLA compatibele transfusies in afwezigheid van klinisch verklarende factoren, in een Corrected Count Increment (CCI) van < 7,5 resulteren, wordt serologische analyse naar trombocytspecifieke antigenen (HPA) aanbevolen. • De werkgroep is van mening dat vroegtijdig overleg tussen de behandelaar, de zieken-huistransfusiedienst en de Klinisch Consultatieve Dienst van Sanquin Bloedvoorziening een voorwaarde is voor een doelmatige toepassing en effectieve ondersteuning met HLA gematchte trombocytentransfusies.	Level 2/3
Beleid bij trombocytopenie en bloeding WHO-graad 2-4: • Pas bij kinderen en volwassenen met een bloeding WHO-graad 2 en een trombocyten aantal lager dan 30*109/L, afhankelijk van de locatie van de bloeding en lokale hemostase mogelijkheden, een therapeutische trombocytentransfusie (TT) toe volgens de aanbevelingen in tabel 2 Overweeg, na een doorgemaakte bloeding WHO-graad 2, kortdurend een profylactische transfusietrigger van 20*109/L volgens de aanbevelingen in tabel 2 • Pas bij kinderen en volwassenen met een trombocytopenie en bloeding WHO-graad 3 of 4 een therapeutische trombocytentransfusie (TT) toe met, afhankelijk van kliniek en overige hemostase mogelijkheden, een maximale target van 100*109/L Handhaaf, nadat hemostase is bereikt, tenminste 48 uur voor een profylactische trombocytentransfusie een trigger van 20*109/L (bloeding WHO-graad 3) respectievelijk 50*109/L (bloeding WHO-graad 4) volgens de aanbevelingen in tabel 2	Geen studies
Ondersteunende behandeling bij trombocytopenie en bloeding WHO-graad 2-4) • Bij patiënten met trombocytopenie en bloeding, die niet of slecht te corrigeren is met trombocytentransfusies, wordt aanbevolen het verhogen van het hematocriet tot > 0,30 L/L te overwegen teneinde de bloedingsneiging te verminderen. • Bij patiënten met trombocytopenie en slijmvliesbloedingen (neus-, tandvlees-bloedingen, menorragie) kan overwogen worden met anti-fibrinolytische medicatie de bloedingsneiging te verminderen. Fibrinolyseremming is gecontra-indiceerd bij hematurie in verband met het risico op trombusvorming in de urinewegen. • Aanbevolen wordt dat er een (bij voorkeur landelijke) registratie komt van recombinant factor VII (rFVII) gebruik bij bloeding met trombocytopenie en dat protocollen worden ontwikkeld voor evaluatie en rapportage van het effect van het gebruik van rFVII voor deze indicatie.	Level 2/3
Trigger trombocytentransfusie neonaten tromboytopenie • Geef aan alle (premature) neonaten met een ernstige trombocytopenie een trombocytentransfusie bij trombocytenwaarde < 25 x 109/L.	Moderate Low

• Geef aan alle (premature) neonaten met een ernstige trombocytopenie bij wie een manifeste bloeding geconstateerd is of een indicatie voor een ingreep is, een trombocytentransfusie bij trombocytenwaarde < 50 x 109/L	
<u>Trombocytentransfusies neonaten trombocytopenie</u> Overweeg bij profylactische transfusie bij neonaten het standaard trombocytenproduct voor neonaten te gebruiken.	Geen studies
<u>Dosering bij kinderen met lichaamsgewicht tot 30kg</u> Het doseringsadvies voor trombocytentransfusie bij kinderen, namelijk van 5-10 x 109/kg, blijft gehandhaafd.	Level 2, level 3
<u>Alternatieven bij tijdelijke of chronische trombocytopenie</u> Bij gebrek aan studies kunnen geen aanbevelingen worden gedaan voor alternatieven voor profylactische trombocytentransfusies bij tijdelijke of chronische aanmaakstoornis; noch voor behandelingen met tranexaminezuur.	Laag – moderate

<u>Perifere trombopenie</u>
Trombocytentransfusies bij trombocytopenie door verbruiksoorzaken of afbraakstoornissen
• Profylactische trombocytentransfusie
  ○ Bij TTP, HUS, HELLP en HIT(T) zijn profylactische trombocytentransfusies relatief gecontra-indiceerd / niet geïndiceerd.
  ○ Bij DIS of ITP is de effectiviteit van trombocytentransfusies nooit vastgesteld.
  ○ Bij trombotische trombocytopenische purpura (TTP) zijn profylactische trombocytentransfusies ter preventie van spontane bloedingen zelfs afgeraden in verband met een mogelijk risico op het optreden dan wel verergeren van trombo-embolieën.
• Trombocytentransfusie rondom ingrepen
  ○ Bij TTP, HUS, HELLP en HIT(T) kunnen profylactische trombocytentransfusies rondom ingrepen met een hoog bloedingsrisico overwogen worden.
  ○ Bij trombotische trombocytopenische purpura (TTP) dient het voordeel van de transfusie te worden afgewogen tegen het potentiele arteriële tromboserisico /verergeren van het ziektebeeld.
• Therapeutische trombocytentransfusies bij bloedingen
  ○ In het geval van WHO > graad 2 bloedingen bij een patiënt met TTP, HUS, HELLP, HIT(T) bestaat er geen absolute contra-indicatie tegen een trombocytentransfusie.
  ○ Zie tabel 1 voor indicaties en contra-indicaties voor trombocytentransfusies bij trombocytopenie door verbruiks- en/of afbraakstoornissen (TTP, HUS, HELLP, DIS, HIT(T) en ITP).
	Level 2 - 4

7 Overzicht conclusies van evidence en aanbevelingen uit richtlijnen

7.1 Medicamenteuze behandeling van Hematologische verschijnselen

Pharmacological treatment haematological symptoms								
Treatment	Conclusions of evidence	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children (2013)	Level of evidence[1,2]
Anaemia								
Erythropoietin vs no treatment/placebo	No significant effect on haemoglobin levels in children with cancer- or chemotherapy related anaemia. In one study, haemoglobin levels did increase in the intervention group (no significant effect).	LOW, 2 RCTs(2, 3)	Not identified	-	Not identified	-	Do not give; Strong recommendation	Level 2 child evidence(dependent on condition)(2, 3) ; Level 2 adult evidence (4)
	no significant effect on the number of required blood cell transfusions in children with cancer- or chemotherapy-related anaemia	LOW, 2 RCTs(2, 3)						
	Adverse effects in both intervention and control group. Most common adverse effects were hypertension, fever, infection and mucositis.	LOW, 2 RCTs(2, 3)						
Erythropoietin vs placebo	no significant effect on quality of life scores in children with cancer- or chemotherapy-related anaemia	LOW, 2 RCTs(3)	Not identified	-	Not identified	-		
Vitamins	Unknown effect	No studies	Not identified	-	Not identified	-	Do not give; strong recommendation	Level 4 child evidence
Iron	Unknown effect	No studies	Not identified	-	Not identified	-	Do not give; strong recommendation	Level 4 child evidence
Erythrocyte transfusion	Unknown effect	No studies	Use restrictive red blood cell transfusion thresholds for patients who need red blood cell transfusions and who do not: have major	3 studies (5;NP)	Recommendation is the same for both children and adults	3 studies (5;NP)	Consider; weak recommendation	Level 3 child evidence(6-9); Level 3 adult evidence (10)

			haemorrhage or; have acute coronary syndrome or;need regular blood transfusions for chronic anaemia.					
Thrombocytopenia								
Platelet transfusion	Unknown effect	No studies	Offer platelet transfusions to patients with thrombocytopenia who have clinically significant bleeding (World Health Organization [WHO] grade 2) and a platelet count below 30×109 per litre.	Expert opinion (5;NP, 11;NP)	Recommendation is the same for both children and adults	Expert opinion (5;NP, 11;NP))	Consider; weak recommendation	Level 4 child evidence (6, 9)
			Consider a short term prophylactic transfusion trigger of 20x109 / L after a WHO Grade 2 bleeding	Expert opinion (11;NP)	Recommendation is the same for both children and adults	Expert opinion (11;NP)		
			Offer platelet transfusion with a maximum target of 100x109L to patients with thrombocytopenia and bleeding of WHO grade 3 or 4 with a maximum	Expert opinion (11;NP)	Recommendation is the same for both children and adults	Expert opinion (11;NP)		
			After achieving haemostasis maintain a trigger of 20x109L (WHO grade 3 bleeding) and 50x109L (WHO grade 4 bleeding)	Expert opinion (11;NP)	Recommendation is the same for both children and adults	Expert opinion (11;NP))		
Bleeding								
Desmopressin	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 child evidence (9)
Tranexamic acid	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 child evidence (8, 9, 12, 13)
Vitamin K	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 child evidence (9)
Recombinant factor VII	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 child evidence (9)
Adrenalin	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 child evidence

Xylometazoline	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 child evidence
FFP	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 child evidence (9)
Thrombosis								
Heparin	Unknown effect	No studies	Not identified	-	Not identified	-	Do not give; strong recommendation	Level 4 child evidence (8)
Low Molecular Heparin	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 child evidence (8); Level 1 adult evidence (14-16)
DOAC	Unknown effect	No studies	Not identified	-	Not identified	-	No recommendation	-

Legend
P: Palliative context
NP: Non-palliative context
Not identified: No recommendations on specific pharmacological intervention were identified.
Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.

[1]Level of evidence:
Level 1: Based on a systematic review or at least two randomized controlled trials of good quality
Level 2: Based on one at randomized controlled trial or at least two comparative clinical studies
Level 3: Based on one comparitive study or on non-comparitive studies
Level 4: Based on expert opinion

References

2. Büyükpamukçu M, Varan A, Kutluk T, Akyüz C. Is epoetin alfa a treatment option for chemotherapy-related anemia in children? Medical and Pediatric Oncology. 2002;39(4):455-8.
3. Razzouk BI, Hord JD, Hockenberry M, Hinds PS, Feusner J, Williams D, et al. Double-blind, placebo-controlled study of quality of life, hematologic end points, and safety of weekly epoetin alfa in children with cancer receiving myelosuppressive chemotherapy. J Clin Oncol. 2006;24(22):3583-9.
4. Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, et al. A systematic review and economic evaluation of epoetin alpha, epoetin beta and darbepoetin alpha in anaemia associated with cancer, especially that attributable to cancer treatment. Health Technol Assess. 2007;11(13):1-202, iii-iv.
5. National institute for Health and Care Excellence. Blood transfusion [Internet]. London: NICE; 2015 [cited 2021 March 1]. Available from: https://www.nice.org.uk/guidance/ng24/history.
6. Beardsmore S, Fitzmaurice N. Palliative care in paediatric oncology. Eur J Cancer. 2002;38(14):1900-7; discussion 8-10.
7. Gleeson C, Spencer D. Blood transfusion and its benefits in palliative care. Palliat Med. 1995;9(4):307-13.
8. Goldman A, Hain R, Liben S. Oxford Textbook of Palliative Care for Children: Oxford University Press; 2006.
9. Wolfe J, Hinds P. Textbook of Interdisciplinary Pediatric Palliative Care: Saunders; 2011.
10. Monti M, Castellani L, Berlusconi A, Cunietti E. Use of red blood cell transfusions in terminally ill cancer patients admitted to a palliative care unit. Journal of Pain and Symptom Management. 1996;12(1):18-22.
11. Federatie Medisch Specialisten. Bloedtransfusiebeleid 2019. Available from: https://richtlijnendatabase.nl/richtlijn/bloedtransfusiebeleid/startpagina_-_bloedtransfusiebeleid.html.
12. Dean A, Tuffin P. Fibrinolytic inhibitors for cancer-associated bleeding problems. J Pain Symptom Manage. 1997;13(1):20-4.
13. Seto AH, Dunlap DS. Tranexamic acid in oncology. Ann Pharmacother. 1996;30(7-8):868-70.
14. Akl EA, Vasireddi SR, Gunukula S, Barba M, Sperati F, Terrenato I, et al. Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer. Cochrane Database Syst Rev. 2011(6):CD006649.
15. Crowther M, Hirsh J. Low-molecular-weight heparin for the out-of-hospital treatment of venous thrombosis: rationale and clinical results. Semin Thromb Hemost. 1997;23(1):77-81.
16. Hirsh J, Siragusa S, Cosmi B, Ginsberg JS. Low molecular weight heparins (LMWH) in the treatment of patients with acute venous thromboembolism. Thromb Haemost. 1995;74(1):360-3.

E Hoesten

Inhoudsopgave_Toc102114906

1 Uitgangsvragen

Vraag 5A: Wat is de meest effectieve niet-medicamenteuze behandeling van hoesten bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Niet-medicamenteuze behandeling van hoesten
C: Geen behandeling/placebo
O: Effect op hoesten en kwaliteit van leven

Vraag 5B: Wat is de meest effectieve behandeling van hoesten bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Medicamenteuze behandeling van hoesten
C: Geen behandeling/placebo
O: Effect op hoesten en kwaliteit van leven

2 Resultaten van het literatuuronderzoek

Jaar	Bibliografie	Studie karakteristieken
5A: Wat is de meest effectieve niet-medicamenteuze behandeling van hoesten bij kinderen tussen 0 en 18 jaar in de palliatieve fase?*		
2010	IKNL. Hoesten. 2010. www.pallialine.nl [1]	Richtlijn volwassenen
5B: Wat is de meest effectieve behandeling van hoesten bij kinderen tussen 0 en 18 jaar in de palliatieve fase?*		
2010	IKNL. Hoesten. 2010. www.pallialine.nl [1]	Richtlijn volwassenen

[1] Aanbevelingen uit de richtlijnen worden gebruikt in de overwegingen. Aanbevelingen uit richtlijnen over Hoesten bij volwassenen in de palliatieve fase worden gebruikt omdat er geen aanbevelingen uit richtlijnen hoesten bij kinderen in de palliatieve fase zijn gevonden.

* Systematisch gezocht, zie: bijlage 7 zoekverantwoording – search 1

3 Evidence tabellen

Niet van toepassing.

Uit de systematische zoekstrategie resulteerden geen gerandomiseerde studies over niet-medicamenteuze en medicamenteuze behandeling van hoesten

4 Samenvatting en gradering van bewijs

Niet van toepassing.

Uit de systematische zoekstrategie resulteerden geen gerandomiseerde studies over niet-medicamenteuze en medicamenteuze behandeling van hoesten

5 Conclusies van evidence

5.1 Niet-medicamenteuze behandeling van Hoesten

Non pharmacological treatment of coughing		
Intervention	**Conclusions of evidence**	**Quality of evidence**
Postural drainage and advise *'Huffen'* *Nebulization with fysiological salt*	Unknown effect	No studies

5.2 Medicamenteuze behandeling van Hoesten

Pharmacological treatment of coughing		
Intervention	**Conclusions of evidence**	**Quality of evidence**
Dextromethorphan *Codeine and other opioids*	Unknown effect	No studies

6 Aanbevelingen uit richtlijnen

6.1 Niet-medicamenteuze behandeling van Hoesten

Non pharmacological treatment of coughing – Adult guideline	
Integraal Kankercentrum Nederland (IKNL). Hoesten. 2010	
Recommendation	**Level of evidence[1]**
Niet-medicamenteuze symptomatische behandeling bij productieve hoest: • houdingsdrainage • 'huffen' • assistentie bij het hoesten door middel van compressie van de thorax tijdens de uitademing. • houdingsadviezen • bij reflux: patiënt overeind/hoofdeinde van het bed op klossen • vernevelen van fysiologisch zout • bij ribfracturen: brede, strak aangelegde kleefpleister van wervelkolom naar sternum	Level 4
[1]Level of evidence: Level 1:gebaseerd op systematische review of ten minste twee gerandomiseerde onderzoeken van goede kwaliteit. Level 2:gebaseerd op ten minste twee vergelijkende klinische onderzoeken van matige kwaliteit of onvoldoende omvang of andere vergelijkende onderzoeken. Level 3: gebaseerd op één vergelijkend onderzoek of op niet-vergelijkend onderzoek. Level 4: gebaseerd op mening van deskundigen	

6.2 Medicamenteuze behandeling van Hoesten

Pharmacological treatment of coughing – Adult guideline	
Integraal Kankercentrum Nederland (IKNL). Hoesten. 2010	
Recommendation	**Level of evidence[1]**
Medicamenteuze symptomatische behandeling: • dextromethorfan 4-6 dd 15 mg p.o. • codeïne 6 dd 10-20 mg p.o. of slow release morfine 2 dd 10-20 mg • bij therapieresistente hoestklachten: verneveling met lidocaïne 2% tot 4 dd 5 ml of met bupivacaïne 0,25% tot 6 dd 5 ml in combinatie met salbutamol: 0,5-1 ml van een 0,5% oplossing • bij onvoldoende effect van opioïden: paroxetine 1 dd 20 mg p.o. • corticosteroïden (prednison 1 dd 30-60 mg of 1 dd 4-8 mg dexamethason p.o.) bij centrale obstructie, lymphangitis carcinomatosa, pneumonitis door radiotherapie of chemotherapie en vena cava superior syndroom	 Level 3 Level 3 Level 3 Level 4 Level 4
[1]Level of evidence: Level 1:gebaseerd op systematische review of ten minste twee gerandomiseerde onderzoeken van goede kwaliteit. Level 2:gebaseerd op ten minste twee vergelijkende klinische onderzoeken van matige kwaliteit of onvoldoende omvang of andere vergelijkende onderzoeken. Level 3: gebaseerd op één vergelijkend onderzoek of op niet-vergelijkend onderzoek. Level 4: gebaseerd op mening van deskundigen.	

7 Overzicht conclusies van evidence en aanbevelingen uit richtlijnen

7.1 Niet-medicamenteuze behandeling van Hoesten

Non pharmacological treatment for coughing								
Treatment	Conclusions of evidence(RCTs on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence[1]	Recommendation for children 2013(2)	Level of evidence[1,]
Postural drainage and advise	Unknown effect	No studies	Not identified	-	Do (3;P)	Level 4	Consider; weak recommendation	Level 4 adult evidence[2]
'Huffen'	Unknown effect	No studies	Not identified	-	Do (3;P)	Level 4	Consider; weak recommendation	Level 4 adult evidence[2]
Nebulization with fysiological salt	Unknown effect	No studies	Not identified	-	Do (3;P)	Level 4	Consider; weak recommendation	Level 4 adult evidence[2]

Legend
P: Palliative context
Not identified: No recommendations on specific pharmacological intervention were identified.
Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.

[1]Level of evidence:
Level 1: Based on a systematic review or at least two randomized controlled trials of good quality
Level 2: Based on one at randomized controlled trial or at least two comparative clinical studies
Level 3: Based on one comparative study or on non-comparative studies
Level 4: Based on expert opinion
[2]Adult evidence is extracted from guidelines of pallialine.nl (3)

References

2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.
3. Integraal Kankercentrum Nederland. Hoesten (2.0). 2010. Available from: www.pallialine.nl/hoesten.

7.2 Medicamenteuze behandeling van Hoesten

Pharmacological treatment for coughing								
Treatment	Conclusions of evidence(RCTs on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence[1]	Recommendation for children 2013(2)	Level of evidence[1, 2]
Dextromethorphan	Unknown effect	No studies	Not identified	-	Do (3;P)	Level 3	Consider; weak recommendation	Level 4 child evidence (4); Level 3 adult evidence (5-7)[2]
Codeine and other opioids	Unknown effect	No studies	Not identified	-	Do (3;P)	Level 3	No recommendation can be given	Level 4 child evidence (4); Level 3 adult evidence (5-9)[2]

Legend
P: Palliative context
Not identified: No recommendations on specific pharmacological intervention were identified.
Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.

[1]Level of evidence:
Level 1: Based on a systematic review or at least two randomized controlled trials of good quality
Level 2: Based on one at randomized controlled trial or at least two comparative clinical studies
Level 3: Based on one comparative study or on non-comparative studies
Level 4: Based on expert opinion
[2]Adult evidence is extracted from guidelines of pallialine.nl (3)

References

2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.
3. Integraal Kankercentrum Nederland. Hoesten (2.0). 2010. Available from: www.pallialine.nl/hoesten.
4. Wolfe J, Hinds P. Textbook of Interdisciplinary Pediatric Palliative Care: Saunders; 2011.
5. Eddy NB, Friebel H, Hahn KJ, Halbach H. Codeine and its alternates for pain and cough relief . 4. Potential alternates for cough relief. Bull World Health Organ. 1969;40(5):639-719.
6. Homsi J, Nelson KA, Sarhill N, Rybicki L, LeGrand SB, Davis MP, et al. A phase II study of methylphenidate for depression in advanced cancer. Am J Hosp Palliat Care. 2001;18(6):403-7.
7. Matthys H, Bleicher B, Bleicher U. Dextromethorphan and codeine: objective assessment of antitussive activity in patients with chronic cough. J Int Med Res. 1983;11(2):92-100.
8. Homsi J, Walsh D, Nelson KA, Sarhill N, Rybicki L, Legrand SB, et al. A phase II study of hydrocodone for cough in advanced cancer. Am J Hosp Palliat Care. 2002;19(1):49-56.
9. Luporini G, Barni S, Marchi E, Daffonchio L. Efficacy and safety of levodropropizine and dihydrocodeine on nonproductive cough in primary and metastatic lung cancer. Eur Respir J. 1998;12(1):97-101.

F Huidklachten

Inhoudsopgave

1 Uitgangsvragen

Vraag 6A: Wat is de meest effectieve niet-medicamenteuze behandeling van huidklachten (o.a. wonden, decubitus en jeuk) bij kinderen tussen 0 en 18 jaar in de palliatieve fase?
P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Niet-medicamenteuze behandeling van huidklachten
C: Geen behandeling/placebo
O: Effect op huidklachten en kwaliteit van leven

Vraag 6B: Wat is de meest effectieve medicamenteuze behandeling van huidklachten (o.a. wonden, decubitus en jeuk) bij kinderen tussen 0 en 18 jaar in de palliatieve fase?
P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Medicamenteuze behandeling van huidklachten
C: Geen behandeling/placebo
O: Effect op huidklachten en kwaliteit van leven

2 Resultaten van het literatuuronderzoek

Jaar	Bibliografie	Studie karakteristieken
6A: Wat is de meest effectieve niet-medicamenteuze behandeling van huidklachten (o.a. wonden, decubitus en jeuk) bij kinderen tussen 0 en 18 jaar in de palliatieve fase?*		
Wonden		
Geen literatuur		
Decubitus		
2011	***Integraal Kanker Instituut Nederland.*** Decubitus. 2011. www.pallialine.nl[1 2]	Richtlijn volwassenen
Jeuk		
2010	***Integraal Kanker Instituut Nederland.*** Jeuk. 2010. www.pallialine.nl[1 2]	Richtlijn volwassenen
6B: Wat is de meest effectieve medicamenteuze behandeling van huidklachten (o.a. wonden, decubitus en jeuk) bij kinderen tussen 0 en 18 jaar in de palliatieve fase?*		
Wonden, Decubitus		
Geen literatuur		
Jeuk		
2010	***Integraal Kanker Instituut Nederland.*** Jeuk. 2010. www.pallialine.nl[1 2]	Richtlijn volwassenen
2005	***Maxwell LG et al.*** The effects of a Small-Dose Naloxone Infusion on Opioid-Induced Side Effects and Analgesia in Children and Adolescents Treated with Intravenous Patient-Controlled Analgesia: A Double-Blind, Prospective, Randomized, Controlled Study. Anesth Analg 2005;100:953–8	RCT kinderen

[1] Aanbevelingen uit de richtlijnen over huidklachten worden gebruikt in de overwegingen.
[2] Aanbevelingen uit richtlijnen over huidklachten bij volwassenen in de palliatieve fase worden gebruikt in de overwegingen wanneer er geen aanbevelingen uit richtlijnen over huidklachten bij kinderen al dan niet in de palliatieve fase zijn gevonden.
* Systematisch gezocht, zie: bijlage 7 zoekverantwoording – search 1

3 Evidence tabellen

3.1 Medicamenteuze behandeling van huidklachten

3.1.1 Jeuk

Pharmacological treatment of itching (pruritus)				
Maxwell LG et al. The effects of a Small-Dose Naloxone Infusion on Opioid-Induced Side Effects and Analgesia in Children and Adolescents Treated with Intravenous Patient-Controlled Analgesia: A Double-Blind, Prospective, Randomized, Controlled Study. Anesth Analg 2005;100:953–8				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: Double-Blind, Prospective, RCT Setting: 1 centre, USA Duration: Pain and opioid induced side effects were monitored every 4h during the first 24h after surgery Study years: Not reported Protocol published in register: Not reported	Number and type of participants: Total 46 pediatric patients, with acute, moderate to severe, postoperative pain. Surgical procedures included major orthopaedic, neurosurgical, or pectus excavatum surgery/ • Intervention group: n = 20 • Control group: n = 26 Age: • Intervention group: Mean (SD): 13.7 (2.7), Range 6-18 • Control group: Mean (SD): 13.7 (2.3), Range 6-18 Sex: • Intervention group: M: 10 (50.0%), F: 10 (50.0%) • Control group: M: 11 (42.3%), F: 15 (57.7%) There were no differences in the demographic data between the groups.	After surgery all patients were started on intravenous pump cassette which contained 100g of morphine sulfate in 100ml normal saline (1mg/mL). The following routine settings were established: • Initial dose of up to 100µg/kg or more and • Maintenance basal infusion rate of 20 $\mu g \cdot kg^{-1} \cdot h^{-1}$, • Demand dose of 20µg/kg, Lockout time interval of 8min • Maximum of five doses per hour. Type of intervention: The intervention group received 0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ of naloxone by continuous infusion. The naloxone was administered by a continuous infusion pump 'piggy-backed' into the patients catheter. The naloxone solution was prepared in the pharmacy by mixing 2mg of naloxone in 250mL of 0.9% saline (final concentration = 8 µg/mL). Type of control: The placebo group, received only saline by the infusion pump. The study solutions were prepared by the pharmacist and diluted in saline to produce equal volumes to ensure proper blinding.	Outcome definitions: Incidence and severity of pruritus Incidence and severity of nausea Incidence and severity of vomiting Incidence of respiratory depression Mean (SD) pain scores at rest Mean (SD) pain scores with activity Results (per outcome) – (Placebo vs intervention) Incidence and severity of pruritus: 77% vs 20%, p < 0.05. Incidence and severity of nausea: 70% vs 35%, p <0.05. Incidence and severity of vomiting: 46% vs 25%, not significant Incidence of respiratory depression: 0 Mean (SD) pain scores at rest: 4 (2) vs 3 (2), not significant Mean (SD) pain scores with activity 6 (2) vs 6 (2), not significant	Strengths: Double-blinded, prospective, randomized placebo-controlled study. Limitations: Only one concentration of naloxone was evaluated Some side effects associated with opioid administration (urinary retention, constipation) could not be evaluated. **Risk of bias** A. Selection bias: Low risk Reason: Patients were randomly assigned by the hospital's investigational drug pharmacy, using computer-generated random numbers. Patient, patient's family, anaesthesiologist, pediatric pain service, nursing staff and observers all unaware of randomization. B. Attrition bias: Low risk Reason: Outcome was assessed for 100% of the intervention group and 89% of the placebo group (dropout, n = 3) C. Performance bias Low risk Reason: Participants and personnel were blinded from knowledge of which intervention was received. D. Detection bias Unclear Reason: Blinding of outcome assessors was not reported in the study

4 Samenvatting en gradering van bewijs

4.1 Medicamenteuze behandeling van huidklachten

4.1.1 Jeuk

4.1.1.1 Included outcomes

Included outcomes
Incidence of pruritus

4.1.1.2 Naloxone

Naloxone				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Incidence of pruritus				
1) Maxwell, 2005	1) Children with post-operative opioid-induced side effects (pruritus,) aged 6 – 18 years.	1) 46 (20 vs 26)	1) 0.25 µg · kg^{-1} · h^{-1} of naloxone by continuous infusion vs placebo, saline was administered via the infusion pump.	**Incidence of pruritus control vs. intervention:** Percentage of patients with pruritus: 77% vs 20%, $p < 0.05$.
Grade assessment				
Study design:	+4	1 Randomized Controlled Trials		
Study limitations	-1	Some limitations - Selection bias: Low; Attrition bias low; Performance bias: low; Detection bias: unclear		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	-1	Outcomes are direct. Unclear if outcomes are generalizable to children receiving palliative care.		
Precision:	-2	Serious imprecision due to small sample sizes. Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence that Naloxone infusion decreases incidence of pruritus in children with post-operative opioid-induced side effects as compared to treatment with placebo.**		

5 Conclusies van evidence

5.1 Niet-medicamenteuze behandeling van huidklachten

Non pharmacological treatment of skin complaints		
Intervention	**Conclusions of evidence**	**Quality of evidence**
Wounds and pressure ulcers		
Skin care on high-risk areas (bone and pressure points) *Turning patient regularly* *Pressure reducing mattress* *Good nutrition* *Wound care*	Unknown effect	No studies
Itching		
Skin care (cooling) *Hypnosis*	Unknown effect	No studies

5.2 Medicamenteuze behandeling van huidklachten

Pharmacological treatment of skin complaints		
Intervention	**Conclusions of evidence**	**Quality of evidence**
Itching		
Antihistamines *Ondansetron* *Cimetidine* *Prednisone + cimetidine* *SSRI (paroxetine, sertraline)* *Mirtazapine* *Cholestyramine* *Ursodeoxycholic acid* *Rifampicin* *Phenobarbital*	Unknown effect	No studies
Naloxone infusion *vs. placebo*	↓ incidence of pruritus in children with post-operative opioid-induced side effects after intervention	⊕⊖⊖⊖ VERY LOW (1RCT)

6 Aanbevelingen uit richtlijnen

6.1 Niet-medicamenteuze behandeling van huidklachten

6.1.1 Wonden en decubitus

Non pharmacological treatment of decubitus – Adult guideline	
Integraal Kanker Instituut Nederland. Decubitus. 2010. *www.pallialine.nl*	
Recommendation	**Level of evidence[1]**
Drukverdeling	
Geef de zorgvrager wisselhouding met regelmatige tussenpozen, in overeenstemming met de wensen van de zorgvrager.	C
• Pas het draai- en wisselhoudingschema, wanneer dit medisch uitvoerbaar is, aan de zorgvrager aan en stem het af op de doelen en wensen van de zorgvrager, de huidige gezondheidstoestand en eventuele comorbiditeit.	C
• Zorg voor een soepel wisselhoudingschema, gebaseerd op de voorkeuren van de zorgvrager, wat deze verdragen kan en gebaseerd op de drukreducerende eigenschappen van het matras.	C
• Geef zorgvragers, die veel pijn ervaren bij beweging, een pre-medicatie volgens voorschrift van een arts 20 tot 30 minuten voorafgaand aan een geplande houdingsverandering.	C
• Leg de reden voor het draaien uit en ga na welke voorkeuren of voorkeurshouding de zorgvrager heeft.	C
• Bij stervende personen of personen die in een toestand zijn waarbij slechts één positie comfort biedt, is comfort belangrijker dan preventie en wondzorg.	C
• Overweeg een ander type matras om drukverdeling en comfort te verbeteren.	C
• Streef er naar om een zorgvrager die palliatieve zorg ontvangt ten minste elke vier uur van houding te veranderen op een drukreducerend matras.	B
• Rapporteer het draaien en de wisselhouding evenals de factoren die van invloed waren op deze beslissingen (bijvoorbeeld persoonlijke wensen of medische noodzaak).	C
Voeding en vocht	
Zorg voor voldoende voeding en vocht in overeenstemming met de toestand en wensen van de zorgvrager	C
Laat de zorgvrager vocht en voeding naar keuze nemen.	C
Bied meerdere kleine maaltijden per dag aan.	C
Geef dagelijks 1,25 - 1,5 gram eiwit per kg lichaamsgewicht bij een zorgvrager met decubitus categorie I of II en 1,5-1,7 gram bij zorgvragers met een categorie III of IV decubitus (bij BMI ≤ 27), wanneer dit overeenkomt met de zorgdoelen. Beoordeel opnieuw wanneer de condities veranderen.	C
Huidzorg	
Zorg dat de huid intact blijft. • Breng een zalf of vetcrème aan volgens de gebruiksvoorschriften, zodat uitdrogen van de huid wordt voorkomen • Bescherm de huid tegen blootstelling aan extreme vochtigheid met behulp van een barrièremiddel en verminder hiermee het risico op drukschade.	C
Decubituszorg	
Bepaal, samen met de zorgvrager en/of de familie, behandeldoelen die aansluiten bij de behoeften van de zorgvrager. • Stel als doel om de kwaliteit van leven te verbeteren, ook als dit decubitus niet kan genezen • Beoordeel de impact van de decubitus op de kwaliteit van leven van zowel de zorgvrager als zijn familie. • Beoordeel de toestand van de zorgvrager tijdens de anamnese en bij elke belangrijke verandering in de toestand en pas het zorgplan zo nodig aan.	C
Beoordeel de decubitus tijdens de anamnese en vervolgens bij elke verbandwissel en leg de bevindingen vast. Evalueer ten minste twee wekelijks (tenzij de zorgvrager terminaal is). • Evalueer de wond op geur en exsudaat en beoordeel of de doelen van comfort en pijnreductie gehaald worden.	C
Verzorg de decubituswond en de huid rondom de wond regelmatig en houd daarbij rekening met de persoonlijke wensen. • Maak de wond bij elke verbandwissel schoon met kraanwater of fysiologisch zout, om beschadiging van de wond te beperken en de geur te verminderen. • Voer een debridement uit van dood weefsel in de wondbodem of aan de wondranden van de decubitus wanneer de toestand van de zorgvrager toelaat en het overeenkomstig is met de zorgdoelen	C

○ Vermijd een scherp debridement bij kwetsbare weefsels die makkelijk bloeden. • Kies voor een verband dat het aanwezige exsudaat kan opnemen, geur kan verminderen, de huid rondom de wond droog houdt en uitdroging van de wond voorkomt ○ Gebruik een wondverband dat zorgt voor een vochtig wondmilieu en dat comfortabel is voor de zorgvrager ○ Gebruik een verband dat gedurende een langere periode kan blijven zitten om te zorgen voor een comfortabele decubituszorg ○ Gebruik een wondverband dat aansluit bij de behoeften van de zorgvrager wat betreft comfort en decubituszorg. ▪ Overweeg het gebruik van een antimicrobieel verband om het aantal bacteriën en geur te verminderen • Bescherm de huid rondom de wond bij overmatig exsudaat met een huid beschermend barrièremiddel of een verband.	
Besteed aandacht aan de beheersing van de geur van de wond. • Maak de wond en het weefsel rondom de wond schoon en wees voorzichtig met het verwijderen van dood weefsel • Beoordeel de wond op tekenen van wondinfectie: toenemende pijn, kwetsbaar, oedemateus, bleek, donker granulatieweefsel, sterke geur, achteruitgang van de wond, abcesvorming of langzame wondgenezing. • Gebruik antimicrobiële middelen die geschikt zijn voor het behandelen van zowel infectie als kritische kolonisatie ○ Overweeg om geur te verminderen het gebruik van antiseptische oplossingen in de juiste verdunning en gedurende een korte periode. ○ Overweeg het gebruik van lokale metronidazol, voor een effectieve vermindering van geur bij decubituswonden die veroorzaakt wordt door infecties met anaerobe bacteriën en protozoën. Houdt in de overweging rekening met de snelle ontwikkeling van resistentie voor het middel. ○ Overweeg het gebruik van geïmpregneerde antimicrobiële verbanden (bijvoorbeeld cadexomeerjodium, medische honing), die bijdragen aan het verminderen van het aantal bacteriën en de geur. • Overweeg het gebruik van koolstof of geactiveerd koolstofverband om geur te verminderen • Overweeg het gebruik van middelen die de geur in de kamer absorberen (bijvoorbeeld geactiveerd koolstof of kattenbakvulling). Gebruik geen voedingsmiddelen of aan voeding gerelateerde producten (bijvoorbeeld koffie, vanille, potpourri) om negatieve associaties in de toekomst te voorkomen.	C C B C C C
[1] Level of evidence adapted from GRADE **A:** High; Further research is very unlikely to change confidence in the estimate of the clinical effect. **B:** Moderate; Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **C:** Low or very low; Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain.	

6.1.2 Jeuk

Non pharmacological treatment of itching (pruritus) – Adult guideline	
Integraal Kanker Instituut Nederland. Jeuk. 2010. *www.pallialine.nl*	
Recommendation	**Level of evidence[1]**
• goede verzorging van de huid • voorkomen van huidirritatie • aandacht voor geestelijk welbevinden	Level 1, bij dermatologische aandoeningen

[1]Level of evidence:
Level 1:gebaseerd op systematische review of ten minste twee gerandomiseerde onderzoeken van goede kwaliteit.
Level 2:gebaseerd op ten minste twee vergelijkende klinische onderzoeken van matige kwaliteit of onvoldoende omvang of andere vergelijkende onderzoeken.
Level 3: gebaseerd op één vergelijkend onderzoek of op niet-vergelijkend onderzoek.
Level 4: gebaseerd op mening van deskundigen.

6.2 Medicamenteuze behandeling van huidklachten

6.2.1 Jeuk

Pharmacological treatment of itching (pruritus) – Adult guideline	
Integraal Kanker Instituut Nederland. Jeuk. 2010. *www.pallialine.nl*	
Recommendation	**Level of evidence[1]**
Behandeling van de oorzaak	
• Behandeling van de onderliggende oorzaak (indien mogelijk): o aanpassen van medicatie o behandeling van infectie o opheffen van galgangobstructie, evt. nasobiliary drainage o chemotherapie (bijv. bij maligne lymfoom) o radiotherapie (bijv. bij ziekte van Hodgkin of prostaatcarcinoom) o antidepressiva bij depressie	Consensus-based
Lokale behandeling	
• indifferent emolliens, evt. met toevoeging van levomenthol en/of ureum • corticosteroïden bij eczemateuze huidafwijkingen • desinfectantia en lokale toediening van antimycotica of fusidinezuur bij resp. schimmel- of bacteriële infecties	Onbekend
Systemische behandeling (m.n. systemische en neurologische jeuk	
bij jeuk door cholestase • naltrexon startdosis 1 dd 12,5, evt. op te hogen tot 3 dd 50 mg (na voorbehandeling met naloxon) • paroxetine 1 dd 20 m • buprenorfine pleister 17,5 of 35 ug/uur • ondansetron 2 dd 8 mg	 Level 1 Level 2/3 Level 2 Level 4
bij jeuk door de ziekte van Hodgkin • prednison 2 dd 10-30 mg • cimetidine 4 dd 200-400 mg • mirtazapine 1 dd 15-30 mg	 Level 4 Level 4 Level 4
bij jeuk door polycythaemia vera • acetylsalicylzuur 1 dd 300 mg • paroxetine 1 dd 20 mg	 Level 3 Level 2/3
bij jeuk bij solide tumoren: • paroxetine 1 dd 20 mg (in een opbouwend schema) • mirtazapine 1 dd 15-30 m • lidocaïne 100-300 mg/24 uur s.c./i.v.	 Level 2/3 Level 4 Level 4
bij jeuk bij gebruik van opioïden: • ondansetron 2 dd 8 mg	 Level 1
bij jeuk door andere oorzaken of jeuk niet-reagerend op andere middelen: • paroxetine 1 dd 20 mg (in een opbouwend schema) • bij onvoldoende effect mirtazapine 1 dd 15-30 mg toevoegen	 Level 2/3 Level 4

[1]Level of evidence:
Level 1:gebaseerd op systematische review of ten minste twee gerandomiseerde onderzoeken van goede kwaliteit.
Level 2:gebaseerd op ten minste twee vergelijkende klinische onderzoeken van matige kwaliteit of onvoldoende omvang of andere vergelijkende onderzoeken.
Level 3: gebaseerd op één vergelijkend onderzoek of op niet-vergelijkend onderzoek.
Level 4: gebaseerd op mening van deskundigen.

7 Overzicht conclusies van evidence en aanbevelingen uit richtlijnen

7.1 Niet-medicamenteuze behandeling van huidklachten

Non pharmacological treatment for skin complaints								
Treatment	Conclusions of evidence (RCTs on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children 2013 (2)	Level of evidence[1,2]
Wounds and pressure ulcers								
Pressure distribution								
Inform family on risks for skin problems	Unknown effect	No studies	Not identified	-	Not identified	-	Do; strong recommendation	Child evidence (3, 4)
Turning patient regularly	Unknown effect	No studies	Not identified	-	Do (use schedule for changing positions; turn every four hours)	VERY LOW/ LOW (5;P)	Do; strong recommendation	Child evidence (3, 4); adult evidence[2]
Pressure reducing mattress	Unknown effect	No studies	Not identified	-	Use (consider other type of mattress if necessary)	VERY LOW/ LOW (5;P)	Do; strong recommendation	
Nutrition and hydration								
Sufficient nutrition	Unknown effect	No studies	Not identified	-	Do	VERY LOW/ LOW (5;P)	Do; strong recommendation	Child evidence (3, 4); adult evidence[2]
Offer multiple small meals	Unknown effect	No studies	Not identified	-	Do	VERY LOW/ LOW (5;P)	No recommendation	-
Give proteins	Unknown effect	No studies	Not identified	-	Do	VERY LOW/ LOW (5;P)	No recommendation	-
Skin care								
Skin care on high-risk areas (bone and pressure points)	Unknown effect	No studies	Not identified	-	Do	VERY LOW/ LOW (5;P)	Do; strong recommendation	Child evidence (3, 4); adult evidence[2]
Protect skin from extreme humidity	Unknown effect	No studies	Not identified	-	Do	VERY LOW/ LOW (5;P)	No recommendation	-
Wound care								
Indicate goal of treatment: healing of the wound or symptom management	Unknown effect	No studies	Not identified	-	Do	VERY LOW/ LOW (5;P)	Do; strong recommendation	Child evidence (3, 4); adult evidence[2]
Assess wound for signs of wound infection: increasing pain, fragility, oedematous, colour (pale/dark),strong smell, wound deterioration,	Unknown effect	No studies	Not identified	-	Do	MODERATE (5;P)	No recommendation	-

abscess formation or slow wound healing								
Clean wound with water or fysiological salt	Unknown effect	No studies	Not identified	-	Do	VERY LOW/ LOW (5;P)	Do for yellow/black wounds or strong smell); strong recommendation	Child evidence (3, 4);
Use of high quality dressing materials in case of symptoms like smell extreme exudate and bleeding	Unknown effect	No studies	Not identified	-	Do	VERY LOW/ LOW (5;P)	Do; strong recommendation	
Use wound dressings appropriate for the wound	Unknown effect	No studies	Not identified	-	Do	VERY LOW/ LOW (5;P)	Do; strong recommendation	
Consult a physiotherapist or occupational therapies	Unknown effect	No studies	Not identified	-	Not identified	-	Do (if necessary); strong recommendation	Child evidence (3, 4)
Surgical debridement of necrotic tissue	Unknown effect	No studies	Not identified	-	Do	VERY LOW/ LOW (5;P)	Consider (to aid wound healing and prevent/cure infections); weak recommendation	Child evidence (3, 4); adult evidence[2]
Control the smell of the wound								
Reduce smell by using • *Antiseptic solutions* • *Local metronizadol* • *Impregnated antimicrobial dressings* • *Carbon or activated carbon dressing* • *Agents that absorb smell in room (cat litter/activated carbon).*	Unknown effect	No studies	Not identified	-	Consider	VERY LOW/ LOW (5;P)	No recommendation	-
Evaluation								
Use of diary for evaluation	Unknown effect	No studies	Not identified	-	Not identified	-	Do; strong recommendation	(Child evidence (3, 4); adult evidence[2]
Itching								
Skin care (Cooling)	Unknown effect	No studies	Not identified	-	Do (good skin care and prevent irritation of the skin)	Level 1, for dermato-logical conditions (6;P)	Consider; weak recommendation	Level 4 child evidence (4); Level 1 adult evidence (7, 8)[2]

Hypnosis	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 3 adult evidence (9-11)
Attention for mental well-being	Unknown effect	No studies	Not identified	-	Do	Level 1, for dermato-logical conditions (6;P)		

Legend
P: Palliative context
Not identified: No recommendations on specific pharmacological intervention were identified.

[1]Level of evidence:
Level 1: Based on a systematic review or at least two randomized controlled trials of good quality
Level 2: Based on one at randomized controlled trial or at least two comparative clinical studies
Level 3: Based on one comparative study or on non-comparative studies
Level 4: Based on expert opinion
[2]Adult evidence is extracted from guidelines of pallialine.nl (IKNL. Jeuk.2010)

References

2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.
3. Goldman A, Hain R, Liben S. Oxford Textbook of Palliative Care for Children: Oxford University Press; 2006.
4. Wolfe J, Hinds P. Textbook of Interdisciplinary Pediatric Palliative Care: Saunders; 2011.
5. Integraal Kankercentrum Nederland. Decubitus (2.0). 2011. Available from: www.pallialine.nl/decubitus.
6. Integraal Kankercentrum Nederland. Jeuk (2.0).2010 27-07-2010. Available from: www.pallialine.nl/jeuk.
7. Bosonnet L. Pruritus: scratching the surface. Eur J Cancer Care (Engl). 2003;12(2):162-5.
8. Evers AWM, Casteleen G, Duller P, Eland P, Kennedy C, Korte Jd, et al. Multidisciplinaire diagnostiek en behandeling van complexe jeukproblematiek bij huidaandoeningen [Multidisciplinary diagnostics and treatment of complex itching problems in skin diseases.]. Nederlands Tijdschrift voor Dermatologie & Venereologie. 2005;15:433-8.
9. Rucklidge JJ, Saunders D. Hypnosis in a case of long-standing idiopathic itch. Psychosom Med. 1999;61(3):355-8.
10. Rucklidge JJ, Saunders D. The efficacy of hypnosis in the treatment of pruritus in people with HIV/AIDS: a time-series analysis. Int J Clin Exp Hypn. 2002;50(2):149-69.
11. Sampson RN. Hypnotherapy in a case of pruritus and Guillain-Barre syndrome. Am J Clin Hypn. 1990;32(3):168-73.

7.2 Medicamenteuze behandeling van huidklachten

Pharmacological treatment of skin complaints								
Treatment	Conclusions of evidence (RCTs on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence[1]	Recommendation for children 2013 (2)	Level of evidence[1]
Itching								
Treatment of underlying cause: • *Adjust medication* • *Treatment of infection* • *Elimination of bile duct obstruction* • *Chemotherapy* • *Radiotherapy* • *antidepressants*	Unknown effect	No studies	Not identified	-	Do	Expert opinion (6;P)	No recommendation	-
Local treatment								
Indifferent emollients + levomenthol or urea	Unknown effect	No studies	Not identified	-	Give	Unknown (6;P)	No recommendation	-
Corticosteroids	Unknown effect	No studies	Not identified	-	Give (for eczematous skin lesions)	Unknown (6;P)	No recommendation	-
Disinfectants (topical administration of antimyotics or fusidic acid)	Unknown effect	No studies	Not identified	-	Give (for fungal or bacterial infections)	Unknown (6;P)	No recommendation	-
Opioid-induced								
Antihistamines	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Controversy in level 3 child evidence (Ko, 2004[3])
Ondansetron	Unknown effect	No studies	Not identified	-	Give	Level 1 (6;P)	Consider; weak recommendation	Level 1 adult evidence (12-16)[2]
Naloxone infusion	↓ incidence of pruritus in children with post-operative opioid-induced side effects after intervention	VERY LOW 1 RCT (3;P)	Not identified	-	Not identified	-	Consider; weak recommendation	Level 1 child evidence (17) Level 1 adult evidence (18)[2]
For haematological conditions								

Cimetidine	Unknown effect	No studies	Not identified	-	Give (for Hodgkin disease)	Level 4 (6;P)	Consider (for haematological conditions); weak recommendation	Level 4 adult evidence (19-25)[2]
Prednisone	Unknown effect	No studies	Not identified	-	Give (for Hodgkin disease)	Level 4 (6;P)	No recommendation	-
Prednisone + cimetidine	Unknown effect	No studies	Not identified	-	-	-	Consider (for haematological conditions); weak recommendation	Level 4 adult evidence (26)[2]
Mirtazapine	Unknown effect	No studies	Not identified	-	Give (for Hodgkin disease)	Level 4 (6;P)	No recommendation	
Paroxetine (SSRI)	Unknown effect	No studies	Not identified	-	Give (for polycythaemia Vera)	Level 2/3 (6;P)	Consider (for haematological conditions); weak recommendation	Level 3 child evidence (27); Level 2 adult evidence (28)[2]
Acetylsalicylic acid	Unknown effect	No studies	Not identified	-	Give (for polycythaemia Vera)	Level 3 (6;P)	No recommendation	-
For solid tumours								
Paroxetine (SSRI)	Unknown effect	No studies	Not identified	-	Give (for Solid tumours)	Level 2/3 (6;P)	No recommendation	-
Mirtazapine	Unknown effect	No studies	Not identified	-	Give (for solid tumours)	Level 4 (6;P)	No recommendation	-
Lidocaine	Unknown effect	No studies	Not identified	-	Give(for Solid tumours)	Level 4 (6;P)	No recommendation	-
For cholestasis								
Ondansetron	Unknown effect	No studies	Not identified	-	Give	Level 4 (6;P)	Consider; weak recommendation	Level 2 adult evidence (29-31)[2]
Mirtazapine	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 adult evidence (32-34)[2]
Paroxetine, sertraline (SSRIs)	Unknown effect	No studies	Not identified	-	Give	Level 2/3 (6;P)	Consider; weak recommendation	Unknown level of evidence(35-39)[2]
Cholestyramine	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 3 adult evidence (40-42)[2]
Ursodeoxycholic acid	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 3 child evidence(43, 44)
Rifampicin	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 3 child evidence (45);

								Level 1 adult evidence (42, 46)[2]
Phenobarbital	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 3 child evidence (47), (Cies 2010[3])
Naloxone	Unknown effect	No studies	Not identified	-	Pre-treatment for treatment with naltrexone	Level 1 (6;P)	Consider; weak recommendation	Child evidence (48); Level 1 adult evidence (42, 49-52)[2]
Naltrexone	Unknown effect	No studies	Not identified	-	Give (after pre-treatment with naloxone)	Level 1 (6;P)	No recommendation	-
For uraemia								
Cholestagel	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 adult evidence (53)[2]

Legend
P: Palliative context
Not identified: No recommendations on specific pharmacological intervention were identified.

[1]Level of evidence:
Level 1: Based on a systematic review or at least two randomized controlled trials of good quality
Level 2: Based on one at randomized controlled trial or at least two comparative clinical studies
Level 3: Based on one comparative study or on non-comparative studies
Level 4: Based on expert opinion
[2]Adult evidence is extracted from guidelines of pallialine.nl (IKNL. Jeuk.2010)
[3] Full references are unknown

References

2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.
6. Integraal Kankercentrum Nederland. Jeuk (2.0).2010 27-07-2010. Available from: www.pallialine.nl/jeuk.
12. Borgeat A, Stirnemann HR. Ondansetron is effective to treat spinal or epidural morphine-induced pruritus. Anesthesiology. 1999;90(2):432-6.
13. Charuluxananan S, Somboonviboon W, Kyokong O, Nimcharoendee K. Ondansetron for treatment of intrathecal morphine-induced pruritus after cesarean delivery. Reg Anesth Pain Med. 2000;25(5):535-9.
14. Dimitriou V, Voyagis GS. Opioid-induced pruritus: repeated vs single dose ondansetron administration in preventing pruritus after intrathecal morphine. Br J Anaesth. 1999;83(5):822-3.
15. Gurkan Y, Toker K. Prophylactic ondansetron reduces the incidence of intrathecal fentanyl-induced pruritus. Anesth Analg. 2002;95(6):1763-6, table of contents.
16. Kyriakides K, Hussain SK, Hobbs GJ. Management of opioid-induced pruritus: a role for 5-HT3 antagonists? Br J Anaesth. 1999;82(3):439-41.
17. Maxwell LG, Kaufmann SC, Bitzer S, Jackson EVJ, McGready J, Kost-Byerly S, et al. The Effects of a Small-Dose Naloxone Infusion on Opioid-Induced Side Effects and Analgesia in Children and Adolescents Treated with Intravenous Patient-Controlled Analgesia: A Double-Blind, Prospective, Randomized, Controlled Study. Anesthesia & Analgesia. 2005;100(4):953-8.
18. Kjellberg F, Tramer MR. Pharmacological control of opioid-induced pruritus: a quantitative systematic review of randomized trials. Eur J Anaesthesiol. 2001;18(6):346-57.
19. Aymard JP, Lederlin P, Witz F, Colomb JN, Herbeuval R, Weber B. Cimetidine for pruritus in Hodgkin's disease. Br Med J. 1980;280(6208):151-2.
20. Harrison AR, Littenberg G, Goldstein L, Kaplowitz N. Pruritus, cimetidine, and polycythemia. N Engl J Med. 1979;300(8):433-4.
21. Hess CE. Cimetidine for the treatment of pruritus. N Engl J Med. 1979;300(7):370.
22. Schapira DV, Bennett JM. Cimetidine for pruritus. Lancet. 1979;1(8118):726-7.
23. Staubli M, Graf W, Straub PW. [Pruritus in Hodgkin's disease responding to cimetidine]. Schweiz Med Wochenschr. 1981;111(20):723-4.

24. Weick JK, Donovan PB, Najean Y, Dresch C, Pisciotta AV, Cooperberg AA, et al. The Use of Cimetidine for the Treatment of Pruritus in Polycythemia Vera. Archives of Internal Medicine. 1982;142(2):241-2.
25. Zappacosta AR, Hauss D. Cimetidine doesn't help pruritus of uremia. N Engl J Med. 1979;300(22):1280.
26. Korfitis C, Trafalis DT. Carbamazepine can be effective in alleviating tormenting pruritus in patients with hematologic malignancy. J Pain Symptom Manage. 2008;35(6):571-2.
27. Zylicz Z, Smits C, Krajnik M. Paroxetine for pruritus in advanced cancer. J Pain Symptom Manage. 1998;16(2):121-4.
28. Zylicz Z, Krajnik M, Sorge AA, Costantini M. Paroxetine in the treatment of severe non-dermatological pruritus: a randomized, controlled trial. J Pain Symptom Manage. 2003;26(6):1105-12.
29. O'Donohue J, Haigh C, Williams R. Ondansetron in the treatment of the pruritus of cholestasis: a randomised controlled trial. Gut. 1997;40(3S).
30. O'Donohue JW, Pereira SP, Ashdown AC, Haigh CG, Wilkinson JR, Williams R. A controlled trial of ondansetron in the pruritus of cholestasis. Aliment Pharmacol Ther. 2005;21(8):1041-5.
31. Muller C, Pongratz S, Pidlich J, Penner E, Kaider A, Schemper M, et al. Treatment of pruritus in chronic liver disease with the 5-hydroxytryptamine receptor type 3 antagonist ondansetron: a randomized, placebo-controlled, double-blind cross-over trial. Eur J Gastroenterol Hepatol. 1998;10(10):865-70.
32. Davis MP, Frandsen JL, Walsh D, Andresen S, Taylor S. Mirtazapine for pruritus. J Pain Symptom Manage. 2003;25(3):288-91.
33. Demierre MF, Taverna J. Mirtazapine and gabapentin for reducing pruritus in cutaneous T-cell lymphoma. J Am Acad Dermatol. 2006;55(3):543-4.
34. Hundley JL, Yosipovitch G. Mirtazapine for reducing nocturnal itch in patients with chronic pruritus: a pilot study. J Am Acad Dermatol. 2004;50(6):889-91.
35. Browning J, Combes B, Mayo MJ. Long-term efficacy of sertraline as a treatment for cholestatic pruritus in patients with primary biliary cirrhosis. Am J Gastroenterol. 2003;98(12):2736-41.
36. Diehn F, Tefferi A. Pruritus in polycythaemia vera: prevalence, laboratory correlates and management. Br J Haematol. 2001;115(3):619-21.
37. Mayo MJ, Handem I, Saldana S, Jacobe H, Getachew Y, Rush AJ. Sertraline as a first-line treatment for cholestatic pruritus. Hepatology. 2007;45(3):666-74.
38. Stander S, Bockenholt B, Schurmeyer-Horst F, Weishaupt C, Heuft G, Luger TA, et al. Treatment of chronic pruritus with the selective serotonin re-uptake inhibitors paroxetine and fluvoxamine: results of an open-labelled, two-arm proof-of-concept study. Acta Derm Venereol. 2009;89(1):45-51.
39. Tefferi A, Fonseca R. Selective serotonin reuptake inhibitors are effective in the treatment of polycythemia vera-associated pruritus. Blood. 2002;99(7):2627.
40. Datta DV, Sherlock S. Cholestyramine for long term relief of the pruritus complicating intrahepatic cholestasis. Gastroenterology. 1966;50(3):323-32.
41. Di Padova C, Tritapepe R, Rovagnati P, Rossetti S. Double-blind placebo-controlled clinical trial of microporous cholestyramine in the treatment of intra- and extra-hepatic cholestasis: relationship between itching and serum bile acids. Methods Find Exp Clin Pharmacol. 1984;6(12):773-6.
42. Tandon P, Rowe BH, Vandermeer B, Bain VG. The efficacy and safety of bile Acid binding agents, opioid antagonists, or rifampin in the treatment of cholestasis-associated pruritus. Am J Gastroenterol. 2007;102(7):1528-36.
43. Dinler G, Koçak N, Yüce A, Gürakan F, Ozen H. Ursodeoxycholic acid therapy in children with cholestatic liver disease. The Turkish journal of pediatrics. 1999;41(1):91-8.
44. Balistreri WF. Bile acid therapy in pediatric hepatobiliary disease: the role of ursodeoxycholic acid. Journal of pediatric gastroenterology and nutrition. 1997;24(5):573-89.
45. El-Karaksy H, Mansour S, El-Sayed R, El-Raziky M, El-Koofy N, Taha G. Safety and efficacy of rifampicin in children with cholestatic pruritus. The Indian Journal of Pediatrics. 2007;74(3):279-81.
46. Khurana S, Singh P. Rifampin is safe for treatment of pruritus due to chronic cholestasis: a meta-analysis of prospective randomized-controlled trials. Liver International. 2006;26(8):943-8.
47. Ghent C, Bloomer J, Hsia Y, Lietman PS. Efficacy and safety of long-term phenobarbital therapy of familial cholestasis. The Journal of pediatrics. 1978;93(1):127-32.
48. Chang L, De K, Yan-sheng W. Clinical Observation on Treatment of Acute Cerebral Infarction with Large Dose of Edaravone Plus Naloxone. Clinical Journal of Medical Officers. 2008;4.
49. Bergasa NV, Alling DW, Talbot TL, Swain MG, Yurdaydin C, Turner ML, et al. Effects of naloxone infusions in patients with the pruritus of cholestasis. A double-blind, randomized, controlled trial. Ann Intern Med. 1995;123(3):161-7.
50. Bergasa NV, Talbot TL, Alling DW, Schmitt JM, Walker EC, Baker BL, et al. A controlled trial of naloxone infusions for the pruritus of chronic cholestasis. Gastroenterology. 1992;102(2):544-9.
51. Connolly CS, Kantor GR, Menduke H. Hepatobiliary pruritus: what are effective treatments? J Am Acad Dermatol. 1995;33(5 Pt 1):801-5.
52. Jones EA, Neuberger J, Bergasa NV. Opiate antagonist therapy for the pruritus of cholestasis: the avoidance of opioid withdrawal-like reactions. QJM. 2002;95(8):547-52.
53. Cho YL, Liu HN, Huang TP, Tarng DC. Uremic pruritus: roles of parathyroid hormone and substance P. J Am Acad Dermatol. 1997;36(4):538-43.

G Misselijkheid en Braken

Inhoudsopgave

1 Uitgangsvragen

Vraag 7A**:** Wat is de meest effectieve niet-medicamenteuze behandeling van misselijkheid en braken bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Niet-medicamenteuze behandeling van misselijkheid en braken
C: Geen behandeling/placebo
O: Effect op misselijkheid en braken en kwaliteit van leven

Vraag 7B: Wat is de meest effectieve medicamenteuze behandeling van misselijkheid en braken bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Medicamenteuze behandeling van misselijkheid en braken
C: Geen behandeling/placebo
O: Effect op misselijkheid en braken en kwaliteit van leven

2 Resultaten van het literatuuronderzoek

Jaar	Bibliografie	Studie karakteristieken
7A: Wat is de meest effectieve niet-medicamenteuze behandeling van misselijkheid en braken bij kinderen tussen 0 en 18 jaar in de palliatieve fase?*		
1994	***Jacknow DS et al.*** Hypnosis in the prevention of chemotherapy-related nausea and vomiting in children: a prospective study. J Dev Behav Pediatr 1994;15(4):258-64	RCT kinderen
2014	***Depuis LL et al.*** Guideline for the prevention and treatment of anticipatory nausea and vomiting due to Chemotherapy in Pediatric Cancer Patients. Pediatr blood cancer 2014; 61: 1506–1512. [1]	Richtlijn kinderen
2016	***Flank J et al.*** Guideline for the treatment of breakthrough and the prevention of refractory chemotherapy-induced nausea and vomiting in children with cancer. Pediatr Blood Cancer 2016; 63: 1144-1151 [1]	Richtlijn kinderen
2014	***Integraal Kankerinstituut Nederland.*** Misselijkheid en Braken (4). Pallialine, 16-6-2014 [2]	Richtlijn volwassenen
7B: Wat is de meest effectieve medicamenteuze behandeling van misselijkheid en braken bij kinderen tussen 0 en 18 jaar in de palliatieve fase?*		
2014	***Depuis LL et al.*** Guideline for the prevention and treatment of anticipatory nausea and vomiting due to Chemotherapy in Pediatric Cancer Patients. Pediatr blood cancer 2014; 61: 1506–1512.	Richtlijn kinderen
2016	***Flank J et al.*** Guideline for the treatment of breakthrough and the prevention of refractory chemotherapy-induced nausea and vomiting in children with cancer. Pediatr Blood Cancer 2016; 63: 1144-1151 [1]	Richtlijn kinderen
2014	***Integraal Kankerinstituut Nederland.*** Misselijkheid en Braken (4). Pallialine, 16-6-2014 [2]	Richtlijn volwassenen
2015	***National institute for health and care (NICE).*** Care of dying adults in the last days of life. 2015 [2]	Richtlijn volwassenen
1996	***Brock P et al. An*** increased loading dose of ondansetron: a north european, double-blind randomised study in children, comparing 5 mg/m2 with 10 mg/m2. Eur J Cancer 1996 Sep;32A(10):1744-8	RCT kinderen
1999	***Parker RI et al***. Randomized, double-blind, crossover, placebo-controlled trial of intravenous ondansetron for the prevention of intrathecal chemotherapy-induced vomiting in children. Biol Blood Marrow Transplant 1999;5(6):386-93	RCT kinderen
1994	***Orchard PJ et al.*** A prospective randomized trial of the anti-emetic efficacy of ondansetron and granisetron during bone marrow transplantation. J Dev Behav Pediatr 1994;15(4):258-64	RCT kinderen
1998	***Kóseoglu V et al.*** Comparison of the efficacy and side-effects of ondansetron and metoclopramide-diphenhydramine administered to control nausea and vomiting in children treated with antineoplastic chemotherapy: a prospective randomized study. Eur J Pediatr 1998 Oct;157(10):806-10	RCT kinderen
2001	***Aksoylar S et al.*** Comparison of tropisetron and granisetron in the control of nausea and vomiting in children receiving combined cancer chemotherapy. Pediatr Hematol Oncol 2001 Sep;18(6):397-406.	RCT kinderen
2009	***Gore L et al.*** Aprepitant in adolescent patients for prevention of chemotherapy-induced nausea and vomiting: a randomized, double-blind, placebo-controlled study of efficacy and tolerability. Pediatr Blood Cancer 2009;52:242–247	RCT kinderen
2007	***Riad, W. et al.*** Effect of midazolam, dexamethasone and their combination on the prevention of nausea and vomiting following strabismus repair in children. European Journal of Anaesthesiology 2007; 24: 697-701	RCT kinderen

[1] Aanbevelingen uit de richtlijnen over misselijkheid en braken bij kinderen in de palliatieve fase worden gebruikt in de overwegingen.
[2] Aanbevelingen uit richtlijnen over misselijkheid en braken bij volwassenen in de palliatieve fase worden alleen gebruikt in de overwegingen wanneer er geen aanbevelingen uit richtlijnen over misselijkheid en braken bij kinderen in de palliatieve fase zijn gevonden. Aanbevelingen over misselijkheid en braken bij volwassenen tijdens chemotherapie hoeven niet toegevoegd te worden
[*] Systematisch gezocht, zie: bijlage 7 zoekverantwoording – search 1

3 Evidence tabellen

3.1 Niet-medicamenteuze behandeling van Misselijkheid en Braken

Non pharmacological treatment of nausea and vomiting - Self-hypnosis				
Jacknow DS et al. Hypnosis in the prevention of chemotherapy-related nausea and vomiting in children: a prospective study. J Dev Behav Pediatr 1994;15(4):258-64				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: Prospective, single-blind RCT Setting: 2 centres, USA Duration: Study outcomes were assessed during first two courses of chemotherapy and 1 to 2 months and 4 to 6 months after diagnosis Study years: October 1990 – January 1992 Protocol published in register: Not reported	Number and type of participants: Total of 20 newly diagnosed children with cancer. • Intervention group: 10 • Control group: 10 Age: • Intervention group: Mean: 11.9, Range: 6-15 yr. • Control group: Mean: 12.2, Range 7-18 yr. Sex: • Intervention group: M: 5 (50%), F: 5 (50%) • Control group: M: 5 (50%), F: 5 (50%) Duration of chemotherapy (course 1) • Intervention group: Mean: 3.5 days, Range (1-6 days) • Control group: Mean: 2.7 days, Range (1-5 days) Duration of chemotherapy (course 2) • Intervention group: Mean: 2.6 days, Range (1-6 days) • Control group: Mean: 1.8 days, Range (1-5 days) No significant differences between groups for all variables mentioned above. Diagnosis • Intervention group:	Type of intervention: Children were taught self-hypnosis by a therapist in two to three sessions during the initial course of chemotherapy, using standard hypnotic techniques. Hypnosis procedure was geared to the developmental level of the child, emphasis was placed on active involvement of imagination. Sessions were 45 minutes long. Children were told to practice twice daily. Children used the same anti-emetics as the control group but received no standard doses. Anti-emetics were only used if necessary. Type of control: Children in the control group received an equivalent amount of individual time consisting of informal conversation with the therapist. A single therapist provided all hypnosis training and individualized time. Patients in the control group were al on standard anti-emetic regimen: • First line anti-emetics (until April 1991), thiethylperazine/ chloropromazine (until April 1991), with diphenhydramine. • First line anti-emetics (from May 1991): Ondansentron • Second line ant-emetics, metoclopramide with diphenhydramine Patients received a dose of antiemetic medication at time 0 of chemotherapy, at 4 to hours of chemotherapy and sometimes at 8 to 12 hours of	Outcome definitions: **Use of anti-emetic medication** Supplemental anti-emetic usage. Medical records were reviewed daily for antiemetic medication usage. Standard doses given to the control group were subtracted from the total medication usage, leaving only p.r.n (pro re nata) antiemetic usage as the outcome variable **Mean nausea and vomiting score** Patient and parent reported nausea and vomiting were assessed at a standard time each day during the chemotherapy course using to instruments • *Severity of nausea:* This was assessed using a graphic rating scales (five faces with expressions ranging from smiling to frowning) • *Frequency of vomiting and/or retching:* This was assessed using a 9 point Likert scale ranging from 'none' to 'all the time' As patient and parents report on all nausea and vomiting measures were highly correlated (r = 0.72 to r = 0.93; P <0.001) only patient scores were used. Correlations for nausea and vomiting scores were high within each course of chemotherapy (r = 0.73 to 0.76, p = 0.001). Therefore nausea and vomiting variables at each course of chemotherapy were standardized and combined into a single score for data analysis. **Mean anticipatory nausea and vomiting** (assessed at ½ months and 4/6 months after diagnosis. Three components of nausea were assessed • *Severity of nausea* • *Frequency of nausea* • *Time of onset of nausea before chemotherapy* Correlations between the three components of anticipatory symptoms were 0.78 to 0.97n (p < 0.001) Therefore the three scores were standardized and summed into an index of severity of anticipatory nausea. To eliminate negative numbers a constant of 2 was added to the scores. **Mean anticipatory vomiting** (assessed at 1/2 months and 4/6 months after diagnosis. Two components of vomiting were assessed	Strengths: Limitations: • Differences in supplemental anti-emetic medication usage could have been affected by the potential difference in expectation regarding antiemetic use. Patients in the intervention group may have believed they had failed if they requested antiemetic medication. • Relatively low number of patients included in the study • Possibility of selection bias because subjects were matched on age and emetogenicity of chemotherapy. **Risk of bias** A. Selection bias: Unclear Reason: Subjects underwent stratified random assignment. Patients were matched on age and emetogenicity of their chemotherapeutic regimens. Allocation concealment was not reported B. Attrition bias: Low risk

	Leukaemia: 20%, Hodgkin's lymphoma: 40%, Solid tumours: 40% • Control group: Leukaemia: 30%, Hodgkin's lymphoma: 40%, Solid tumours: 30%	chemotherapy. Thereafter, anti-emetics were delivered every 4 to 6 hours if necessary.	• Frequency of vomiting • Time of onset before vomiting Because of small sample at 1/2 months and 4/6 months statistical analysis was not performed. Results (per outcome) **Use of anti-emetic medication** The intervention group used significantly less supplemental anti-emetic medication • *Course 1 of chemotherapy (intervention vs control):* Mean (SD): 0.17 (0.33) vs 1.01 (1.33), p <0.04 • *Course 2 of chemotherapy (intervention vs control):* Mean (SD): 0.34 (0.93) vs 2.10 (2.66), p<0.02 **Mean nausea and vomiting score** • *Course 1 of chemotherapy (intervention vs control):* Mean (SD): 1.79 (1.77) vs 3.21(2.01), p = NS • *Course 2 of chemotherapy (intervention vs control):* Mean (SD): 1.82 (2.01) vs 3.18 (1.81), p = NS **Anticipatory nausea** • *1 to 2 months post diagnosis (intervention vs control):* Mean (SD): 0.82 (2.60) vs 3.17 (2.60), p<0.013 • *4 to 6 months post diagnosis (intervention vs. control):* Mean (SD): 1.69 (3.64) vs 2.54 (2.47), p = NS **Anticipatory vomiting** Two patients in the control group experienced anticipatory vomiting vs zero patients in the intervention group	Reason: Outcomes of all patients included in the study were assessed C. Performance bias High risk Reason: Both participants and personnel were not blinded from knowledge of which intervention was received D. Detection bias Unclear Reason: Blinding of outcome assessors was not reported

3.2 Medicamenteuze behandeling van Misselijkheid en Braken

Pharmacological treatment of nausea and vomiting - low dose ondansetron vs high dose ondansetron				
Brock P et al. An increased loading dose of ondansetron: a north european, double-blind randomised study in children, comparing 5 mg/m2 with 10 mg/m2. Eur J Cancer 1996 Sep;32A(10):1744-8				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: Double-blind RCT Setting: 18 oncology units in Belgium, the Netherlands, Denmark, Sweden and Finland. Duration: Follow-up during the whole chemotherapy course. Study years: November 1992 – June 1994 Protocol published in register: Not reported	Number and type of participants: A total of 187 children who had not received prior chemotherapy and who were scheduled to receive highly emetogenic chemotherapy. *Number of patients at baseline* Group 1: 93, Group 2: 94 *Number of patients with outcome measured* Outcome was measured in 158 children. 27 children were excluded due to protocol violation, 2 dropouts. Group 1: 79, Group 2: 79 • *Number of patients receiving cisplatin chemotherapy* Group 1: 14, Group 2: 17 • *Number of patients receiving ifosfamide* Group 1: 14, Group 2: 14 • *Number of patients with treatment failures* Group 3: 15, Group 4: 19 Age (at baseline): • Group 1 - 5mg/m^2 ondansetron: Mean: 8.4 yrs., Range: 2 – 16.7 yrs. • Group 2- 10mg/m^2 ondansetron: Mean 8.5 yrs., 1.9 – 16.3 yrs. Sex (at baseline): • Group 1 - 5mg/m^2 ondansetron: M: 50 (54%), F: 43 (46%) • Group 2- 10mg/m^2 ondansetron: M: 52 (55%), F: 42 (45%) Mean surface area (m^2) (at baseline)	Group 1: 5mg/m^2 ondansetron Intravenous intake: The initial intravenous loading-dose of ondansetron 5mg/m^2 (maximum 8 mg) was administered immediately prior to chemotherapy as a 15 min infusion. Two additional intravenous doses of ondansetron were administered 8 and 16 h after the initial dose. Oral intake: on subsequent days when chemotherapy was given, ondansetron was administered orally three times a day at a dose according to the surface area of the child: 4mg < 1 m^2, 8 > 1m^2. The first intake was given 24h after the start of chemotherapy and it was continued for 3 days after the last day of chemotherapy or 5 days if nausea or vomiting persisted. Group 2: 10mg/m^2 ondansetron Initial intravenous loading-dose of ondansetron was 10mg/m^2 (maximum of 16mg). The rest of the procedure regarding intravenous and oral intake were similar to group 1. *Treatment failures* Only patients were included that were considered treatment failures: Patients suffered more than five emetic episodes in any 24-h period during their first course of chemotherapy, patients received rescue medication and/or there was any change in anti-emetic drug treatment. Group 3 treatment failures 10mg/m^2 dexamethasone + 5mg/m^2 ondansetron Patients were given dexamethasone at a dose of 10mg/m^2 (maximum 16 mg) as an intravenous infusion over 15 mg, 30 in prior the chemotherapy, in addition to	Outcome definitions: **Anti-emetic efficacy (first 24 hr)** Anti-emetic efficacy of the two loading doses of ondansetron was analysed during the first 24h of chemotherapy by comparing • the percentage of complete or major responders • mean number of emetic episodes • grade of nausea *Categories* • Complete/none: No emetic episode/not feeling sick at all • Major/mild: 1-2 emetic episodes/feeling sick *Emetic episode (vomiting/retching):* A single vomit or retch or any number of continuous vomits or retches. Each emetic episode was separated by the absence of vomiting or retching for at least 1 minute. *Categories for emetic efficacy:* • Complete response: No emetic episode • Major response: 1-2 emetic episodes • Minor response: 3-5 emetic episodes • Failure: more than 5 emetic episodes *Nausea:* feeling of wanting to be sick without retching. • None: not feeling sick at all • Mild: feeling sick • Severe: feeling very sick *Appetite* *Grading of appetite:* better than usual, as usual, worse than usual Results (per outcome) *All patients* **Anti-emetic efficacy** Anti-emetic efficacy over the first 24h of chemotherapy. • Percentage of patients with two or fewer emetic episodes (group 1 vs group 2): 71% vs 72%, p = NS. • Percentage of patients with no or mild nausea (group 1 vs group 2): 90% vs 86%, p = NS. • Percentage of patients with usual or better appetite: 44-45%	Strengths: Limitations: Definition of the worst day is not reported in the article. Good control of emesis and nausea was defined as patients having 2 or less emetic episodes and patients reporting none to mild patients. However it is not reported where this definition of good control is based on. **Risk of bias** A. Selection bias: Low risk Reason: Patients were randomized according to randomisation code. B. Attrition bias: High risk Reason: Outcome was measured in 160 children. 27 children were excluded due to protocol violation. Outcome was assessed for more than 90% in each treatment arm. C. Performance bias Low risk Reason: the anti-emetic loading dose of ondansetron was blinded to the clinicians, the patients, the parents and the nurses. D. Detection bias unclear Reason: not reported if outcome assessors were blinded

	• Group 1 - 5mg/m^2 ondansetron: 1.1 m^2 • Group 2- 10mg/m^2 ondansetron: 1.1 m^2	ondansetron. Loading-dose of ondansetron was the same as in the first course of chemotherapy, 5mg/m^2. <u>Group 4 treatment failure - 10mg/m^2 dexamethasone + 10mg/m^2 ondansetron</u> Patients were given dexamethasone at a dose of 10mg/m^2 (maximum 16 mg) as an intravenous infusion over 15 mg, 30 in prior the chemotherapy, in addition to ondansetron. Loading-dose of ondansetron was the same as in the first course of chemotherapy, 10 mg/m^2	Anti-emetic efficacy on the worst day • Percentage of patients with two or fewer emetic episodes (group 1 vs group 2): 61% vs 60%, p = NS. • Percentage of patients with no or mild nausea (group 1 vs group 2): 80% vs 70%, p = NS. • Percentage of patients with usual or better appetite: 27-28% *Cisplatin Chemotherapy* Anti-emetic efficacy over the first 24h of chemotherapy. • Percentage of patients with two or fewer emetic episodes (group 1 vs group 2): 50% vs 53%, p = NS. • Percentage of patients with no or mild nausea (group 1 vs group 2): 100% vs 86%, p = NS. *Ifosfamide* • Percentage of patients with two or fewer emetic episodes (group 1 vs group 2): 79% vs 64%, p = NS. • Percentage of patients with no or mild nausea (group 1 vs group 2): 78% vs 77%, p = NS *Treatment failures* **Anti-emetic efficacy** • Percentage of patients with two or fewer emetic episodes (group 3 vs group 4): 60% vs 60%, • Percentage of patients with no or mild nausea (group 3 vs group 4): 60% vs 60%, • Percentage of patients with usual or better appetite (group 3 vs group 4): 60% vs 72%.	

Pharmacological treatment of nausea and vomiting - low dose ondansetron vs high dose ondansentron vs placebo				
Parker RI et al. Randomized, double-blind, crossover, placebo-controlled trial of intravenous ondansetron for the prevention of intrathecal chemotherapy-induced vomiting in children. Biol Blood Marrow Transplant 1999;5(6):386-93				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: Randomized, Double-Blind Crossover, Placebo-controlled study Setting: 1 centre, USA Duration: 24h after treatment Study years: Not reported Protocol published in register: Not reported	Number and type of participants: A total of 26 children with newly diagnosed acute lymphoid or nonlymphoid leukaemia. Each patient acted as their own control. • Intervention group: 26 • Control group: 26 Age: • Intervention group: Mean: 6yr, Range: 2-17 yr. • Control group: Mean: 6yr, Range: 2-17 yr. Sex: • Intervention group: M: 12 (46.2%), F: 14 (53.8%) • Control group: : M: 12 (46.2%), F: 14 (53.8%) Total intrathecal treatments: 146 intrathecal treatments; mean 5.62/patient; range 3-7 • 51 placebo treatments • 47 low dose ondansetron • 48 high dose ondansetron Total vomiting episodes: 52 vomiting episodes; mean 2.0/patient; range: 0-7 patient	Each patient acted as his or her control; treatments (placebo, low-dose ondansetron, high-dose ondansetron) were administered in random order for up to 6 intrathecal treatments. During the first three treatments, each patient would receive each of the interventions one time. Intervention 1: Low dose ondansetron Ondansetron at 0.15 mg/kg (low dose) by a 15-minute intravenous infusion 30 minutes before undergoing a lumbar puncture for the administration of intrathecal chemotherapy. Patients who had two or more vomiting episodes after the intrathecal chemotherapy would then receive antiemetic therapy with diphenhydramine HCl, Prochlorperazine, or trimethobenzamide HCl. Intervention 2: High dose ondansetron: Ondansetron at 0.45 mg/kg (high dose). Procedure is the similar to the procedure in the other groups Placebo Patients received normal saline (placebo). Procedure is the similar to the procedure in the other groups	Outcomes **Treatments with vomiting episodes in 24h** • Percentage of treatments with vomiting episodes • RR of vomiting Results (per outcome) **Treatments with vomiting episodes in 24-h** N (%) of patients: 23 (88.5%) Percentage of treatments with vomiting (vs placebo) • Total: 35.6% vs 62.7%, • Low dose ondansetron 27.7% vs 62.7%, p<0.001 • High dose ondansetron: 14.6% vs 62.7%, p<0.001 • Any dose ondansetron: 21.1% vs 62.7%, p<0.001 Percentage of treatments with vomiting (vs low dose ondansetron) • High dose ondansetron: 14.6% vs 27.7 %, p<0.1 RR of vomiting in the placebo group • Placebo vs low dose ondansetron = 2.3 • Placebo vs high dose ondansetron = 4.3 • Placebo vs any dose ondansetron = 3.0 Reduction of RR by pre-administrating ondansetron: 65.7% **Treatments with ≥ 2 vomiting episodes** N (%) of patients: 17 (65%) Percentage of treatments with vomiting (vs placebo) • Total: 21.2% vs 43.1%, • Low dose ondansetron 12.8% vs 43.1%, p<0.001 • High dose ondansetron: 6.3% vs 43.1%, p<0.001 • Any dose ondansetron: 9.5% vs 43.1%, p<0.001 Percentage of treatments with vomiting (vs low dose ondansetron) • High dose ondansetron: 6.3% vs 12.8 %, p<0.3 RR of vomiting in the placebo group • Placebo vs low dose ondansetron = 3.4 • Placebo vs high dose ondansetron = 6.8 • Placebo vs any dose ondansetron = 4.5 Reduction of RR by pre-administrating ondansetron: 77.5% **Treatments with ≥ 4 vomiting episodes** Percentage of treatments with vomiting (vs placebo) • Total: 20.3% vs 25.5%, • Low dose ondansetron 4.3% vs 25.5%, p<0.005	Strengths: Limitations: Nausea is not studied Small study population **Risk of bias** A. Selection bias: Unclear Reason: Patients were randomly assigned to receive one of three interventions in a double-blinded fashion. allocation concealment was not reported B. Attrition bias: Low risk Reason: One child was withdrawn from the study. Outcomes were assessed for more than 90% of the study population C. Performance bias Low risk Reason: Participants and personnel were blinded from knowledge of the intervention received, as the study was double-blinded. D. Detection bias Unclear Reason: Blinding of outcome assessors was not reported

			• High dose ondansetron: 0.0% vs 25.5%, p<0.001 • Any dose ondansetron: 2.1% vs 25.5%, p<0.001 Percentage of treatments with vomiting (vs low dose ondansetron) • High dose ondansetron: 0.0% vs 4.3 %, p<0.1 RR of vomiting in the placebo group • Placebo vs low dose ondansetron = 5.8 • Placebo vs high dose ondansetron • Placebo vs any dose ondansetron = 12.1 Reduction of RR by pre-administrating ondansetron: 91.6% **Incidence of vomiting (10 y or older vs younger than 10 y):** 19.0% vs 38.4%, p < 0.05	

Pharmacological treatment of nausea and vomiting - granisetron vs ondansetron				
Orchard PJ et al. A prospective randomized trial of the anti-emetic efficacy of ondansetron and granisetron during bone marrow transplantation. J Dev Behav Pediatr 1994;15(4):258-64				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: Prospective randomized trial Setting: 1 centre, USA Duration: Outcomes were measured from the first day of the preparative regimen through day 2 (0 – 48h) Study years: Not reported Protocol published in register: Not reported	Number and type of participants: A total of 187 patients 2-65 years of age undergoing hematopoietic cell transplantation, patients were not being treated with anti-emetic medications and were not having a history of recent emetic episodes preceding conditioning therapy. • Granisetron: 90 • Ondansetron: 97 Age: • Granisetron: Median: 41 yrs., Range: 3-62 yr. N (%) <18 yrs.: 23 (26%) N (% ≥ 18 yrs.: 67 (74%) • Ondansetron: Median: 36 yrs., Range: 5-62 N (%) <18 yrs.: 28 (29%) N (% ≥ 18 yrs.: 69 (71%) Sex: • Granisetron: M: 54 (60%), F: 36 (40%) • Control group: M: 53 (55%), F: 44 (45%) Type of transplant • Granisetron: Autologous N (%): 34 (38%) Allogeneic N (%): 24 (27%) Unrelated N (%): 32 (35%) • Control group: Autologous N (%): 34 (35%) Allogeneic N (%): 27 (28%) Unrelated N (%): 36 (37%)	Granisetron A single intravenous dose of granisetron was given before the start of chemotherapy or total body irradiation (TBI) followed by intermittent intravenous dosing of granisetron every 12 hours. Patients received a placebo consisting of a continuous infusion of 5% dextrose. • *Patients < 18 yrs.:* Patients received a 10µg/kg/dose every 12 hours. • *Patients ≥ 18 yrs.:* Patients received an 7.5µg/kg/dose (0.5mg for a 70 kg patient) every 12 hours; Ondansetron Patients received an initial loading dose of ondansetron before the start of the first dose of chemotherapy or TBI, followed by continuous infusion. A placebo consisting of an intermittent dose of 5% dextrose was administered every 12 hours. • *Patients < 18 yrs.:* Patients received a 0.15 mg/kg load along with a 0.03mg/kg/h drip rounded to the nearest 0.1 mg • *Patients ≥ 18 yrs.:* Patients received an 8 mg load followed by a 0.015 mg/kg/h drip rounded to the nearest 0.5mg/h, amounting to 24 mg/day for a 70kg individual. All patients Received dexamethasone	Outcome definitions: **Emetic episodes** Expulsion of stomach contents separated by 1 minute from a previous episode **Retching** Non-productive emptying of stomach contents. A series of retches lasting <5 minutes was considered one emetic episode. **Nausea** A visual analogue scale (smiling or frowning faces) was used to determine severity of nausea, score ranging from 0 (no nausea to 5 (worst nausea ever experienced), higher score indicating higher severity of nausea **Control of emesis** • Complete control: no emetic episodes • Major control: one to two emetic episodes in 24 hours • Minor control: three to five emetic episodes in 24h • Treatment failure: more than five emetic episodes in 24hrs, administration of more than two doses of rescue drugs per day. Results (per outcome) **mean (9%%CI) emetic episodes per day** • *Granisetron vs ondansetron:* 0.73 (95%CI 0.55-1.91) vs 0.86 (95%CI 0.67-1.05), p = 0.32 o *Age <18 yrs.*: 0.54 (95%CI 0.27-0.81) vs 0.87 (95%CI 0.63-1.11), p = 0.08 o *age ≥ 18 yrs.:* 0.80 (95%CI 0.57-1.03) vs 0.86 (95%CI 0.63-1.09), p = 0.71 • *Female vs Male:* 0.97 (95%CI 0.63-1.30) vs 0.69 (95%CI 0.52-0.86), p = 0.08 • *Age <18 yrs. vs age ≥ 18 yrs.:* 0.82 (95%CI 0.47-1.17) vs 0.88 (95%CI 0.59-1.16), p = 0.71 • *TBI vs Chemotherapy alone:* 0.73 (95%CI 0.73 (0.56-0.89) vs 1.06 (95% CI 0.77-1.34), p = 0.04 **Nausea score, mean (9%%CI)** • *Granisetron vs ondansetron:* 1.17 (95%CI 1.00-1.34) vs 1.29 (95%CI 1.12-1.45), p = 0.32 o *Age <18 yrs.*: 0.82 (95%CI 0.55-1.09) vs 1.14 (95%CI 0.90-1.38), p = 0.09	Strengths: In addition to the randomization between granisetron and ondansetron a stratification was performed based on age, Limitations: **Risk of bias** A. Selection bias: Unclear Reason: The study was designed as a double-blind, randomized trial, in which patients received either granisetron or ondansetron 30 minutes before initiation of the ablative regimen. Allocation concealment was not reported. B. Attrition bias Low risk Reason: Outcome was assessed for 100% of the population in each treatment arm. C. Performance bias Low risk Reason: The study was designed in a double-blind fashion D. Detection bias Unclear Reason: Blinding of outcome assessors was unclear.

		• *Patients < 18 yrs.:* 10 mg/m^2/day • *Patients ≥ 18 yr:*10mg/day For breakthrough nausea and vomiting additional medications were available on request, lorazepam, prochlorperazine or promethazine.	○ *age ≥ 18 yr1.29* (95%CI 1.09-1.49) vs 0.1.36 (95%CI 1.15-1.56), p = 0.65 • *Female vs Male:* 1.63 (95%CI 1.34-1.92) vs 01.31 (95%CI 1.06-1.26, p <0.01 • *Age <18 yrs. vs age ≥ 18 yrs.:* 1.33 (95%CI 1.03-1.63)) vs 1.6 (95%CI 1.36-1.84), p = 0.05 • *TBI vs Chemotherapy alone:* 1.14 (95%CI 1.00-1.29)) vs 1.33 (95% CI 1.07-1.60), p = 0.2 **Control of emesis (granisetron vs. ondansetron)** Percentage of days with complete control of emesis: 63% vs 61%, p = 0.68 Percentage of days with major control of emesis: 27% vs 27% Percentage of days with minor control of emesis: 7% vs 8% Percentage of days with treatment failure: 3% vs 4% **Safety** Both drugs were well tolerated. In one case granisetron was discontinued because of headaches.	

Pharmacological treatment of nausea and vomiting - Ondansetron vs metoclopramide				
Kóseoglu V et al. Comparison of the efficacy and side-effects of ondansetron and metoclopramide-diphenhydramine administered to control nausea and vomiting in children treated with antineoplastic chemotherapy: a prospective randomized study. Eur J Pediatr 1998 Oct;157(10):806-10				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: A prospective randomized study Setting: 1 centre, turkey Duration: 24 hour follow-up, every day until 5 days after chemotherapy. Study years: Not reported Protocol published in register: Not reported	Number and type of participants: A total of 15 patients diagnosed with a malignant disease excluding CNS involvement, gastro-intestinal tract obstruction or any accompanying disease were evaluated. A total of 64 chemotherapy courses were given to the patients. Age: Mean age: 7.6 yrs. Sex: M: 9 (60%), F: 6 (40%) Other There was differentiated between therapies that included cisplatin. • Ondansetron: 9 chemotherapy courses with cisplatin, 23 chemotherapy courses non- cisplatin • Metoclopramide: 9 chemotherapy courses with cisplatin, 23 chemotherapy courses non-cisplatin	Ondansetron Ondansetron was administered at a dose of 5mg/m^2 intravenously (maximum 8mg) 15 min before the chemotherapy and was continued orally (4mg/m2 per day) twice a day for 5 days. Metoclopramide Metoclopramide (1mg/kg) was administered intravenously 30 min before the chemotherapy and continued orally (0.14 mg/kg per day) four times a day for 5 days. To prevent side effects, diphenhydramine (5mg/kg per day) was given orally for 5 days.	Outcome definitions: **Vomiting attack** A rejection or refusal of the content of the stomach. A vomiting attack recurring 1 min after the previous one, was accepted as a separate attack. **Vomiting efficacy** • Complete efficacy: No vomiting attack in the 24h follow up period, it was accepted as a complete efficacy. • Major efficacy: 1-2 vomiting attacks • Minor efficacy: 3-5 vomiting attacks • No efficacy: ≥ 5 vomiting attacks **Nausea** No nausea, Mild nausea: without interfering with daily activities Moderate nausea: moderately interfering with daily activities Serious nausea: seriously interfering with daily activities. Results (per outcome) **Vomiting attack efficacy first 24h (ondansetron vs metoclopramide)** *Cisplatin* N with complete efficacy: 5 vs. 1, p < 0.05 N with major efficacy: 3 vs 1, p = ns N with minor efficacy: 1 vs 3, p = ns N with no efficacy: 0 vs 4, p = ns *Non-cisplatin* N with complete efficacy: 21 vs. 17, p < 0.05 N with major efficacy: 2 vs 1, p = ns N with minor efficacy: 0 vs 1, p = ns N with no efficacy: 0 vs 4, p = ns **Vomiting attack in 2nd -5th day after chemotherapy (ondansetron vs metoclopramide** N of courses in which there was a vomiting attack: *Cisplatin*: 4 vs 8, p <0.05 *Non-cisplatin:* 2 vs 6, p = ns **Nausea** *Cisplatin* N with no nausea: 7 vs. 0, p < 0.05 N with mild nausea: 1 vs 2, p = ns N with moderate nausea: 1 vs 2, p = ns	Strengths: Limitations: The study did not elaborate on the process of assigning patients to the ondansetron/metoclopramide group. It is expected that patients received a different medication each chemotherapy course, however this is not reported in the paper. Small study population **Risk of bias** A. Selection bias: High risk Reason: The study did not report on how randomization took place. B. Attrition bias: Low risk Reason: Outcome was assessed for all patients and chemotherapy courses. C. Performance bias High risk Reason: Blinding from knowledge of which intervention was received was not reported in the study D. Detection bias Unclear Reason: Blinding of outcome assessors was not reported.

			N with serious nausea: 0 vs 5, p = ns *Non-cisplatin* N with no nausea: 22 vs. 19, p < 0.05 N with mild nausea: 1 vs 1, p = ns N with moderate nausea: 0 vs 2, p = ns N with serious nausea: 5 vs 1, p = ns **Safety** Side effects metoclopramide: extrapyramidal symptoms Side effects ondansetron: headache	

Pharmacological treatment of nausea and vomiting -Tropisetron vs Granisetron				
Aksoylar S et al. Comparison of tropisetron and granisetron in the control of nausea and vomiting in children receiving combined cancer chemotherapy. Pediatr Hematol Oncol 2001 Sep;18(6):397-406.				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: Prospective randomised study Setting: 1 centre, turkey Duration: 24 hour follow-up after chemotherapy Study years: Not reported Protocol published in register:	Number and type of participants: A total of 51 children receiving highly emetogenic chemotherapy were studied in 133 chemotherapy cycles. Emetogenic chemotherapy cycles were randomised (1:1) to receive either tropisetron or granisetron as an antiemetic agent. Age: Median: 6.5, Range: 1-17. 12 (23.5%)children were < 2 yrs. old Sex: M: 32 (62.7%), F: 19 (37.3%) Diagnosis: Lymphoblastic leukaemia: 43% Lymphoma: 18% Rhabdomyosarcoma: 8% Acute myeloblastic leukaemia: 8% Neuroblastoma: 6% PNET and Ewing sarcoma: 6% Wilm's tumour: 4% Germ cell therapy: 4% Other: 3% Chemotherapy: Highly emetogenic chemotherapy (grade 3): 84/133 chemotherapy cycles (63%) Very highly emetogenic chemotherapy (grade 4): 49/133 chemotherapy cycles (37%) There was no significant difference of patient characteristics between tropisetron/granisetron groups.	Tropisetron: A single daily dose of tropisetron of 0.2 mg/kg/day (max 5 mg) was given intravenously in saline, 30 min before cytotoxic drug administration. Tropisetron was administered each day the children received chemotherapy. No concomitant antiemetic therapy was given to the patients. Granisetron A single daily dose of granisetron 40 µg/kg/day (max 3 mg) was given intravenously in saline, 30 min before cytotoxic drug administration. Granisetron was administered each day the children received chemotherapy. No concomitant antiemetic therapy was given to the patients.	Outcome definitions: **Vomiting efficacy** A single episode of vomiting was defined as 1 event. 1 vomit is 1 emetic episode Complete control: No emetic episode within 24hr Partial control: 1-4 episodes within 24hr Failure: > 4 emetic episodes within 24 hr **Nausea** Nausea continuing for 1 hour was defined as a single episode of nausea, regardless of severity. Complete control: No episode of nausea within 24 hr Partial control: 1-4 episodes of nausea within 24hr Failure: > 4 episodes of nausea **Overall response** Complete control: no vomiting, no nausea Partial control: 1-4 emetic episodes and/or 1-4 episodes of nausea Failure >4 emetic episodes and/or >4 episodes of nausea Results (per outcome) **Acute Nausea and vomiting** *Acute vomiting (tropisetron vs granisetron)* Complete control: 74% vs 88%, p = 0.04 Partial control: 20% vs 12% Failure: 6% vs 0% *Acute nausea (tropisetron vs granisetron)* Complete control: 56% vs 82%, p = 0.002 Partial control: 38% vs 18% Failure: 6% vs 0% **Overall response on the worst day (tropisetron vs granisetron)** Complete control: 29% vs 55%, p = 0.007 Partial control: 62% vs 40% Failure: 9% vs 5% *Grade 3 chemotherapy (tropisetron vs granisetron)* Complete control: 28% vs 67%, p = 0.002 Partial control: 64% vs 29% Failure: 8% vs 4%	Strengths: It was studied whether the efficacy of both tropisetron and granisetron was different depending on the emogenicity of the chemotherapy and body weight. Limitations: Definition of 'worst day chemotherapy' was not given. **Risk of bias** A. Selection bias: Unclear Reason: Patients receiving highly and very highly emetogenic chemotherapy cycles were randomised (1:1) to reive either tropisetron or granisetron as an antiemetic agent. Allocation concealment was not reported B. Attrition bias: Low risk Reason: Outcome was assessed for all patients and chemotherapy courses C. Performance bias High risk Reason: Blinding from knowledge of which intervention was received was not reported in the study

			Grade 4 chemotherapy (tropisetron vs granisetron) Complete control: 30% vs 32%, p = 0.7 Partial control: 60% vs 64% Failure: 11% vs 4% *Body weight < 25 ((tropisetron vs granisetron)* Complete control: 45% vs 63%, p = 0.14 Partial control: 48% vs 37% Failure: 7% vs 0% *Body weight > 25 (tropisetron vs granisetron)* Complete control: 18% vs 47%, p = 0.02 Partial control: 71% vs 44% Failure: 11% vs 9% **Adverse events** Adverse events were reported in 9 (6%) of the chemotherapy cycles (p = NS) - Headache (n = 6) - Constipation (n=2)	D. Detection bias Unclear Reason: Blinding of outcome assessors was unclear

Pharmacological treatment of nausea and vomiting - Aprepipant + Dexamethasone + ondansetron vs Dexamethasone + ondansetron				
Gore L et al. Aprepitant in adolescent patients for prevention of chemotherapy-induced nausea and vomiting: a randomized, double-blind, placebo-controlled study of efficacy and tolerability. Pediatr Blood Cancer 2009;52:242–247				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: Randomized, double-blind, placebo-controlled study Setting: 12 sites, USA Duration: Outcomes were measured for 5 days after first chemotherapy infusion. 6-8 days patients were followed up in a clinic visit. Study years: April 2004 – September 2004 Protocol published in register:	Number and type of participants: Total of 46 children with cancer • Intervention group: 28 + 4 additional patients who received open-label aprepitant. • Control group: 18 Age: • Intervention group: Mean (SD): 15 (1.73), Range: 12-19 yr. • Control group: Mean (SD): 15 (1.91), Range: 11-17 Sex: • Intervention group: M: 24 (75%), F: 8 (25%) • Control group: M: 12 (66.6%), F: 6 (33.3%) Most common diagnosis: • Intervention group: Bone sarcoma: 53.1% • Control group: Bone sarcoma 83.3% There was no significant difference of patient characteristics between intervention/control groups.	Intervention - Aprepipant + Dexamethasone + ondansetron Day 1: Aprepitant 125 mg was administered 1 hr before chemotherapy. Dexamethasone 8mg and ondansetron (0.15mg/kg x 3 doses) started 30 minutes before chemotherapy Day 2: Dexamethasone 4mg, ondansetron 0.15 mg/kg x 3 doses), aprepitant 80mg Day 3: Dexamethasone 4mg, aprepitant 80mg Day 4: dexamethasone 4mg Control – Dexamethasone + ondansetron Day 1: Placebo was administered 1 hr before chemotherapy. Dexamethasone 16 mg and ondansetron (0.15mg/kg x 3 doses) started 30 minutes before chemotherapy Day 2: Dexamethasone 8mg, ondansetron 0.15 mg/kg x 3 doses) Day 3: Dexamethasone 8mg Day 4: dexamethasone 8mg	Outcome definitions: **Safety and Tolerability** Adverse events **Efficacy:** Complete response: no vomiting and no use of rescue therapy **Pharmacokinetics** Results (per outcome): **Adverse events (intervention vs control)** *>1 clinical adverse event:* 27 (84.4%) vs 13 (172.2%) *Drug related clinical adverse events (i.e. hiccups):* 7 (21.9%) vs 1 (5.6%) *Serious clinical adverse events (i.e. neutropenia):* 10 (31.3%) vs 3 (16.7%) *>1 laboratory adverse event (neutropenia, hypokalaemia, leukopenia):* 6 (18.8%) vs 6 (33.3%) *No deaths, no discontinuation due to adverse events, no serious drug-related adverse events, no drug-related laboratory adverse events* **Vomiting efficacy (intervention (n=28) vs control (n=18))** *Proportion of patients with complete response* Acute (0-24 hr): 60.7% (95%CI 40.6% - 78.5%) vs 38.9% (95%CI 17.3% - 64.3%) Delayed (24-120 hr): 35.7% (95%CI 18.6% - 55.9%) vs 5.6% (95%CI 0.1% - 27.3%) Overall phase (0-120 hr): 28.6% (95%CI 13.2% - 48.7%) vs 5.6% (95%CI 0.1% - 27.3%) *Proportion of patients with no vomiting* Acute (0-24 hr): 64.3% (95%CI 44.1% - 81.4%) vs 44.4% (95%CI 21.5 % - 69.2%) Delayed (24-120 hr): 39.3% (95%CI 21.5% - 59.4%) vs 5.6% (95%CI 0.1% - 27.3%) Overall phase (0-120 hr): 32.1% (95%CI 15.9% - 52.4%) vs 5.6% (95%CI 0.1% - 27.3%) *Proportion of patients with no use of rescue therapy* Acute (0-24 hr): 71.4% (95%CI 51.3% - 86.8%) vs 61.1 (95%CI 35.7% - 82.7%) Delayed (24-120 hr): 50.0% (95%CI 30.6% - 69.4%) vs 27.8% (95%CI 9.7 % - 53.53%) Overall phase (0-120 hr):	Strengths: Limitations: Lack of statistical significance due to a small sample size. **Risk of bias** A. Selection bias: Unclear Reason: Eligible patients were randomized 2:1 to receive either aprepitant triple therapy or the placebo controlled regimen B. Attrition bias: Low risk Reason: Outcome was assessed for all patients and chemotherapy courses C. Performance bias Low risk Reason: In 4 (intervention group) of the 50 patients, patients and personnel were not blinded. However, in the analysis on vomiting/nausea efficacy these patients were not included. For the rest of the study population both patients and personnel were blinded. D. Detection bias Unclear Reason: Blinding of outcome assessors was unclear

			42.9% (95%CI 24.9% - 62.8%) vs 22.2% (95%CI 6.4% - 17.6%) No nausea (Overall phase) 44.4% (95%CI 25.5% - 64.7%) vs 17.6% (95%CI 3.8% - 43.46%) Although overlap of the exact 95% Cis was noted for all CR endpoints, response rates were numerically higher for the intervention group. **Pharmacokinetics** Pharmacokinetic parameters in 17 adolescent cancer patients were compared with data from 12 healthy adult subjects from a previous study of the same 3-day aprepitant dosing regimen as the current study. Geometric mean ratio (Adolescent patients/healthy adults) AUC0-24hr (ng/hr/ml): 0.81 (95%CI 0.63-1.06) CMax (ng/ml): 0.78 (95%CI 0.61-1.00) C24 hr (ng/ml): 0.83 (95%CI 0.57-1.20) C48 hr (ng/ml): 0.67 (95%CI 0.38-1.19) C72hr (ng/ml): 0.61 (95%CI 0.33-1.13) The 90% CIs for the GMRs (adolescent/adult) forAUC0–24 h, Cmax, C24 h, C48 h, and C72 h containe1.0, which suggested that age did not affect these parameters	

Pharmacological treatment of nausea and vomiting - Midazolam vs Dexamethasone vs Midazolam + dexamethasone vs placebo				
Riad, W. et al. Effect of midazolam, dexamethasone and their combination on the prevention of nausea and vomiting following strabismus repair in children. European Journal of Anaesthesiology 2007; 24: 697-701				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: Prospective randomized and double-blind study Setting: Single centre, Saudi Arabia Duration: Episodes of nausea, and retching and vomiting were recorded during the first 24h after surgery Study years: 2006/2007, no exact data mentioned Protocol published in register: Not reported	Number and type of participants: Total of 100 children who were scheduled to undergo elective strabismus surgery • Intervention group 1: 25 children • Intervention group 2: 25 children • Intervention group 3: 25 children • Control group: 25 children Age: • Intervention group 1: Mean/SD: 7.2 (2.4), Range: 4-12 yr. • Intervention group 2: Mean/SD: 8.3 (3.6), Range: 4-12 yr. • Intervention group 3: Mean/SD: 8.3 (3.9), Range: 4-12 yr. • Control group: • Mean/SD: 6.7 (2.9), Range: 4-12 yr. Sex: • Intervention group 1: M: 15 (60%), F: 10 (40%) • Intervention group 2: M: 12 (48%), F: 13 (52%) • Intervention group 3: M 11 (44%). F: 14 (56%) • Control group: M 14 (56%), F: 11 (44%) There was no statistically significant difference between groups with regard to age, weight, sex, duration of surgery, n of operated muscles and occurrence of oculocardiac reflex. Other: Recovery time in minutes (SD) • Intervention group 1: 17 minutes (1.7) • Intervention group 2: 24 minutes (1.9) • Intervention group 3: 23 minutes (2.5) • Control group: 15 minutes (2.1) Recovery time was significantly delayed for intervention group 2 and 3.	Type of intervention: • Intervention group 1: midazolam 50µgkg^{-1} • Intervention group 2: dexamethasone 0.5mgkg^{-1} (maximum dose, 8mg) • Intervention group 3: combination of midazolam 50µgkg^{-1} and dexamethasone 0.5mgkg^{-1} (maximum dose, 8mg) Type of control: Placebo	Outcome definitions: • Post-operative nausea: subjective feeling that was reported by the patients Post-operative vomiting: forceful expulsion of liquid or solid gastric contents Results (per outcome): *Incidence post-operative nausea* • Group 1 – midazolam: N = 3 (12%), p < 0.001 compared with placebo • Group 2 – dexamethasone: N=8 (32%), p < 0.01 compared with placebo • Group 3 – Midazolam + dexamethasone N = 0 (0%), p<0.001 compared with placebo • Placebo: N=12 (48%) *Incidence post-operative vomiting* • Group 1 – midazolam: N = 0 (0%), p < 0.001 compared with placebo, p < 0.05 compared with dexamethasone • Group 2 – dexamethasone: N = 8 (32%), p < 0.001 compared with placebo • Group 3 – Midazolam + dexamethasone N = 0 (0%), p<0.001 compared with placebo, p < 0.05 compared with dexamethasone • Placebo: N=13 (52%)	Strengths: Double-blinded, randomized study Limitations: Limited information on effect the interventions, 95% confidence intervals not reported. Difference between midazolam and midazolam/dexamethasone is unclear. **Risk of bias** A. Selection bias: Low risk Reason: patients were randomly divided into one of four groups. Randomization was performed using a table of random numbers and sealed envelopes. B. Attrition bias: Low risk Reason: All patients were followed-up 24 hours after surgery C. Performance bias Low risk Reason: the children and all personnel involved with patient care were unaware of the content of the syringes. D. Detection bias Unclear Reason: unclear if outcome assessors were blinded from knowledge of which intervention was received

4 Samenvatting en gradering van bewijs

4.1 Niet-medicamenteuze behandeling van Misselijkheid en Braken

4.1.1 Geïncludeerde uitkomstmaten

Included outcomes
Supplemental anti-emetic medication usage
Nausea and vomiting

4.1.2 Zelfhypnose vs standaard behandeling

Self-hypnosis vs standard treatment				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Supplemental anti-emetic medication usage, supplemental use in control group was calculated by subtracting standard dose from total anti-emetic medication usage				
Jacknow, 1994	1) Newly diagnosed children with cancer aged 6 to 18 yrs.	20 (10 vs. 10)	Self-hypnosis was thought in two/three sessions of 45 minutes with a therapist + anti-emetic use if necessary vs informal conversations with the therapist during two/three sessions of 45 minutes + standard anti-emetic regimen (i.e. thiethylperazine/chloropromazine; diphenhydramine; ondansetron)	**Supplemental anti-emetic medication usage in chemotherapy course 1 (intervention vs control)** Mean (SD): 0.17 (0.33) vs 1.01 (1.33), p <0.04 **Supplemental anti-emetic medication usage in chemotherapy course 2 (intervention vs control)** Mean (SD): 0.34 (0.93) vs 2.10 (2.66), p<0.02
Grade assessment				
Study design:	+4	1 Randomized Controlled Trial		
Study limitations	-2	Serious limitations - Selection bias: Unclear; Attrition bias: low; Performance bias: high; Detection bias: unclear		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	-2	Important imprecision due to small sample size. Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence that self-hypnosis decreases supplemental anti-emetic medication usage within 24h in children with cancer receiving chemotherapy as compared to standard treatment with anti-emetics.**		

Self-hypnosis vs standard treatment				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Nausea and vomiting, combined score of: (1) the severity of nausea visual analogue scale, score ranging from 0 (smiling face) to 5 (frowning face), higher score indicating higher severity of nausea (2) frequency of vomiting and retching, score ranging from 1 (none) to 9 (all the time), higher score indicating higher frequency of vomiting.				
Jacknow, 1994	Newly diagnosed children with cancer aged 6 to 18 yrs.	20 (10 vs. 10)	1Self-hypnosis was thought in two/three sessions of 45 minutes with a therapist + anti-emetic use if necessary vs informal conversations with the therapist during two/three sessions of 45 minutes + standard anti-emetic regimen (i.e. thiethylperazine/chloropromazine; diphenhydramine; ondansetron)	**Nausea and vomiting in chemotherapy course 1 (intervention vs control)** Mean (SD): 1.79 (1.77) vs 3.21 (2.01), p = NS **Nausea and vomiting in chemotherapy course 2 (intervention vs control)** Mean (SD): 1.82 (2.01) vs 3.18 (1.81), p = NS

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-2	Serious limitations - Selection bias: Unclear; Attrition bias: low; Performance bias: high; Detection bias: unclear
Consistency:	0	No important inconsistency. Only 1 study performed
Directness:	0	Results are direct. Outcomes are generalizable.
Precision:	-2	Important imprecision due to small sample size. Only 1 study performed
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence that there is no significant effect of self-hypnosis on nausea and vomiting within 24h in children with cancer receiving chemotherapy as compared to standard treatment with anti-emetics.**

Self-hypnosis vs standard treatment				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Anticipatory Nausea, combined index of (1) severity of nausea, (2) frequency and (3) time of onset before chemotherapy. A constant of 2 was added to eliminate negative numbers, higher score indicating higher frequency/severity of nausea. **Anticipatory Vomiting,** number of patients who experienced anticipatory vomiting				
1) Jacknow, 1994	1) Newly diagnosed children with cancer aged 6 to 18 yrs.	1) 20 (10 vs 10)	1) Self-hypnosis was thought in two/three sessions of 45 minutes with a therapist + anti-emetic use if necessary vs informal conversations with the therapist during two/three sessions of 45 minutes + standard anti-emetic regimen (i.e. thiethylperazine/chloropromazine; diphenhydramine; ondansetron)	**Anticipatory nausea 1 to 2 months post diagnosis (intervention vs control):** Mean (SD): 0.82 (2.60) vs 3.17 (2.60), p < 0.013 **Anticipatory nausea 4 to 6 months post diagnosis (intervention vs. control***):* Mean (SD): 1.69 (3.64) vs 2.54 (2.47), p = NS

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-2	Serious limitations - Selection bias: Unclear; Attrition bias: low; Performance bias: high; Detection bias: unclear
Consistency:	0	No important inconsistency. Only 1 study performed
Directness:	0	Results are direct. Outcomes are generalizable.
Precision:	-2	Important imprecision due to small sample size. Only 1 study performed
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		**⊕⊕⊖⊖ LOW**
Conclusion:		**There is very low quality of evidence that self-hypnosis decreases anticipatory nausea 1 to 2 months post diagnosis in children with cancer receiving chemotherapy as compared to standard treatment with anti-emetics. However, no significant effect of anticipatory nausea was found 4 to 6 months post diagnosis.**

4.2 Medicamenteuze behandeling van Misselijkheid en Braken

4.2.1 Geïncludeerde uitkomstmaten

Included outcomes
Occurrence of emetic episodes in 24h
Occurrence of severity of Nausea in 24h
Safety

4.2.2 Hoge dosis ondansetron of lage dosis ondansetron vs placebo

high dose ondansetron or low dose ondansetron vs placebo				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Emetic episodes in 24h				
1) Parker, 2001	1) Newly diagnosed children with cancer receiving chemotherapy (lymphoid or nonlymphoid leukaemia) aged 18 months to 15 yrs.	1) Total patients: 26 (each patient acted as their own control) Total intrathecal treatments: 146 (5.6 per patient)	1) Low dose ondansetron at 0.15 mg/kg by a 15-minute intravenous infusion vs high dose ondansetron at 0.45 mg/kg by a 14-minute intravenous infusion vs placebo of normal saline. *Each patient acted as his/her control; treatments (low dose ondansetron, high dose ondansetron, and placebo) were administered in random order for up to 6 intrathecal treatments.*	Placebo vs Low dose ondansetron Treatments with vomiting episodes: 62.7% vs 27.7%, p<0.001, RR = 2.3 Treatments with ≥ 2 vomiting episodes: 43.1% vs 12.8% p<0.001, RR = 3.4 Treatments with ≥ 4 vomiting episodes: 25.5% vs 4.3%, p<0.005, RR = 5.8 Placebo vs High dose ondansetron Treatments with vomiting episodes: 62.7% vs 14.6%, p<0.001, RR =4.3 Treatments with ≥ 2 vomiting episodes: 43.1% vs 6.3%, p<0.001, RR = 6.8 Treatments with ≥ 4 vomiting episodes: 25.5% vs 0%, p<0.001 Placebo vs Any dose ondansetron Treatments with vomiting episodes: 62.7% vs 21.1%, p<0.001, RR = 3.0, reduction of RR (after pre-administrating ondansetron) 65.7% Treatments with ≥ 2 vomiting episodes: 43.1% vs9.1%, p<0.001, RR = 4.5, reduction of RR (after pre-administrating ondansetron) 77.5% Treatments with ≥ 4 vomiting episodes: 25.5% vs 2.1%, p<0.001, RR = 12.1, reduction of RR (after pre-administrating ondansetron) 91.6%
Grade assessment				
Study design:	+4	1 Randomized Controlled Trial		
Study limitations	-1	Some limitations - Selection bias: unclear; Attrition bias: low; Performance bias: low; Detection bias: unclear		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	-1	No important imprecision. Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	+1	Large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊕⊕⊖ **MODERATE**		
Conclusion:		**There is moderate quality evidence that treatment with ondansetron (low and high dose) decreases the incidence of emetic episodes within 24h in children with cancer receiving chemotherapy as compared to placebo.**		

4.2.3 *Hoge dosis ondansetron vs lage dosis ondansetron*

high dose ondansetron vs low dose ondansetron				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Emetic episodes in 24h				
1) Brock, 1996	1) Newly diagnosed children with cancer receiving chemotherapy aged 2 to 16	1) 158 (79 vs 79) • Cisplatin: 31 (14 vs 17) • Ifosfamide: 28 (14 vs 14)	1) Low dose ondansetron, 5mg/m^2 (maximum 8 mg/m^2) vs high dose ondansetron, 10mg/m^2 (maximum of 16mg/m^2)	**1) Low dose vs high dose ondansetron** Patients with ≤ 2 emetic episodes: 71% vs 72%, p = NS; Patients receiving cisplatin chemotherapy with ≤ 2 emetic episodes: 50% vs 53%, p = NS Patients receiving ifosfamide with ≤ 2 emetic episodes: 79% vs 64%, p = NS
2) Parker, 2001	2) Newly diagnosed children with cancer receiving chemotherapy (lymphoid or nonlymphoid leukaemia) aged 18 months to 15 yrs.	2) Total patients: 26 (each patient acted as their own control) Total intrathecal treatments: 146 (5.6 per patient)	2) Low dose ondansetron at 0.15 mg/kg by a 15-minute intravenous infusion vs high dose ondansetron at 0.45 mg/kg by a 14-minute intravenous infusion *Each patient acted as his/her control; treatments (low dose ondansetron, high dose ondansetron, and placebo) were administered in random order for up to 6 intrathecal treatments.*	**2) Low dose vs. high dose ondansetron** Treatments with vomiting episodes: 27.7% vs 14.6%, p<0.1 Treatments with ≥ 2 vomiting episodes: 12.8% vs 6.3%, p<0.3 Treatments with ≥ 4 vomiting episodes: 4.3% vs 0.0% vs, p<0.1

Grade assessment		
Study design:	+4	2 Randomized Controlled Trials
Study limitations	-1	Some limitations - Selection bias: low in 1/2, unclear in 1/2; Attrition bias: high in 1/2 and low in 1/2; Performance bias: low in 2/2; Detection bias: unclear in 2/2
Consistency:	0	No important inconsistency.
Directness:	0	Results are direct. Outcomes are generalizable.
Precision:	0	No important imprecision, large sample size.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		**⊕⊕⊕⊖ MODERATE**
Conclusion:		**There is moderate quality of evidence that there is no significant effect of treatment with high dose ondansetron on the incidence of emetic episodes within 24h in children with cancer receiving chemotherapy as compared to treatment with low dose ondansetron.**

high dose ondansetron vs low dose ondansetron				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Severity of Nausea in 24h: None: not feeling sick at all; Mild: feeling sick; Severe: feeling very sick				
1) Brock, 1996	1) Newly diagnosed children with cancer receiving chemotherapy aged 2 to 16	1) 158 (79 vs 79) • Cisplatin: 31 (14 vs 17) • Ifosfamide: 28 (14 vs 14)	1) Low dose ondansetron, 5mg/m^2 (maximum 8 mg/m^2) vs high dose ondansetron, 10mg/m^2 (maximum of 16mg/m^2)	**Low dose vs high dose ondansetron** Patients with no or mild nausea: 90% vs 86%, P = NS Patients receiving cisplatin chemotherapy with no or mild nausea: 100% vs 86%, p = NS Patients receiving ifosfamide with no or mild nausea: 78% vs 77%, p = NS
Grade assessment				
Study design:	+4	1 Randomized Controlled Trial		
Study limitations	-2	Serious limitations - Selection bias: Unclear; Attrition bias: low; Performance bias: high; Detection bias: unclear		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	-1	No important imprecision due to large sample size. Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence that there is no significant effect of treatment with high dose ondansetron on nausea severity within 24h in children with cancer receiving chemotherapy as compared to treatment with low dose ondansetron.**		

4.2.4 Hoge dosis ondansetron + dexamethason vs lage dosis ondansetron + dexamethason

High dose ondansetron + dexamethasone vs low dose ondansetron + dexamethasone				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Emetic episodes in 24h Complete response: No emetic episode; Major response: 1-2 emetic episodes; Minor response: 3-5 emetic episodes; treatment failure: more than 5 emetic episodes				
1) Brock, 1996	1) Newly diagnosed children with cancer receiving chemotherapy aged 2 to 16	1) Treatment failures 34 (15 vs 19)	1) Treatment failures: Low dose ondansetron, 5mg/m^2 (maximum 8 mg/m^2) + 10mg/m^2 dexamethasone vs vs high dose ondansetron, 10mg/m^2 (maximum of 16mg/m^2) + 10mg/m^2 dexamethasone	**Low dose vs high dose ondansetron** Patients that were initially treatment failures[1] (≥ 5 emetic episodes) with ≤ 2 emetic episodes: 9 (60%) vs 15 (84%), p-value unknown

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-1	Some limitations - Selection bias: low; Attrition bias: high; Performance bias: low; Detection bias: unclear
Consistency:	0	No important inconsistency. Only 1 study performed
Directness:	0	Results are direct. Outcomes are generalizable.
Precision:	-2	Important imprecision due to small sample size. Only 1 study performed
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		**⊕⊖⊖⊖ VERY LOW**
Conclusion:		**There is very low quality evidence that treatment with high dose ondansetron and dexamethasone decreases the incidence of emetic episodes within 24h in children with cancer receiving chemotherapy that initially were treatment failures (>5 emetic episodes during chemotherapy course) as compared to treatment with low dose ondansetron and dexamethasone (unclear if significant).**

[1] Complete response: No emetic episode; Major response: 1-2 emetic episodes; Minor response: 3-5 emetic episodes; treatment failure: more than 5 emetic episodes

High dose ondansetron + dexamethasone vs low dose ondansetron + dexamethasone				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Severity of Nausea in 24h, None: not feeling sick at all; Mild: feeling sick; Severe: feeling very sick				
1) Brock, 1996	1) Newly diagnosed children with cancer receiving chemotherapy aged 2 to 16	1) Treatment failures 34 (15 vs 19)	1) Treatment failures: Low dose ondansetron, 5mg/m^2 (maximum 8 mg/m^2) + 10mg/m^2 dexamethasone vs vs high dose ondansetron, 10mg/m^2 (maximum of 16mg/m^2) + 10mg/m^2 dexamethasone	**Low dose vs high dose ondansetron** Patients that were initially treatment failures[1] (> 5 emetic episodes) with no or mild nausea, 60% vs 84%, p = unknown

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-1	Some - Selection bias: low; Attrition bias: high; Performance bias: low; Detection bias: unclear
Consistency:	0	No important inconsistency. Only 1 study performed
Directness:	0	Results are direct. Outcomes are generalizable.
Precision:	-2	Important imprecision due to small sample size. Only 1 study performed
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality evidence that treatment with high dose ondansetron and dexamethasone decreases nausea severity within 24h in children with cancer receiving chemotherapy that initially were treatment failures (>5 emetic episodes during chemotherapy course) as compared to treatment with low dose ondansetron and dexamethasone (unclear if significant).**

4.2.5 Ondansetron vs metoclopramide

Ondansetron vs Metoclopramide				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Emetic episodes in 24h				
1) Kóseoglu, 1998	1) Children diagnosed with malignant disease, mean age 7.6	1) Total patients: 15 (each patient received both treatments during different chemotherapy courses) Chemotherapy treatments 64 (32 vs 32), 4.3 courses per patient	Ondansetron, 5mg/m^2 (maximum 8mg) was administered intravenously 15 min before the chemotherapy and was continued orally (4mg/m2 per day) twice a day for 5 days vs Metoclopramide, 1mg/kg was administered intravenously 30 min before the chemotherapy and continued orally (0.14 mg/kg per day) four times a day for 5 days. To prevent side effects, diphenhydramine (5mg/kg per day) was given orally for 5 days *Each patient acted as their own control and received both treatments (ondansetron and metoclopramide) during different chemotherapy courses.*	**Ondansetron vs metoclopramide** *Cisplatin chemotherapy* Treatments with 0 emetic episodes: 5 vs. 1, p < 0.05 Treatments with 1-2 emetic episodes: 3 vs 1, p = ns Treatments with 3-5 emetic episodes: 1 vs 3, p = ns Treatments with ≥ 5 emetic episodes: 0 vs 4, p = ns *Non-cisplatin chemotherapy* Treatments with 0 emetic episodes 21 vs. 17, p < 0.05 Treatments with 1-2 emetic episodes: 2 vs 1, p = ns Treatments with 3-5 emetic episodes: 0 vs 1, p = ns Treatments with ≥ 5 emetic episodes: 0 vs 4, p = ns
Grade assessment				
Study design:	+4	1 Randomized Controlled Trial		
Study limitations	-2	Serious limitations - Selection bias: high; Attrition bias: low; Performance bias: high; Detection bias: unclear		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	-2	Important imprecision due to small sample size. Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence that treatment with ondansetron decreases the incidence of emetic episodes within 24h in children with cancer receiving chemotherapy as compared to treatment with metoclopramide.**		

Ondansetron vs Metoclopramide				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Severity of Nausea in 24h, No nausea; Mild nausea: without interfering daily activities; moderate nausea: Moderately interfering daily activities; serious nausea: seriously interfering daily activities				
1) Kóseoglu, 1998	1) Children diagnosed with malignant disease, mean age 7.6	1) Total patients: 15 (each patient received both treatments during different chemotherapy courses) Chemotherapy treatments 64 (32 vs 32), 4.3 courses per patient	Ondansetron, 5mg/m^2 (maximum 8mg) was administered intravenously 15 min before the chemotherapy and was continued orally (4mg/m2 per day) twice a day for 5 days vs Metoclopramide, 1mg/kg was administered intravenously 30 min before the chemotherapy and continued orally (0.14 mg/kg per day) four times a day for 5 days. To prevent side effects, diphenhydramine (5mg/kg per day) was given orally for 5 days *Each patient acted as their own control and received both treatments (ondansetron and metoclopramide) during different chemotherapy courses.*	**Ondansetron vs metoclopramide** *Cisplatin* Treatments with no nausea: 7 vs. 0, p < 0.05 Treatments with mild nausea: 1 vs 2, p = ns Treatments with moderate nausea: 1 vs 2, p = ns Treatments with serious nausea: 0 vs 5, p = ns *Non-cisplatin* Treatments with no nausea: 22 vs. 19, p < 0.05 Treatments with mild nausea: 1 vs 1, p = ns Treatments with moderate nausea: 0 vs 2, p = ns Treatments with serious nausea: 5 vs 1, p = ns

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-2	Serious limitations - Selection bias: high; Attrition bias: low; Performance bias: high; Detection bias: unclear
Consistency:	0	No important inconsistency. Only 1 study performed
Directness:	0	Results are direct. Outcomes are generalizable.
Precision:	-2	Important imprecision due to small sample size. Only 1 study performed
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		**⊕⊖⊖⊖ VERY LOW**
Conclusion:		**There is very low quality of evidence that treatment with ondansetron decreases the incidence of nausea severity within 24h in children with cancer receiving chemotherapy as compared to treatment with metoclopramide.**

Ondansetron vs. Metoclopramide				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Safety, adverse events				
1) Kóseoglu, 1998	1) Children diagnosed with malignant disease, mean age 7.6	1) Total patients: 15 (each patient received both treatments during different chemotherapy courses) Chemotherapy treatments 64 (32 vs 32), 4.3 courses per patient	Ondansetron, 5mg/m^2 (maximum 8mg) was administered intravenously 15 min before the chemotherapy and was continued orally (4mg/m2 per day) twice a day for 5 days vs Metoclopramide, 1mg/kg was administered intravenously 30 min before the chemotherapy and continued orally (0.14 mg/kg per day) four times a day for 5 days. To prevent side effects, diphenhydramine (5mg/kg per day) was given orally for 5 days *Each patient acted as their own control and received both treatments (ondansetron and metoclopramide) during different chemotherapy courses.*	Ondansetron vs metoclopramide Number chemotherapy cycles with adverse events • Headache: 3 vs 3, P = NS • Dizziness: 0 vs 1, p = NS • Extrapyramidal reactions 0 vs 5, p < 0.05
Grade assessment				
Study design:	+4	1 Randomized Controlled Trial		
Study limitations	-2	Serious limitations - Selection bias: high; Attrition bias: low; Performance bias: high; Detection bias: unclear		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	-2	Important imprecision due to small sample size. Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality evidence that treatment with ondansetron causes less extrapyramidal symptoms as adverse effects in children with cancer receiving chemotherapy as compared to metoclopramide.**		

4.2.6 Granisetron vs ondansetron

Granisetron vs Ondansetron				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Emetic episodes in 24h				
1) Orchard, 1994	1) Patients undergoing hematopoietic cell transplantations aged 2 – 65. *Only child outcomes are used*	1) Children aged <18 yrs.: 51 (23 vs 28)	1) A single intravenous granisetron dose followed by intravenous granisetron dose of 10µg/kg/dose per 12h vs an initial loading dose of ondansetron followed by continuous infusion of a 0.15 mg/kg load along with a 0.03mg/kg/h drip rounded to the nearest 0.1 mg	**Granisetron vs ondansetron** Mean number of Emetic episodes in 24h Mean (95%CI): 0.54 (95%CI 0.27-0.81) vs 0.87 (95%CI 0.63-1.11), p = 0.08

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-1	Some limitations - Selection bias: Unclear; Attrition bias: low; Performance bias: low; Detection bias: unclear
Consistency:	0	No important inconsistency. Only 1 study performed
Directness:	0	Results are direct. Outcomes are generalizable.
Precision:	-2	Important imprecision due to small sample size. Only 1 study performed
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		**⊕⊖⊖⊖ VERY LOW**
Conclusion:		**There is very low quality evidence that there is no significant effect of treatment with granisetron on the incidence of emetic episodes within 24h in children with cancer receiving chemotherapy as compared to treatment with ondansetron.**

Granisetron vs Ondansetron				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Severity of Nausea in 24h, Visual Analogue scale, score ranging from 0 to 5, higher score indicating more severe nausea				
1) Orchard, 1994	1) Patients undergoing hematopoietic cell transplantations aged 2 – 65. *Only child outcomes are used*	1) Children aged <18 yrs.: 51 (23 vs 28)	1) A single intravenous granisetron dose followed by intravenous granisetron dose of 10µg/kg/dose per 12h vs an initial loading dose of ondansetron followed by continuous infusion of a 0.15 mg/kg load along with a 0.03mg/kg/h drip rounded to the nearest 0.1 mg	**Granisetron vs ondansetron** Mean Nausea Score: Mean (95%CI): 0.82 (95%CI 0.55-1.09) vs 1.14 (95%CI 0.90-1.38), p = 0.09

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-1	Some limitations - Selection bias: Unclear; Attrition bias: low; Performance bias: low; Detection bias: unclear
Consistency:	0	No important inconsistency. Only 1 study performed
Directness:	0	Results are direct. Outcomes are generalizable.
Precision:	-2	Important imprecision due to small sample size. Only 1 study performed
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality evidence that there is no significant effect of treatment with granisetron on nausea severity within 24h in children with cancer receiving chemotherapy as compared to treatment with ondansetron.**

Granisetron vs Ondansetron				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Safety, adverse events and adverse effects				
1) Orchard, 1994	1) Patients undergoing hematopoietic cell transplantations aged 2 – 65. *Only child outcomes are used*	1) 187 children and adolescents aged 2-65 (90 vs 97)	1) A single intravenous granisetron dose followed by intravenous granisetron dose of 10µg/kg/dose per 12h vs an initial loading dose of ondansetron followed by continuous infusion of a 0.15 mg/kg load along with a 0.03mg/kg/h drip rounded to the nearest 0.1 mg	**Granisetron vs ondansetron** Safety (children and adults) 28 (13 with headache, 6 with diarrhoea, 4 with dizziness, 5 with joint pain) vs 19 (13 with headache, 2 with diarrhoea, 2 with dizziness, 1 with joint pain). In one case granisetron was discontinued because of headaches.

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-1	Some limitations - Selection bias: Unclear; Attrition bias: low; Performance bias: low; Detection bias: unclear
Consistency:	0	No important inconsistency. Only 1 study performed
Directness:	-1	Unclear if outcome is generalizable, as the outcome is measured in both children and adults.
Precision:	-2	Important imprecision due to small sample size. Only 1 study performed
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality evidence that treatment with granisetron or ondansetron causes adverse effects in children with cancer receiving chemotherapy. It is unclear there is a significant differences between both treatment groups. Most commonly reported adverse effect was headache.**

4.2.7 Granisetron vs tropisetron

Granisetron vs tropisetron				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Emetic episodes in 24h				
1) Aksoylar, 2001	1) Children receiving highly emetogenic chemotherapy, aged 1 to 17 yrs.	1) Total patients: 51 Chemotherapy treatments:133	A single daily dose of tropisetron of 0.2 mg/kg/day (max 5 mg) vs A single daily dose 24-h of granisetron 40 µg/kg/day (max 3 mg) *Chemotherapy cycles were randomized 1:1 to receive either tropisetron or granisetron as anti-emetic agent.*	**Tropisetron vs granisetron** Treatments with 0 emetic episodes: 74% vs 88%, p = 0.04 Treatments with 1-4 emetic episodes: 20% vs 12% Treatments with > 4 emetic episodes: 6% vs 0%

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-2	Serious limitations - Selection bias: Unclear; Attrition bias: low; Performance bias: high; Detection bias: unclear
Consistency:	0	No important inconsistency. Only 1 study performed
Directness:	0	Results are direct. Outcomes are generalizable.
Precision:	-1	No important imprecision. Only 1 study performed
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence that treatment with granisetron decreases the incidence of emetic episodes within 24h in children with cancer receiving chemotherapy as compared to treatment with tropisetron.**

Granisetron vs tropisetron				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Severity of nausea				
1) Aksoylar, 2001	1) Children receiving highly emetogenic chemotherapy, aged 1 to 17 yrs.	1) Total patients: 51 Chemotherapy treatments:133	A single daily dose of tropisetron of 0.2 mg/kg/day (max 5 mg) vs A single daily dose 24-h of granisetron 40 µg/kg/day (max 3 mg) *Chemotherapy cycles were randomized 1:1 to receive either tropisetron or granisetron as anti-emetic agent.*	**Tropisetron vs granisetron** Episodes of nausea (one episode was defined as nausea continuing for 1 hour) Percentage of treatments with no episodes of nausea: 56% vs 82%, p = 0.002 Percentage of treatments with 1-4 episodes of nausea: 38% vs 18% Percentage of treatments with > 4 episodes of nausea: 6% vs 0%
Grade assessment				
Study design:	+4	1 Randomized Controlled Trial		
Study limitations	-2	Serious limitations - Selection bias: Unclear; Attrition bias: low; Performance bias: high; Detection bias: unclear		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	-1	No important imprecision Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence that treatment with granisetron decreases nausea severity within 24h in children with cancer receiving chemotherapy as compared to treatment with tropisetron.**		

Granisetron vs tropisetron				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Safety, adverse events				
1) Aksoylar, 2001	1) Children receiving highly emetogenic chemotherapy, aged 1 to 17 yrs.	1) Total patients: 51 Chemotherapy treatments:133	A single daily dose of tropisetron of 0.2 mg/kg/day (max 5 mg) vs A single daily dose 24-h of granisetron 40 µg/kg/day (max 3 mg) *Chemotherapy cycles were randomized 1:1 to receive either tropisetron or granisetron as anti-emetic agent.*	**Tropisetron vs granisetron** Adverse events were reported in 9 (6%) of the chemotherapy cycles (p = NS) There were no differences in the tolerability of the two antiemetic therapy modalities (5% in tropisetron and 6% in granisetron group). Most common effect: Headache (n = 6); constipation (n=2)
Grade assessment				
Study design:	+4	1 Randomized Controlled Trial		
Study limitations	-2	Serious limitations - Selection bias: Unclear; Attrition bias: low; Performance bias: high; Detection bias: unclear		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	-1	No important imprecision Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality evidence that there was no significant effect of treatment with granisetron on adverse events in children with cancer receiving chemotherapy as compared to treatment with tropisetron. Most commonly reported adverse events were headache and constipation.**		

4.2.8 Aprepipant + Dexamethason + ondansetron vs Dexamethason + ondansetron

Aprepipant + Dexamethasone + ondansetron vs Dexamethasone + ondansetron				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Emetic episodes in 24h				
1) Gore, 2009	1) Children with cancer who received chemotherapy aged 11 to 19 yrs.	1) 50 (32 vs 18)	Aprepipant (125 mg) administered 1hr before chemotherapy. Dexamethasone(8mg) + ondansetron (0.15/mg/kg x 3 doses) was administered 30min before chemotherapy vs Placebo administered 1hr before chemotherapy. Dexamethasone(8mg) + ondansetron (0.15/mg/kg x 3 doses) was administered 30min before chemotherapy	**Aprepipant + Dexamethasone + ondansetron vs Dexamethasone + ondansetron** Patients with 0 emetic episodes: 64.3% (95%CI 44.1% - 81.4%) vs 44.4% (95%CI 21.5 % - 69.2%) (p-value not reported)
Grade assessment				
Study design:	+4	1 Randomized Controlled Trial		
Study limitations	-1	Some limitations - Selection bias: Unclear; Attrition bias: low; Performance bias: low; Detection bias: unclear		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	-2	Important imprecision due to small sample size. Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence that treatment with aprepipant, dexamethasone and ondansetron decreases the incidence of emetic episodes within 24h in children with cancer receiving chemotherapy as compared to treatment with dexamethasone and ondansetron (unclear if significant).**		

Aprepipant + Dexamethasone + ondansetron vs Dexamethasone + ondansetron				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Safety, adverse events				
1) Gore, 2009	1) Children with cancer who received chemotherapy aged 11 to 19 yrs.	1) 16 (28 (+4) vs 18	Aprepipant (125 mg) administered 1hr before chemotherapy. Dexamethasone(8mg) + ondansetron (0.15/mg/kg x 3 doses) was administered 30min before chemotherapy vs Placebo administered 1hr before chemotherapy. Dexamethasone(8mg) + ondansetron (0.15/mg/kg x 3 doses) was administered 30min before chemotherapy	**Aprepipant + Dexamethasone + ondansetron vs Dexamethasone + ondansetron** >1 clinical adverse event: 27 (84.4%) vs 13 (72.2%) Drug related clinical adverse events (i.e. hiccups): 7 (21.9%) vs 1 (5.6%) Serious clinical adverse events (i.e. neutropenia): 10 (31.3%) vs 3 (16.7%) >1 laboratory adverse event (neutropenia, hypokalaemia, leukopenia): 6 (18.8%) vs 6 (33.3%) No deaths, no discontinuation due to adverse events, no serious drug-related adverse events, no drug-related laboratory adverse events
Grade assessment				
Study design:	+4	1 Randomized Controlled Trial		
Study limitations	-1	Some limitations - Selection bias: Unclear; Attrition bias: low; Performance bias: low; Detection bias: unclear		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	-2	Important imprecision due to small sample size. Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality evidence that treatment with aprepipant, dexamethasone and ondansetron or dexamethasone and ondansetron causes adverse effects in children with cancer receiving chemotherapy. It is unclear there is a significant differences between both treatment groups. Most commonly reported adverse effect was neutropenia**		

4.2.9 Midazolam vs dexamethason vs midazolam + dexamethason vs placebo

Midazolam vs dexamethasone vs midazolam + dexamethasone vs placebo				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and effect size
Incidence of emetic episodes: forceful expulsion of liquid or solid gastric contents				
1) Riad, 2007	1) Children who were scheduled to undergo elective strabismus surgery	1) 100 (25 vs 25 vs 25 vs 25)	midazolam 50µgkg^{-1} vs dexamethasone 0.5mgkg^{-1} (maximum dose, 8mg) vs combination of midazolam 50µgkg^{-1} and dexamethasone 0.5mgkg^{-1} (maximum dose, 8mg) vs placebo	*Incidence post-operative vomiting* • Group 1 – midazolam: N = 0 (0%), p < 0.001 compared with placebo, p < 0.05 compared with dexamethasone • Group 2 – dexamethasone: N = 8 (32%), p < 0.001 compared with placebo • Group 3 – Midazolam + dexamethasone: N = 0 (0%), p<0.001 compared with placebo, p < 0.05 compared with dexamethasone • Placebo: N=13 (52%)

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-1	Some limitations - Selection bias: Low; Attrition bias: low; Performance bias: Low; Detection bias: unclear
Consistency:	0	No important inconsistency. Only 1 study performed
Directness:	-1	Outcomes are direct. However, unclear if the population of children undergoing strabismus surgery is representative for children in palliative care.
Precision:	-2	Important imprecision due to small sample size. Only 1 study performed
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence that treatment with midazolam decreases the incidence of emetic episodes within 24h in children undergoing strabismus surgery as compared to placebo.** **There is very low quality of evidence that treatment with dexamethasone decreases the incidence of emetic episodes within 24h in children undergoing strabismus surgery as compared to placebo.** **There is very low quality of evidence that treatment with midazolam and dexamethasone decreases the incidence of emetic episodes within 24h in children undergoing strabismus surgery as compared to placebo.** **There is very low quality of evidence that treatment with midazolam decreases the incidence of emetic episodes within 24h in children undergoing strabismus surgery as compared to dexamethasone.**

Midazolam vs dexamethasone vs midazolam + dexamethasone vs placebo				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and effect size
Incidence of nausea: subjective feeling that was reported by the patients				
Riad, 2007	1) Children who were scheduled to undergo elective strabismus surgery	1) 100 (25 vs 25 vs 25 vs 25)	midazolam 50μgkg^{-1} vs dexamethasone 0.5mgkg^{-1} (maximum dose, 8mg) vs combination of midazolam 50μgkg^{-1} and dexamethasone 0.5mgkg^{-1} (maximum dose, 8mg) vs placebo	*Incidence post-operative nausea* • Group 1 – midazolam: N = 3 (12%), p < 0.001 compared with placebo, p = NS compared with dexamethasone • Group 2 – dexamethasone: N=8 (32%), p < 0.01 compared with placebo • Group 3 – Midazolam + dexamethasone N = 0 (0%), p<0.001 compared with placebo • Placebo: N=12 (48%)

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial
Study limitations	-1	Some limitations - Selection bias: Low; Attrition bias: low; Performance bias: Low; Detection bias: unclear
Consistency:	0	No important inconsistency. Only 1 study performed
Directness:	-1	Outcomes are direct. However, unclear if the population of children undergoing strabismus surgery is representative for children in palliative care.
Precision:	-2	Important imprecision due to small sample size. Only 1 study performed
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence that treatment with midazolam decreases the incidence of nausea within 24h in children undergoing strabismus surgery as compared to placebo** **There is very low quality of evidence that treatment with dexamethasone decreases the incidence of nausea within 24h in children undergoing strabismus surgery as compared to placebo** **There is very low quality of evidence that treatment with midazolam and dexamethasone decreases the incidence of nausea within 24h in children undergoing strabismus surgery as compared to placebo** **There is very low quality of evidence that there is no significant effect of treatment with midazolam on the incidence of nausea within 24h in children undergoing strabismus surgery as compared to dexamethasone.**

5 Conclusies van evidence

5.1 Niet-medicamenteuze behandeling van Misselijkheid en Braken

Non pharmacological treatment of nausea and vomiting		
Intervention	**Conclusions of evidence**	**Quality of evidence**
Self-hypnosis *vs. standard treatment with anti-emetics*	↓ supplemental anti-emetic medication in children with cancer no significant effect on nausea and vomiting in children with cancer ↓ anticipatory nausea 1 to 2 months post diagnosis in children with cancer; no significant effect of anticipatory nausea 4 to 6 months post diagnosis.	⊕⊖⊖⊖ VERY LOW (1RCT)
Nutrition *Psychological relaxation and diversion techniques*	Unknown effect	No studies

5.2 Medicamenteuze behandeling van Misselijkheid en Braken

Pharmacological treatment of nausea and vomiting			
Intervention		**Conclusions of evidence**	**Quality of evidence**
Haloperidol Domperidone Cyclizine Promethazine (Butyl)scopolamine Chlorpromazine Levomepromazine D-9-tetrahydrocannabinol Dexamethasone Benzodiazepines propofol		Unknown effect	No studies
Pharmacological treatment for nausea and vomiting during chemotherapy			
High dose ondansetron or low dose ondansetron	*Placebo*	↓ incidence emetic episodes within 24h in children with cancer receiving chemotherapy after intervention	⊕⊕⊕⊖ MODERATE (1RCT)
High dose ondansetron	*vs. low dose ondansetron*	no significant effect on incidence of emetic episodes within 24h in children with cancer receiving chemotherapy	⊕⊕⊕⊖ MODERATE (2RCTs)
		no significant effect on nausea severity within 24h in children with cancer receiving chemotherapy	⊕⊖⊖⊖ VERY LOW (1RCT)
High dose ondansetron + dexamethasone	*vs. low dose ondansetron + dexamethasone*	↓ incidence of emetic episodes within 24h in children with cancer receiving chemotherapy that initially were treatment failures (unclear if significant)	⊕⊖⊖⊖ VERY LOW (1RCT)
		↓ nausea severity within 24h in children with cancer receiving chemotherapy that initially were treatment failures (unclear if significant)	
Ondansetron	*vs. metoclopramide*	↓ incidence emetic episodes within 24h in children with cancer receiving chemotherapy after intervention	⊕⊖⊖⊖ VERY LOW (1RCT)
		↓ nausea severity within 24h in children with cancer receiving chemotherapy after intervention	
		↓ extrapyramidal symptoms as adverse effect in children with cancer receiving chemotherapy after intervention	
Granisetron	*vs. Ondansetron*	no significant effect on incidence of emetic episodes within 24h in children with cancer receiving chemotherapy	⊕⊖⊖⊖ VERY LOW (1RCT)
		no significant effect on nausea severity within 24h in children with cancer receiving chemotherapy	
		Adverse effects are reported for both treatments in children with cancer receiving chemotherapy (unclear if significant difference).Most commonly reported adverse effect was headache	
Granisetron	*vs. Tropisetron*	↓ incidence emetic episodes within 24h in children with cancer receiving chemotherapy after intervention	⊕⊖⊖⊖ VERY LOW (1RCT)
		↓ nausea severity within 24h in children with cancer receiving chemotherapy after intervention	
		No significant effect on adverse events in children with cancer receiving chemotherapy. Most commonly reported adverse events were headache and constipation.	

Aprepipant + dexamethasone + ondansetron	*vs. dexamethasone + ondansetron*	↓ incidence emetic episodes within 24h in children with cancer receiving chemotherapy after intervention (unclear if significant) Adverse effects are reported for both treatments in children with cancer receiving chemotherapy (unclear if significant difference). Most commonly reported adverse effect was neutropenia.	⊕⊖⊖⊖ VERY LOW (1RCT)
Pharmacological treatment for post-operative nausea and vomiting			
Midazolam	*vs. placebo*	↓ incidence of emetic episodes within 24h in children undergoing strabismus surgery ↓incidence of nausea within 24h in children undergoing strabismus surgery	⊕⊖⊖⊖ VERY LOW (1RCT)
Dexamethasone	*vs. placebo*	↓ incidence of emetic episodes within 24h in children undergoing strabismus surgery ↓incidence of nausea within 24h in children undergoing strabismus surgery	⊕⊖⊖⊖ VERY LOW (1RCT)
Midazolam + dexamethasone	*vs. placebo*	↓ incidence of emetic episodes within 24h in children undergoing strabismus surgery ↓incidence of nausea within 24h in children undergoing strabismus surgery	⊕⊖⊖⊖ VERY LOW (1RCT)
Midazolam	*vs. Dexamethasone*	↓ incidence of emetic episodes within 24h in children undergoing strabismus surgery no significant effect on incidence of nausea within 24h in children undergoing strabismus surgery	⊕⊖⊖⊖ VERY LOW (1RCT

6 Aanbevelingen uit richtlijnen

6.1 Niet-medicamenteuze behandeling van Misselijkheid en Braken

Non pharmacological treatment of nausea and vomiting – Child guideline	
Depuis LL et al. Guideline for the prevention and treatment of anticipatory nausea and vomiting due to Chemotherapy in Pediatric Cancer Patients. Pediatr blood cancer 2014; 61: 1506 – 1512.	
Recommendation[1]	**Level of evidence[2]**
Grade 2: We suggest that psychological interventions such as hypnosis or systematic desensitization may be offered to children with anticipatory CINV.	C: Low
Flank J et al. Guideline for the treatment of breakthrough and the prevention of refractory chemotherapy-induced nausea and vomiting in children with cancer. Pediatr Blood Cancer 2016; 63: 1144-1151	
Grade 2: For children experiencing refractory CINV despite initiation of the previous recommendations, we suggest that one of the following interventions be added to the CINV prophylaxis provided: • interventions that were employed successfully for the treatment of breakthrough CINV in previous treatment blocks (olanzapine, methotrimeprazine or metoclopramide); • or stimulation of Nei Gaun (P6) by means of acupressure or electroacupuncture.	C: very low

[1] **Grades of recommendation adapted from GRADE**
1: Strong; Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost.
2: Weak; Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, or higher cost or resource consumption.

[2] **Level of evidence adapted from GRADE**
A: High; Further research is very unlikely to change confidence in the estimate of the clinical effect.
B: Moderate; Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
C: Low or very low; Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain

Non pharmacological treatment of nausea and vomiting – Adult guideline	
Integraal Kankerinstituut Nederland. Misselijkheid en Braken (4). Pallialine, 16-6-2014	
Recommendation	**Level of evidence**
• Voedingsmiddelen die goed worden verdragen en waarvan de smaak wordt gewaardeerd • Frequente kleine maaltijden en tussendoortjes om een lege maag te voorkomen (mits geen sprake is van maagretentie) • Eventueel koude maaltijden, als de geur van eten tot klachten leidt • Gebruik van maaltijden en tussendoortjes op momenten dat de klachten minder aanwezig zijn; benut goede momenten • Voldoende vocht (minimaal 1,5 l/dag) • Eventueel drinken van cola (met of zonder prik) • Eventueel zuigen op ijsklontje of waterijsje. Soms worden ook stukjes ingevroren/gekoeld fruit gewaardeerd • De inzet van dieetpreparaten, indien handhaving of verbetering van de voedingstoestand wordt nagestreefd (zie richtlijnen Anorexie en gewichtsverlies, Algemene voedings- en dieetbehandeling en Ondervoeding bij patiënten met kanker). Een consult van een diëtist is hierbij noodzakelijk.	Unknown level of evidence
Er zijn aanwijzingen dat acupunctuur en/of acupressuur (in de vorm van drukmassage of een speciaal polsbandje) effectief zijn bij misselijkheid en/of braken, met name na operatie en na chemotherapie.	Unknown level of evidence
Complementaire zorgvormen en psychologische technieken worden met name toegepast bij misselijkheid en/of braken wanneer psychische factoren (angst en spanning) en conditionering (bij anticipatoire misselijkheid en/of braken) een belangrijke rol spelen. Deze vorm van misselijkheid en/of braken reageert vaak slecht op anti-emetica. Deze technieken werken doordat ze ontspanning, afleiding en/of een gevoel van zelfcontrole teweegbrengen. In eerste instantie is instructie door een fysiotherapeut of psycholoog noodzakelijk. In veel gevallen kan de arts of de verpleegkundige dan wel de naaste de techniek daarna zelfstandig toepassen. De hieronder genoemde technieken zijn met name onderzocht bij misselijkheid en/of braken door chemotherapie (zie ook richtlijn Complementaire zorg): • massage van voeten, handen of gezicht • aromatherapie (al dan niet in combinatie met massage) • ontspanningsoefeningen (progressieve spierrelaxatie), met of zonder geleide fantasie • luisteren naar muziek De gekozen benadering moet worden afgestemd op de patiënt. De ene patiënt zal meer baat hebben bij een benadering gericht op lichamelijke ontspanning, terwijl voor de andere een meer actieve gedragstherapeutische wijze van hanteren aangewezen is.	Unknown level of evidence

6.2 Medicamenteuze behandeling van Misselijkheid en Braken

Pharmacological treatment of nausea and vomiting – Child guideline	
Depuis LL et al. Guideline for the prevention and treatment of anticipatory nausea and vomiting due to Chemotherapy in Pediatric Cancer Patients. Pediatr blood cancer 2014; 61: 1506 – 1512.	
Recommendation[1]	**Level of evidence[2]**
Grade 1: Control of acute and delayed CINV should be optimized for each child in order to minimize the risk of the child developing anticipatory CINV.	C: Low
Grade 2: We suggest that lorazepam in a dose of 0.04–0.08 mg/kg/dose (maximum: 2 mg/dose) once at bedtime the night before chemotherapy and once the next day prior to administration of chemotherapy may be used to prevent or treat anticipatory CINV in children	C: Very low
Flank J et al. Guideline for the treatment of breakthrough and the prevention of refractory chemotherapy-induced nausea and vomiting in children with cancer. Pediatr Blood Cancer 2016; 63: 1144-1151	
Grade 1: For children receiving acute CINV prophylaxis recommended for minimally, low, or moderately emetogenic chemotherapy, clinicians should upgrade or escalate the acute CINV prophylaxis provided to that recommended for chemotherapy of the next higher level of emetogenic risk.	C: Low
Grade 2: For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy, we suggest that olanzapine be added to guideline-consistent CINV prophylaxis.	C: Low
Grade 2: For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy and who cannot receive olanzapine, we suggest that one of the following antiemetic agents be added to guideline-consistent CINV prophylaxis: • methotrimeprazine (also known as levomepromazine) or • metoclopramide (in children older than 1 year) Given the possibility of extrapyramidal reactions with these agents, the risks and benefits of their use should be weighed carefully and coadministration of prophylaxis aimed at preventing extrapyramidal symptoms (EPS) should be considered. Patients and families should also be educated about the possible occurrence of EPS.	C: Very low
Grade 1: For children receiving acute CINV prophylaxis recommended for minimally, low, or moderately emetogenic chemotherapy, clinicians should upgrade or escalate the acute CINV prophylaxis provided to that recommended for chemotherapy of the next higher level of emetogenic risk.	C: Very low
Grade 2: For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy, we suggest that the 5-HT3 antagonist given for CINV prophylaxis be changed from ondansetron or granisetron to palonosetron. In jurisdictions where palonosetron is not available, we suggest that granisetron be substituted for ondansetron.	C: very low
Grade 2: For children experiencing refractory CINV despite initiation of previous recommendations and who have not previously received aprepitant because it is known or suspected to interact with the chemotherapeutic agent(s) being given, we suggest that the addition of aprepitant to acute CINV prophylaxis be considered.	C: Low
Grade 2: For children experiencing refractory CINV despite initiation of the previous recommendations, we suggest that one of the following interventions be added to the CINV prophylaxis provided: • interventions that were employed successfully for the treatment of breakthrough CINV in previous treatment blocks (olanzapine, methotrimeprazine or metoclopramide); • or stimulation of Nei Gaun (P6) by means of acupressure or electroacupuncture.	C: very low
[1] Grades of recommendation adapted from GRADE **1:** Strong; Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost. **2:** Weak; Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, or higher cost or resource consumption. **[2] Level of evidence adapted from GRADE** **A:** High; Further research is very unlikely to change confidence in the estimate of the clinical effect. **B:** Moderate; Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **C:** Low or very low; Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain	

Pharmacological treatment of nausea and vomiting – Adult guideline	
National Clinical Guideline Centre. Care of dying adults in the last days of life. 2015	
Recommendation	**Level of evidence**
Assess for likely causes of nausea or vomiting in the dying person. These may include: • certain medicines that can cause or contribute to nausea and vomiting • recent chemotherapy or radiotherapy • psychological causes • biochemical causes, for example hypercalcaemia • raised intracranial pressure • gastrointestinal motility disorder • ileus or bowel obstruction	Expert opinion
Discuss the options for treating nausea and vomiting with the dying person and those important to them.	Expert opinion
Consider non-pharmacological methods for treating nausea and vomiting in a person in the last days of life	Expert opinion
When choosing medicines to manage nausea or vomiting in a person in the last days of life, take into account: • the likely cause and if it is reversible • the side effects, including sedative effects, of the medicine • other symptoms the person has • the desired balancing of effects when managing other symptoms • compatibility and drug interactions with other medicines the person is taking.	Expert opinion
For people in the last days of life with obstructive bowel disorders who have nausea or vomiting, consider: • hyoscine butylbromidee as the first-line pharmacological treatment • octreotidee if the symptoms do not improve within 24 hours of starting treatment with hyoscine butylbromidee.	Expert opinion
Integraal Kankerinstituut Nederland. Misselijkheid en Braken (4). Pallialine, 16-6-2014	
Bij patiënten in de palliatieve fase met misselijkheid en braken door andere oorzaken dan chemotherapie, ileus, hersenmetastasen of vestibulaire oorzaken wordt geadviseerd om te kiezen voor een empirische benadering met een prokineticum (metoclopramide of eventueel domperidon) als eerste keuze.	2 studies, 4 systematic reviews
Metoclopramide wordt geadviseerd als eerste keus anti-emeticum bij de behandeling van misselijkheid en braken bij patiënten in de palliatieve fase, tenzij er sprake is van een ileus (zie richtlijn Ileus), hersenmetastasen (zie richtlijn Hersenmetastasen). terminaal nierfalen of misselijkheid en braken ten gevolge van chemotherapie. In geval van (een grote kans op) hinderlijke centrale bijwerkingen gaat de voorkeur uit naar domperidon.	1 systematic review (domperidone); 4 studies, 3 systematic reviews (metoclopramide)
Haloperidol wordt geadviseerd bij de behandeling van misselijkheid en braken in de palliatieve fase als alternatief voor metoclopramide of domperidon, vooral als er ook anderszins een indicatie voor is (bijvoorbeeld hallucinaties of (beginnend) delier).	4 systematic reviews, 1 study
De werkgroep is van mening dat dexamethason monotherapie kan worden ingezet bij de behandeling van misselijkheid en braken in de palliatieve fase als er onvoldoende reactie is op behandeling met metoclopramide, domperidon of haloperidol.	1 RCT, expert opinion
Behandeling met levomepromazine p.o. (eventueel buccaal of s.c.) wordt geadviseerd bij patiënten in de palliatieve fase met misselijkheid en/of braken die onvoldoende reageren op andere anti-emetica.	2 studies, 3 systematic reviews
Behandeling met olanzapine p.o. wordt geadviseerd bij patiënten in de palliatieve fase met misselijkheid en/of braken die onvoldoende reageren op andere anti-emetica	1 pilot study, 2 case series, 1 systematic review
Bij gebrek aan onderzoeksgegevens en klinische ervaring wordt geen aanbeveling gedaan over het gebruik van cyclizine bij de behandeling van misselijkheid en braken bij patiënten in de palliatieve fase.	No literature, expert opinion
Erytromycine wordt niet geadviseerd voor de behandeling van misselijkheid of braken bij patiënten in de palliatieve fase, tenzij er sprake is van een gastroparese bij diabetes mellitus of na vagotomie.	1 study, 2 retrospective case reports

Medicinale cannabis wordt niet geadviseerd bij patiënten in de palliatieve fase met misselijkheid en/of braken.	No literature, Expert opinion
Gember wordt niet geadviseerd bij patiënten in de palliatieve fase met misselijkheid en/of braken.	1 systematic review
Er wordt geadviseerd bij het maken van een keuze tussen rectale of parenterale toediening van anti-emetica primair de voorkeur en de situatie van de patiënt leidend te laten zijn, echter binnen de mogelijkheden van de zorgsetting.	1 study

7 Overzicht conclusies van evidence en aanbevelingen uit richtlijnen

7.1 Niet-medicamenteuze behandeling van Misselijkheid en Braken

Non pharmacological treatment of nausea and vomiting								
Treatment (colour indicates strength of recommendation)	Conclusions of evidence (RCTs on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children 2013(2)	Level of evidence[1,]
Nutrition advise	Unknown effect	No studies	Not identified	-	Do	Unknown level of evidence (3;P)	Consider; weak recommendation	Level 4 adult evidence (4)[2]
Self-hypnosis (vs standard treatment)	↓ supplemental anti-emetic medication in children with cancer no significant effect on nausea and vomiting in children with cancer ↓ anticipatory nausea 1 to 2 months post diagnosis in children with cancer; no significant effect of anticipatory nausea 4 to 6 months post diagnosis.	VERY LOW, 1RCT (5)*	We suggest that psychological interventions such as hypnosis or systematic desensitization may be offered to children with anticipatory CINV (weak recommendation)	LOW (6;P)	Not applicable	-	Do; strong recommendation	Level 2/3 child evidence (5, 7-10)
Acupuncture/acupressure	Unknown effect	No studies	For children experiencing refractory CINV we suggest that one of the following interventions be added to the CINV prophylaxis provided: Interventions that were employed successfully for the treatment of breakthrough CINV in previous treatment blocks (olanzapine, methotrimeprazine or metoclopramide); Stimulation of Nei Gaun (P6) by means of acupressure or electroacupuncture.	VERY LOW (11;P)	There are indication that acupuncture and/or acupressure (in the form of a pressure massage or a special wristband) are effective for nausea and/or vomiting especially after surgery and chemotherapy	Unknown level of evidence (3;P)	Consider; weak recommendation	Controversy in child evidence (12); Level 2/3 adult evidence (13-18)[2]

Massage	Unknown effect	No studies	Not identified	-	Can be mainly used for nausea and/or vomiting when psychological factors (fear and tension) and conditioning (anticipatory nausea and/or vomiting) play a role. The chosen approach should be tailored to the patient.	Unknown level of evidence (3;P)	Consider; weak recommendation	Level 2 adult evidence (19-21)
Aromatherapy							Consider; weak recommendation	Level 3 adult evidence (22)[2]
Diversion							Consider; weak recommendation	Level 3 child evidence (10); Level 3 adult evidence (23)[2]
Psychological relaxation techniques							Consider; weak recommendation	Level 1/2 adult evidence (24, 25)[2]
Music							Consider; weak recommendation	Level 3 adult evidence (26, 27)[2]

Legend
P: Palliative context
NP: Non-palliative context
P/NP: Both palliative and non-palliative conditions
Not identified: No recommendations on specific pharmacological treatment were identified.
Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.

[1]Level of evidence:
Level 1: Based on a systematic review or at least two randomized controlled trials of good quality
Level 2: Based on one at randomized controlled trial or at least two comparative clinical studies
Level 3: Based on one comparative study or on non-comparative studies
Level 4: Based on expert opinion
[2]Adult evidence is extracted from guidelines of pallialine.nl
[*]Level of child evidence might differ from level of evidence in 2013 as the same RCTs used in 2013 are now graded according to GRADE instead of AGREE.

References

2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.
3. Integraal Kankercentrum Nederland. Misselijkheid en braken (4.0). 2014. Available from: /www.pallialine.nl/misselijkheid-en-braken.
4. Landelijk Expertisecentrum Verpleging en Verzorging. Richtlijn Orale Mucositis bij Patiënten met Kanker [Internet]2007 [cited 2012 July 9]. Available from: https://www.dentalinfo.nl/kennis/richtlijnen-mondzorg/richtlijn-orale-mucositis-bij-patienten-met-kanker/.
5. Jacknow DS, Tschann JM, Link MP, Boyce WT. Hypnosis in the prevention of chemotherapy-related nausea and vomiting in children: a prospective study. Journal of Developmental and Behavioral Pediatrics. 1994.
6. Dupuis LL, Robinson PD, Boodhan S, Holdsworth M, Portwine C, Gibson P, et al. Guideline for the prevention and treatment of anticipatory nausea and vomiting due to chemotherapy in pediatric cancer patients. Pediatr Blood Cancer. 2014;61(8):1506-12.
7. Cotanch P, Hockenberry M, Herman. Self-hypnosis as antiemetic therapy in children receiving chemotherapy. Oncol Nurs Forum. 1985;12(4):41-6.
8. Hockenberry MJ, Cotanch PH. Hypnosis as adjuvant antiemetic therapy in childhood cancer. Nurs Clin North Am. 1985;20(1):105-7.
9. LeBaron S, Zeltzer L. Behavioral intervention for reducing chemotherapy-related nausea and vomiting in adolescents with cancer. Journal of Adolescent Health Care. 1984;5(3):178-82.
10. Zeltzer L, LeBaron S, Zeltzer PM. The effectiveness of behavioral intervention for reduction of nausea and vomiting in children and adolescents receiving chemotherapy. J Clin Oncol. 1984;2(6):683-90.

11. Flank J, Robinson PD, Holdsworth M, Phillips R, Portwine C, Gibson P, et al. Guideline for the Treatment of Breakthrough and the Prevention of Refractory Chemotherapy-Induced Nausea and Vomiting in Children With Cancer. Pediatr Blood Cancer. 2016;63(7):1144-51.
12. Vickers AJ. Can acupuncture have specific effects on health? A systematic review of acupuncture antiemesis trials. J R Soc Med. 1996;89(6):303-11.
13. Brown S, North D, Marvel MK, Fons R. Acupressure wrist bands to relieve nausea and vomiting in hospice patients: do they work? Am J Hosp Palliat Care. 1992;9(4):26-9.
14. Ezzo JM, Richardson MA, Vickers A, Allen C, Dibble SL, Issell BF, et al. Acupuncture-point stimulation for chemotherapy-induced nausea or vomiting. Cochrane Database Syst Rev. 2006(2):CD002285.
15. Naeim A, Dy SM, Lorenz KA, Sanati H, Walling A, Asch SM. Evidence-based recommendations for cancer nausea and vomiting. J Clin Oncol. 2008;26(23):3903-10.
16. Nystrom E, Ridderstrom G, Leffler AS. Manual acupuncture as an adjunctive treatment of nausea in patients with cancer in palliative care--a prospective, observational pilot study. Acupunct Med. 2008;26(1):27-32.
17. Perkins P, Dorman S. Haloperidol for the treatment of nausea and vomiting in palliative care patients. Cochrane Database Syst Rev. 2009(2):CD006271.
18. Wright LD. The use of motion sickness bands to control nausea and vomiting in a group of hospice patients. Am J Hosp Palliat Care. 2005;22(1):49-53.
19. Ahles TA, Tope DM, Pinkson B, Walch S, Hann D, Whedon M, et al. Massage therapy for patients undergoing autologous bone marrow transplantation. J Pain Symptom Manage. 1999;18(3):157-63.
20. Cassileth BR, Vickers AJ. Massage therapy for symptom control: outcome study at a major cancer center. J Pain Symptom Manage. 2004;28(3):244-9.
21. Grealish L, Lomasney A, Whiteman B. Foot massage. A nursing intervention to modify the distressing symptoms of pain and nausea in patients hospitalized with cancer. Cancer Nurs. 2000;23(3):237-43.
22. Gilligan NP. The palliation of nausea in hospice and palliative care patients with essential oils of Pimpinella anisum (aniseed), Foeniculum vulgare var. dulce (sweet fennel), Anthemis nobilis (Roman chamomile) and Mentha x piperita (peppermint). International Journal of Aromatherapy. 2005;15(4):163-7.
23. Vasterling J, Jenkins RA, Tope DM, Burish TG. Cognitive distraction and relaxation training for the control of side effects due to cancer chemotherapy. J Behav Med. 1993;16(1):65-80.
24. Devine EC, Westlake SK. The effects of psychoeducational care provided to adults with cancer: meta-analysis of 116 studies. Oncol Nurs Forum. 1995;22(9):1369-81.
25. Luebbert K, Dahme B, Hasenbring M. The effectiveness of relaxation training in reducing treatment-related symptoms and improving emotional adjustment in acute non-surgical cancer treatment: a meta-analytical review. Psychooncology. 2001;10(6):490-502.
26. Ezzone S, Baker C, Rosselet R, Terepka E. Music as an adjunct to antiemetic therapy. Oncol Nurs Forum. 1998;25(9):1551-6.
27. Standley JM. Clinical Applications of Music and Chemotherapy: The Effects on Nausea and Emesis 1. Music Therapy Perspectives. 1992;10(1):27-35.

7.2 Medicamenteuze behandeling van Misselijkheid en Braken

Pharmacological treatment of nausea and vomiting								
Treatment	Conclusions of evidence (RCTs on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children (2013)	Level of evidence[1, 2]
Anticipatory chemotherapy induced nausea and vomiting								
Lorazepam	Unknown effect	No studies	We suggest that lorazepam in a dose of 0.04–0.08 mg/kg/dose (maximum: 2 mg/dose) once at bedtime the night before chemotherapy and once the next day prior to administration of chemotherapy may be used to prevent or treat anticipatory CINV in children (weak recommendation)	VERY LOW (6;P)	Not applicable	-	No recommendation	-
5HT3 receptor antagonists for chemotherapy induced nausea and vomiting								
High dose ondansetron or low dose ondansetron vs placebo	↓ incidence emetic episodes within 24h in children with cancer receiving chemotherapy after intervention	MODERATE, 1RCT (28)*	For children receiving acute chemotherapy induced nausea and vomiting prophylaxis recommended for highly emetogenic chemotherapy, we suggest that the 5-HT3 antagonist given for CINV prophylaxis be changed from ondansetron or granisetron to palonosetron. In jurisdictions where palonosetron is not available, we suggest that granisetron be substituted for	VERY LOW (11;P)	Not applicable	-	Do; strong recommendation	Level 1 / 2 child evidence (29-31) Level 1 adult evidence (15, 32-38)[2]
High dose ondansetron vs low dose ondansetron	no significant effect on incidence of emetic episodes within 24h in children with cancer receiving chemotherapy	MODERATE, 2RCTs (28, 39)*						
	no significant effect on nausea severity within 24h in children with cancer receiving chemotherapy	VERY LOW, 1RCT (39)*						
High dose ondansetron + dexamethasone vs low dose ondansetron + dexamethasone	↓ incidence of emetic episodes within 24h in children with cancer receiving chemotherapy that initially were treatment	VERY LOW, 1RCT (39)*						

	failures (unclear if significant)		ondansetron (weak recommendation)					
	↓ nausea severity within 24h in children with cancer receiving chemotherapy that initially were treatment failures (unclear if significant)							
Ondansetron vs metoclopramide	↓ incidence emetic episodes within 24h in children with cancer receiving chemotherapy after intervention	VERY LOW, 1RCT (40)*						
	↓ nausea severity within 24h in children with cancer receiving chemotherapy after intervention							
	↓ extrapyramidal symptoms as adverse effect in children with cancer receiving chemotherapy after intervention							
Granisetron vs ondansetron	no significant effect on incidence of emetic episodes within 24h in children with cancer receiving chemotherapy	VERY LOW 1RCT (41)*						
	no significant effect on nausea severity within 24h in children with cancer receiving chemotherapy							
	Adverse effects are reported for both treatments in children with cancer receiving chemotherapy (unclear if significant difference).Most commonly reported adverse effect was headache							

Granisetron vs tropisetron	↓ incidence emetic episodes within 24h in children with cancer receiving chemotherapy after intervention ↓ nausea severity within 24h in children with cancer receiving chemotherapy after intervention No significant effect on adverse events in children with cancer receiving chemotherapy. Most commonly reported adverse events were headache and constipation.	VERY LOW, 1RCT (29)*						
5HT3 receptor antagonists for nausea and vomiting induced by other causes								
5HT3 receptor antagonists	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 2 adult evidence (42-51)[2]
Dopamine2-receptor antagonists (D2)								
Metoclopramide	Unknown effect	No studies	For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy and who cannot receive olanzapine, we suggest that one of the following antiemetic agents be added to guideline-consistent CINV prophylaxis: methotrimeprazine (also known as levomepromazine) or metoclopramide (in children older than 1 year)	VERY LOW (11;P)	For nausea and vomiting induced by causes other than chemotherapy, ileus, brain metastases or vestibular causes it is advised to choose a prokineticum: Metoclopramide is first choice (unless there is ileus, brain metastases, end-stage renal failure or nausea and vomiting caused by chemotherapy. Domperidone is preferred in case of	Unknown level of evidence - general: 2 studies, 4 systematic reviews; Metoclopramide: 4 studies, 3 systematic reviews; Domperidone: 1 systematic review (3;P)	Consider; weak recommendation	Level 4 child evidence; Level 4 adult evidence

			Possibility of extrapyramidal reactions (Weak recommendation)		a (high probability of) central side effects.			
Domperidone	Unknown effect	No studies	Not identified	-				
Haloperidol	Unknown effect	No studies	Not identified	-	Advised as an alternative for metoclopramide or domperidone or in case of indication such as hallucinations or delirium	Unknown level of evidence - 4 systematic reviews, 1 study, (3;P)	Consider; weak recommendation	Level 4 child evidence; Level 4 adult evidence (17, 52)[2]
H1- and Muscarine acetylcholine (AChm)-receptor antagonists								
Cyclizine	Unknown effect	No studies	Not identified	-	No recommendation can be given	No studies, expert opinion (3;P)	Consider; weak recommendation	Level 4 child evidence (53); Level 4 adult evidence[2]
Promethazine	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 child evidence (53)
(Butyl)scopolamine	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 child evidence(53); Level 4 adult evidence
D2-, H1- and Muscarine acetylcholine(AChm)-receptor antagonists								
Chlorpromazine	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 child evidence
Levomepromazine	Unknown effect	No studies	For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy and who cannot receive olanzapine, we suggest that one of the following antiemetic agents be added to guideline-consistent CINV prophylaxis: methotrimeprazine (also known as levomepromazine) or	VERY LOW (11;P)	Advised in case of insufficient response to other anti-emetics	Unknown level of evidence - 2 studies, 3 systematic reviews (3;P)	Consider; weak recommendation	Level 4 child evidence; Level 3 adult evidence (54-57)[2]

			metoclopramide (in children older than 1 year) NB: Possibility of extrapyramidal reactions (Weak recommendation)					
Olanzapine	Unknown effect	No studies	For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy, we suggest that olanzapine be added to guideline-consistent CINV prophylaxis (weak recommendation)	VERY LOW (11;P)	Advised in case of insufficient response to other anti-emetics	Unknown level of evidence - 1 pilot study, 2 case series, 1 systematic review (3;P)	No recommendation	-
NK1-receptor antagonists								
Aprepipant + dexamethasone + ondansetron vs dexamethasone + ondansetron	↓ incidence emetic episodes within 24h in children with cancer receiving chemotherapy after intervention (unclear if significant)	VERY LOW, 1RCT (58)*	For children experiencing refractory CINV despite initiation of previous recommendations and who have not previously received aprepitant because it is known or suspected to interact with the chemotherapeutic agent(s) being given, we suggest that the addition of aprepitant to acute CINV prophylaxis be considered (weak recommendation)	LOW (11;P)	Not applicable	-	Consider for chemotherapy induced nausea and vomiting and perioperative nausea and vomiting; weak recommendation	Level 3 child evidence(58-60); Adult evidence (15, 32, 34, 35, 61)[2]
Cannabinoids								
D-9-tetrahydrocannabinol	Unknown effect	No studies	Not identified	-		-	Consider; weak recommendation	Level 3 adult evidence (62)
Medicinal cannabis	Unknown effect	No studies	Not identified	-	Not advised.	No studies, expert opinion (3;P)	No recommendation	-
Corticosteroids								

General	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Controversy in child evidence (53)
Dexamethasone	Unknown effect	No studies	Not identified	-	Monotherapy with dexamethasone can be used in case of insufficient response to metoclopramide, domperidone or haloperidol.	Unknown level of evidence - 1 RCT; expert opinion (3;P)	Consider in combination with other anti-emetics	Level 3 adult evidence (47, 63-65)[2]
Benzodiazepines for post-operative nausea and vomiting								
Midazolam vs. placebo	↓ incidence of emetic episodes within 24h in children undergoing strabismus surgery	VERY LOW, 1RCT (66;NP)*	Not identified	-	Not identified	-	Consider; weak recommendation	Level 2 child evidence (66); Level 1 adult evidence (67)[2]
	↓incidence of nausea within 24h in children undergoing strabismus surgery							
Dexamethasone vs placebo	↓ incidence of emetic episodes within 24h in children undergoing strabismus surgery							
	↓incidence of nausea within 24h in children undergoing strabismus surgery							
Midazolam + dexamethasone vs placebo	↓ incidence of emetic episodes within 24h in children undergoing strabismus surgery							
	↓incidence of nausea within 24h in children undergoing strabismus surgery							
Midazolam vs dexamethasone	↓ incidence of emetic episodes within 24h in children undergoing strabismus surgery							
	no significant effect on incidence of nausea within							

	24h in children undergoing strabismus surgery							
Benzodiazepines for chemotherapy-induced nausea and vomiting								
Benzodiazepines	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 2 child evidence (68, 69)
Propofol								
Propofol	Unknown effect	No studies	Not identified	-	Not identified	-	Consider for chemotherapy induced nausea and vomiting; weak recommendation	Level 4 child evidence (53); Unknown level adult evidence (70, 71))
							Consider for postoperative nausea and vomiting; weak recommendation	Level 4 child evidence (53); Level 1 adult evidence (72, 73)
Other treatments								
Ginger	Unknown effect	No studies	Not identified	-	Not advised	Unknown level of evidence - 1 systematic review (3;P)	No recommendation	-
Erythromycine	Unknown effect	No studies	Not identified	-	Not advised unless there is gastroparesis in diabetes mellitus or after vagotomy	Unknown level of evidence - 1 study, 2 retrospective case reports (3;P)	No recommendation	-
Hyoscine butylbromidee	Unknown effect	No studies	Not identified	-	For people in the last days of life with obstructive bowel disorders who have nausea or vomiting, consider: hyoscine butylbromidee as the first-line pharmacological treatment or octreotidee if the symptoms do not improve within 24 hours of starting treatment with	Expert opinion (74;P)	No recommendation	-
Octreotidee								

					hyoscine butylbromidee.			

Legend
P: Palliative context
NP: Non-palliative context
P/NP: Both palliative and non-palliative conditions
Not identified: No recommendations on specific pharmacological treatment were identified.
Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.

[1]Level of evidence:
Level 1: Based on a systematic review or at least two randomized controlled trials of good quality
Level 2: Based on one at randomized controlled trial or at least two comparative clinical studies
Level 3: Based on one comparative study or on non-comparative studies
Level 4: Based on expert opinion
[2]Adult evidence is extracted from guidelines of pallialine.nl
[*]Level of child evidence might differ from level of evidence in 2013 as the same RCTs used in 2013 are now graded according to GRADE instead of AGREE.

References

3. Integraal Kankercentrum Nederland. Misselijkheid en braken (4.0). 2014. Available from: /www.pallialine.nl/misselijkheid-en-braken.
6. Dupuis LL, Robinson PD, Boodhan S, Holdsworth M, Portwine C, Gibson P, et al. Guideline for the prevention and treatment of anticipatory nausea and vomiting due to chemotherapy in pediatric cancer patients. Pediatr Blood Cancer. 2014;61(8):1506-12.
11. Flank J, Robinson PD, Holdsworth M, Phillips R, Portwine C, Gibson P, et al. Guideline for the Treatment of Breakthrough and the Prevention of Refractory Chemotherapy-Induced Nausea and Vomiting in Children With Cancer. Pediatr Blood Cancer. 2016;63(7):1144-51.
15. Naeim A, Dy SM, Lorenz KA, Sanati H, Walling A, Asch SM. Evidence-based recommendations for cancer nausea and vomiting. J Clin Oncol. 2008;26(23):3903-10.
17. Perkins P, Dorman S. Haloperidol for the treatment of nausea and vomiting in palliative care patients. Cochrane Database Syst Rev. 2009(2):CD006271.
28. Parker RI, Prakash D, Mahan RA, Giugliano DM, Atlas MP. Randomized, double-blind, crossover, placebo-controlled trial of intravenous ondansetron for the prevention of intrathecal chemotherapy-induced vomiting in children. Journal of pediatric hematology/oncology. 2001;23(9):578-81.
29. Aksoylar S, Akman SA, Ozgenc F, Kansoy S. Comparison of tropisetron and granisetron in the control of nausea and vomiting in children receiving combined cancer chemotherapy. Pediatr Hematol Oncol. 2001;18(6):397-406.
30. Ozkan A, Yildiz I, Yuksel L, Apak H, Celkan T. Tropisetron (Navoban) in the control of nausea and vomiting induced by combined cancer chemotherapy in children. Jpn J Clin Oncol. 1999;29(2):92-5.
31. Uysal KM, Olgun N, Sarialioglu F. Tropisetron in the prevention of chemotherapy-induced acute emesis in pediatric patients. Turk J Pediatr. 1999;41(2):207-18.
32. American Society of Clinical O, Kris MG, Hesketh PJ, Somerfield MR, Feyer P, Clark-Snow R, et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. J Clin Oncol. 2006;24(18):2932-47.
33. Drake R, Longworth J, Collins JJ. Opioid rotation in children with cancer. J Palliat Med. 2004;7(3):419-22.
34. Herrstedt J, Roila F, Group EGW. Chemotherapy-induced nausea and vomiting: ESMO clinical recommendations for prophylaxis. Ann Oncol. 2008;19 Suppl 2:ii110-2.
35. Roila F, Hesketh PJ, Herrstedt J, Antiemetic Subcommitte of the Multinational Association of Supportive Care in C. Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. Ann Oncol. 2006;17(1):20-8.
36. Santucci G, Mack JW. Common gastrointestinal symptoms in pediatric palliative care: nausea, vomiting, constipation, anorexia, cachexia. Pediatr Clin North Am. 2007;54(5):673-89, x.
37. Twycross R. Nausea and vomiting in advanced cancer. Europ J Pall Care 1998;5(2):39-44.
38. Ventaffrida V, Oliveri E, Caraceni A, Spoldi E, De Conno F, Saita L, et al. A retrospective study on the use of oral morphine in cancer pain. Journal of pain and symptom management. 1987;2(2):77-81.
39. Brock P, Brichard B, Rechnitzer C, Langeveld N, Lanning M, Söderhäll S, et al. An increased loading dose of ondansetron: a north European, double-blind randomised study in children, comparing 5 mg/m2 with 10 mg/m2. European Journal of Cancer. 1996;32(10):1744-8.
40. Köseoglu V, Kürekçi A, Sorici Ü, Atay A, Özcan O. Comparison of the efficacy and side-effects of ondansetron and metoclopramide-diphenhydramine administered to control nausea and vomiting in children treated with antineoplastic chemotherapy: a prospective randomized study. European journal of pediatrics. 1998;157(10):806-10.
41. Orchard PJ, Rogosheske J, Burns L, Rydholm N, Larson H, DeFor TE, et al. A prospective randomized trial of the anti-emetic efficacy of ondansetron and granisetron during bone marrow transplantation. Biol Blood Marrow Transplant. 1999;5(6):386-93.
42. Buchanan D, Muirhead K. Intractable nausea and vomiting successfully related with granisetron 5-hydroxytryptamine type 3 receptor antagonists in Palliative Medicine. Palliat Med. 2007;21(8):725-6.

43. Cole RM, Robinson F, Harvey L, Trethowan K, Murdoch V. Successful control of intractable nausea and vomiting requiring combined ondansetron and haloperidol in a patient with advanced cancer. J Pain Symptom Manage. 1994;9(1):48-50.
44. Currow DC, Coughlan M, Fardell B, Cooney NJ. Use of ondansetron in palliative medicine. J Pain Symptom Manage. 1997;13(5):302-7.
45. Ljutic D, Perkovic D, Rumboldt Z, Bagatin J, Hozo I, Pivac N. Comparison of ondansetron with metoclopramide in the symptomatic relief of uremia-induced nausea and vomiting. Kidney Blood Press Res. 2002;25(1):61-4.
46. Mystakidou K, Befon S, Liossi C, Vlachos L. Comparison of the efficacy and safety of tropisetron, metoclopramide, and chlorpromazine in the treatment of emesis associated with far advanced cancer. Cancer. 1998;83(6):1214-23.
47. Mystakidou K, Befon S, Liossi C, Vlachos L. Comparison of tropisetron and chlorpromazine combinations in the control of nausea and vomiting of patients with advanced cancer. J Pain Symptom Manage. 1998;15(3):176-84.
48. Mystakidou K, Befon S, Trifyllis J, Liossi C, Papadimitriou J. Tropisetron versus Metoclopramide in the Control of Emesis in Far-Advanced Cancer. Oncologist. 1997;2(5):319-23.
49. Nicholson S, Evans C, Mansi J. Ondansetron in intractable nausea and vomiting. Lancet. 1992;339(8791):490.
50. Porcel JM, Salud A, Porta J, Schoenenberger JA. Antiemetic efficacy of subcutaneous 5-HT3 receptor antagonists in terminal cancer patients. J Pain Symptom Manage. 1998;15(5):265-6.
51. Sussman G, Shurman J, Creed MR, Larsen LS, Ferrer-Brechner T, Noll D, et al. Intravenous ondansetron for the control of opioid-induced nausea and vomiting. International S3AA3013 Study Group. Clin Ther. 1999;21(7):1216-27.
52. Critchley P, Plach N, Grantham M, Marshall D, Taniguchi A, Latimer E, et al. Efficacy of haloperidol in the treatment of nausea and vomiting in the palliative patient: a systematic review. J Pain Symptom Manage. 2001;22(2):631-4.
53. Wolfe J, Hinds P. Textbook of Interdisciplinary Pediatric Palliative Care: Saunders; 2011.
54. Eisenchlas JH, Garrigue N, Junin M, De Simone GG. Low-dose levomepromazine in refractory emesis in advanced cancer patients: an open-label study. Palliat Med. 2005;19(1):71-5.
55. Kennett A, Hardy J, Shah S, A'Hern R. An open study of methotrimeprazine in the management of nausea and vomiting in patients with advanced cancer. Support Care Cancer. 2005;13(9):715-21.
56. Skinner J, Skinner A. Levomepromazine for nausea and vomiting in advanced cancer. Hosp Med. 1999;60(8):568-70.
57. Twycross R, Barkby GD, Hallwood P. The use of low dose levomepromazine (methotrimeprazine) in the management of nausea and vomiting. Progress in Palliative Care. 1997;5:49-53.
58. Gore L, Chawla S, Petrilli A, Hemenway M, Schissel D, Chua V, et al. Aprepitant in adolescent patients for prevention of chemotherapy-induced nausea and vomiting: a randomized, double-blind, placebo-controlled study of efficacy and tolerability. Pediatr Blood Cancer. 2009;52(2):242-7.
59. Diemunsch P, Gan TJ, Philip BK, Girao MJ, Eberhart L, Irwin MG, et al. Single-dose aprepitant vs ondansetron for the prevention of postoperative nausea and vomiting: a randomized, double-blind phase III trial in patients undergoing open abdominal surgery. Br J Anaesth. 2007;99(2):202-11.
60. Smith AR, Repka TL, Weigel BJ. Aprepitant for the control of chemotherapy induced nausea and vomiting in adolescents. Pediatr Blood Cancer. 2005;45(6):857-60.
61. Diemunsch P, Apfel C, Gan TJ, Candiotti K, Philip BK, Chelly J, et al. Preventing postoperative nausea and vomiting: post hoc analysis of pooled data from two randomized active-controlled trials of aprepitant. Curr Med Res Opin. 2007;23(10):2559-65.
62. Hall W, Degenhardt L. Medical marijuana initiatives : are they justified? How successful are they likely to be? CNS Drugs. 2003;17(10):689-97.
63. Bruera E, Moyano JR, Sala R, Rico MA, Bosnjak S, Bertolino M, et al. Dexamethasone in addition to metoclopramide for chronic nausea in patients with advanced cancer: a randomized controlled trial. J Pain Symptom Manage. 2004;28(4):381-8.
64. Bruera E, Seifert L, Watanabe S, Babul N, Darke A, Harsanyi Z, et al. Chronic nausea in advanced cancer patients: a retrospective assessment of a metoclopramide-based antiemetic regimen. J Pain Symptom Manage. 1996;11(3):147-53.
65. Hardy JR, Rees E, Ling J, Burman R, Feuer D, Broadley K, et al. A prospective survey of the use of dexamethasone on a palliative care unit. Palliat Med. 2001;15(1):3-8.
66. Riad W, Altaf R, Abdulla A, Oudan H. Effect of midazolam, dexamethasone and their combination on the prevention of nausea and vomiting following strabismus repair in children. Eur J Anaesthesiol. 2007;24(8):697-701.
67. Davis MP, Hallerberg G. A systematic review of the treatment of nausea and/or vomiting in cancer unrelated to chemotherapy or radiation. J Pain Symptom Manage. 2010;39(4):756-67.
68. Bishop JF, Olver IN, Wolf MM, Matthews JP, Long M, Bingham J, et al. Lorazepam: a randomized, double-blind, crossover study of a new antiemetic in patients receiving cytotoxic chemotherapy and prochlorperazine. J Clin Oncol. 1984;2(6):691-5.
69. Kearsley JH, Williams AM, Fiumara A-M. Antiemetic superiority of lorazepam over oxazepam and methylprednisolone as premedicants for patients receiving cisplatin-containing chemotherapy. Cancer. 1989;64(8):1595-9.
70. Glover ML, Kodish E, Reed MD. Continuous propofol infusion for the relief of treatment-resistant discomfort in a terminally ill pediatric patient with cancer. J Pediatr Hematol Oncol. 1996;18(4):377-80.
71. Lundström S, Zachrisson U, Fürst CJ. When Nothing Helps: Propofol as Sedative and Antiemetic in Palliative Cancer Care. Journal of Pain and Symptom Management. 2005;30(6):570-7.
72. Borgeat A, Wilder-Smith OH, Saiah M, Rifat K. Subhypnotic doses of propofol possess direct antiemetic properties. Anesth Analg. 1992;74(4):539-41.
73. Gan TJ, Ginsberg B, Grant AP, Glass PS. Double-blind, randomized comparison of ondansetron and intraoperative propofol to prevent postoperative nausea and vomiting. Anesthesiology. 1996;85(5):1036-42.
74. National Institute for Health and Care Excellence. Care of dying adults in the last days of life. [Internet]. London: NICE; 2015 [cited 2021 March, 1]. Available from: www.nice.org.uk/guidance/ng31.

H Neurologische symptomen

Inhoudsopgave

1 Uitgangsvragen

Vraag 8A**:** Wat is de meest effectieve niet-medicamenteuze behandeling (o.a. saneren van medicatie) voor neurologische symptomen (epilepsie, bewegingsstoornissen, spasticiteit en uitvalsverschijnselen) bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Niet-medicamenteuze behandeling van neurologische symptomen
C: Geen behandeling/placebo
O: Effect op neurologische symptomen en kwaliteit van leven

Vraag 8B: Wat is de meest effectieve medicamenteuze behandeling voor neurologische symptomen (epilepsie, bewegingsstoornissen, spasticiteit en uitvalsverschijnselen) bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Medicamenteuze behandeling van neurologische symptomen
C: Geen behandeling/placebo
O: Effect op neurologische symptomen en kwaliteit van leven

2 Resultaten van het literatuuronderzoek

Jaar	Bibliografie	Studie karakteristieken
8A: Wat is de meest effectieve niet-medicamenteuze behandeling (o.a. saneren van medicatie) voor neurologische symptomen (epilepsie, bewegingsstoornissen, spasticiteit en uitvalsverschijnselen) bij kinderen tussen 0 en 18 jaar in de palliatieve fase?*		
Epilepsie		
2017	***Nederlandse Vereniging voor Neurologie.*** Epilepsie. 2017 (previous versions, 2013) via https://epilepsie.neurologie.nl/cmssite7/index.php[1]	Richtlijn kinderen en volwassenen
2019	***National institute for health and care Excellence (NICE).***The epilepsies, the diagnosis and management in adults and children in primary and secondary care.2019 (previous versions, 2012,2013,2015, 2018)[1]	Richtlijn kinderen en volwassenen
Bewegingsstoornissen		
Geen literatuur beschikbaar		
Spasticiteit		
2016	***National institute for health and care Excellence (NICE).*** Spasticity in children and young people with non-progressive brain disorders. 2016 (previous version 2012) [1]	Richtlijn kinderen
Uitvalsverschijnselen		
Geen literatuur beschikbaar		
8B: Wat is de meest effectieve medicamenteuze behandeling voor neurologische symptomen (epilepsie, bewegingsstoornissen, spasticiteit en uitvalsverschijnselen) bij kinderen tussen 0 en 18 jaar in de palliatieve fase?*		
Epilepsie		
2016	***National institute for health and care Excellence (NICE).*** End of life care for infants, children and young people: planning and management. 2016[1]	Richtlijn kinderen
2017	***Nederlandse Vereniging voor Neurologie.*** Epilepsie. 2017 (previous versions, 2013) via https://epilepsie.neurologie.nl/cmssite7/index.php[1]	Richtlijn kinderen en volwassenen
2019	***National institute for health and care Excellence (NICE).***The epilepsies, the diagnosis and management in adults and children in primary and secondary care.2019 (previous versions, 2012,2013,2015, 2018)	Richtlijn kinderen en volwassenen
Bewegingsstoornissen		
Geen literatuur beschikbaar		
Spasticiteit		
2012	***National institute for health and care Excellence (NICE).*** Spasticity in children and young people with non-progressive brain disorders. 2016 (previous versions, 2012)[1]	Richtlijn kinderen
2010	***Olesch CA et al.*** Repeat botulinum toxin-A injections in the upper limb of children with hemiplegia: a randomized controlled trial, Developmental Medicine and Child Neurology, 52, 79-86, 2010 [2]	RCT kinderen
2014	***Copeland I et al.*** Botulinum toxin A for nonambulatory children with cerebral palsy: a double blind randomized controlled trial. J Pediatr 2014;165:140-6).	RCT kinderen
Uitvalsverschijnselen		
Geen literatuur beschikbaar		

[1]Aanbevelingen uit de richtlijnen over neurologische symptomen worden gebruikt in de overwegingen.
[2]RCT is uit de volgende richtlijn gehaald: *National institute for health and care Excellence (NICE*). Spasticity in children and young people with non-progressive brain disorders. 2016 (previous versions, 2012)
* Systematisch gezocht, zie: bijlage 7 zoekverantwoording – search 1

3 Evidence tabellen

3.1 Medicamenteuze behandeling van neurologische symptomen

3.1.1 Spasticiteit

Pharmacological treatment for spasticity				
Olesch CA et al. Repeat botulinum toxin-A injections in the upper limb of children with hemiplegia: a randomized controlled trial, Developmental Medicine and Child Neurology, 52, 79-86, 2010				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: RCT Setting: Single-center, Melbourne, Australia Duration: Outcomes were assessed at baseline, 6 weeks after injection and 16 weeks before the next infection, and after 12 months Study years: *June 2001-April 2005* Protocol published in register: (*clinicaltrials.gov / WHO register*): not mentioned	Number and type of participants: *N=22, children with congenital hemiplegic Cerebal Palsy with spasticity affecting upper-limb but no fixed contracture. Aged between 1year 6mths and 5years-old* • Intervention group: 11 • Control group: 11 Age: *(mean, median, range)* • Intervention group: Mean 3:8 (y:mo) SD 1:0, Range: 1:10 y:mo – 4:10 y:mo • Control group: Mean 3:8, SD 0:10, Range: 1:10 y:mo – 4:10 y:mo Sex: *(N (%))* • Intervention group: M: 10 (90.9%), F: 1 (9.1%)90.9% • Control group: M: 9 (81.8%), F: 2(18.2%) Other: *At baseline there was a clinically relevant differences in QUEST-scores and spasticity in the fore-arm pronators (p-values not mentioned)*	Type of intervention: Children received three series of Botulinum Toxin A injections in 16-week cycles in addition to twice-weekly OT. Occupational therapist and physician determined which muscle groups should be targeted. The same muscle groups were targeted each injection cycle. Total dose was dependent on body weight. Generic OT protocol (not further specified, but available on request) was developed and individualized for each child: twice weekly programme for 6 weeks after injection. First two weeks of intense therapy by study therapist and after this with same intensity by community therapist. Therapists were not blinded. Therapy based on goal-directed approach. Part of the therapy consisted of home-based activities. The adherence to this home-based program was not recorded. Type of control:	Outcome definitions: **Primary outcome:** Parental perception of treatment efficacy (in terms of goal achievement): Assessed by: • Canadian Occuppational Performance Measure (COPM), semi-structured interview. rating of occupational performance difficulties • Goal Attainment Scale (GAS): and setting of individualized goals. **Secondary outcomes:** Level of spasticity: Assessed by an occupational therapist using the Modified Tardieu Scale (MTS). The occupational therapist was blinded for allocation. Motor performance: Assessed by using the Quality of Upper Extremity Skills Test (QUEST) and Peabody Development Motor Scales -Fine motor (PDMS-FM). The QUEST and PDMS-FM were videotaped and scored later by a blinded rater. Results (per outcome) **Parental perception of treatment efficacy:** *COPM performance scores in the intervention group were improved at 12 months.* • Mean (SD) at 12 months (control vs intervention): 1.7 (0.6) vs 2.5 (1.0) • Difference between groups: -0.8 (95% CI -1.5 to 0.0), p = 0.047 *Satisfaction of COPM not significantly improved in the intervention group at 12 months:* • Mean (SD) at 12 months (control vs intervention): : 1.7 (0.9) vs 2.5 (1.1) • Difference between groups (-0.8 (95%CI -1.7 to 0.1), p = 0.090 *GAS T-scores were improved at 12 months in the intervention group* • Mean (SD) at 12 months(control vs intervention): : 48.8 (9.6) vs 5.8 (6.6) • Difference between groups -6.9 (95% -13.8 to -0.1), p = 0.047. **Level of spasticity (measured by Modified Tardieu Scale)** *Level of spasticity at intervention cycle 3 was lower in children treated with BONT-A (intervention group) with regard to:* *Forearm pronators:*	Strengths: -Single centre study -Both groups received, although individualized, the same cycle of OT programme Limitations: -Too small sample size: They did not reach the sample size needed to detect large of moderate effects. -OT was partly based om home-based activities of which the adherence was not recorded. - **Risk of bias** A. Selection bias: low risk Reason: low risk, allocation sequence remained concealed from the investigator enrolling participants until after the interventions were assigned. B. Attrition bias: low risk. Reason: No patients were lost to follow-up. C. Performance bias High risk Parents and treating OT were not blinded.

		Same OT program as mentioned above at a comparable time point as the group with injection.	• Mean (SD) scores at cycle 3 (control vs intervention): 72.2 (28.7) vs 22.7 (3.2 (7.2) • Difference between groups: 50.0 (95%CI 2.4 – 77.6), p = 0.009) *Wrist flexors:* • Mean (SD) scores at cycle 3 (control vs intervention): 24.1 (28.5) vs 3.2 (7.2) • Difference between groups: 20.9 (95%CI 2.4 – 39.4), p = 0.029 *Level of spasticity was not significantly lower in children with BONT-A (intervention group) with regard to:* *Elbow flexors:* • Mean (SD) scores at cycle 3 (control vs intervention): 77.3 (56.2) 34.5 (48.0) • Difference between groups: 42.7 (95%CI -3.8 – 89.2)), p = 0.070 **Motor performance (measured by QUEST)** *Quest summary scores and PDMS-FM were not different between the two groups.* *QUEST* • Mean (SD) total QUEST Score at cycle 3 (control vs intervention): 72.9 (11.5) vs 79.6 (8.0) • Difference between groups: -6.7 (-15.5 to 17.6), p = 0.833 *PDMS-FM* • Mean (SD) Score at cycle 3 (control vs intervention): 537.6 (37.2) vs 542.6 (36.2) • Difference between groups: -5.0 (-37.6 to 27.6), p = 0.753 **Adverse events** Three adverse events were reported: Maculopapular rash (n = 1), weakness of the index finger (n = 1), prolonged weakness in finger flexors (n = 1)	<u>D. Detection bias</u> Unclear Parents who scored the primary outcomes were not blinded. The Occupational therapist who scored spasticity and the person who rated motor performance were blinded

Pharmacological treatment for spasticity				
Copeland I et al. Botulinum toxin A for nonambulatory children with cerebral palsy: a double blind randomized controlled trial. J Pediatr 2014;165:140-6				
Study characteristics	**Patient characteristics**	**Intervention / Control**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: RCT, double blind Setting: Single centre, Australia Duration: Canadian Occupational Performance Measure (COPM) at 4 (immediate effect) and 16 (retention) weeks post intervention. Study years: *Not reported* Protocol published in register: Australia New Zealand Clinical Trials Registry:N12609000360213, PMID 22873758	Number and type of participants: *Total of 41 nonambulant children with cerebral palsy at GMFCS levels IV or V, aged 2-16 years, with spasticity in the upper and/or lower limbs causing discomfort and/or increased burden of care Stratification to primary goal areas (upper or lower limb) prior to randomized allocation.* *Exclusion criteria: weight < 10 kg, medical contraindication to BoNT-A.* • Intervention group: 23 children • Control group: 18 children Age: • Intervention group: Mean/SD: 7y1m (3y7m), Range NA • Control group: Mean/SD: 7y5m (3y9m), Range NA Sex: • Intervention group: M: 16 (70%), F: 7 (30%) • Control group: M: 11 (61%), F: 7 (39%) There were no differences observed between groups on baseline measures regarding GMFCS or MACS level classification, or baseline questionnaire score. Other: *Predominant goal area:* Intervention group: upper limbs 12 (52.2%), lower limbs 11 (47.8%) Control group: upper limbs 9 (50%), lower limbs 9 (50%)	Type of intervention: Intramuscular botulinum toxin A (BoNT-A), 0.5-4 units botox/kg/muscle group, maximum dose 12 U botox/kg/body weight (or total 400 units). Following injections each participant received a block of occupational therapy or physical therapy, which commenced within 2 weeks. Dose of therapy between groups was similar. Type of control: Intramuscular sham. Following sham procedure. Each participant received a block of occupational or physical therapy, within 2 weeks. Treatment regimens were determined prior to randomization based on individual ease of care and comfort goals. Dose of therapy between groups was similar.	Outcome definitions: **Primary outcomes** Parental perception of treatment efficacy: Parent reported change in performance and satisfaction in areas of concern for care and comfort. This was assessed by the Canadian Occupational Performance Measure (COPM) Positive value indicates improvement of COPM scores for the intervention group in comparison to the control. More than 2 points change is clinically meaningful. **Secondary outcomes** For secondary measures of efficacy the following questionnaires were uses: CPCHILD - Caregiver Priorities and Child Health Index of Life with Disabilities: Positive value indicates improvement in score CCHQ - Care and Comfort Hypertonicity Questionnaire: Positive value indicates improvement in score CPQOL-child - Cerebral Palsy Quality of Life Questionnaire for children: Positive value indicates improvement in score PPP - Pediatric Pain Profile: Reduction in score indicate improvement in pain **Adverse events** were measured at 2, 4, 16 weeks. Results (per outcome): **Primary outcomes** *COPM performance* Estimated mean difference (EMD) between groups (baseline - 4 weeks): 2.2 (95% CI 0.9-3.5; p= .001; EMD between groups (baseline – 16 weeks): 1.2 (95%CI -0.0 – 2.5); p= NS Effect was not sustained at 16 weeks. *COPM satisfaction* EMD between groups (baseline - 4 weeks): 2.3, (95%CI 0.6-3.9), p= .007. EMD between groups (baseline – 16 weeks): 1.8 (95% CI 0.2-3.5); p= .03. **Secondary outcomes**	Strengths: Double-blinded, randomized study Limitations: Information on potential difference between previously prescribed oral or intrathecal medication is lacking. Outcomes are parent reported. Reported EMD and p-values were in abstract and results section are not corresponding. **Risk of bias** A. Selection bias: low risk Reason: there was random allocation of patients into groups and allocation concealment B. Attrition bias: low risk Reason: no children withdrew from the study. PPP results were reported for 18 children as not all children reported pain at baseline. C. Performance bias low risk Reason: the participants and

			A significant between groups difference was only observed at 16 weeks for outcome of health status using CPCHILD scores. *CPCHILD* EMD between groups (baseline - 4 weeks): 3.7 (95%CI -2.6 – 9.9; p= .NS; EMD between groups (baseline – 16 weeks): 6.8 (95%CI 1.8 – 11.8); p= .008 *CCHQ* EMD between groups (baseline - 4 weeks): 3.7 (95%CI -0.9 – 0.2; p= .NS; EMD between groups (baseline – 16 weeks): -0.3 (95%CI -0.9 – 0.2); p= NS *CPQOL-Child* EMD between groups (baseline - 4 weeks): 3.7 (95%CI -0.5 - 8.0); p= .NS; EMD between groups (baseline – 16 weeks): 2.0 (95%CI -2.9 – 6.8); p= NS *PPP* EMD between groups (baseline - 4 weeks): -0.7 (95%CI -15.6 – 14.1)); p= .NS; EMD between groups (baseline – 16 weeks): 4.5(95%CI -9.5 – 18.5) p= NS **Adverse events (AE):** All adverse events (mild, moderate and serious) significantly increased compared with the control group (p = 0.02). When Mild AEs were excluded, no significant difference for moderate and serious AEs were found.	personnel were blinded from knowledge of which intervention was received <u>D. Detection bias</u> low risk Reason: outcome assessors were blinded from knowledge of which intervention was received

4 Samenvatting en gradering van bewijs

4.1 Medicamenteuze behandeling van neurologische symptomen

4.1.1 Spasticiteit

4.1.1.1 Geïncludeerde uitkomstmaten

Included outcomes
Parent-reported treatment efficacy
Level of spasticity
Level of motor performance
Quality of life

4.1.1.2 Botulinetoxine type A injecties

Botulinum Toxin A injections				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Parent reported treatment efficacy - Canadian Occupational Performance Measure, range of score is not reported				
1) Olesh, 2010	1) Children with Cerebral Palsy (CP) aged 1 to 5 yrs.	1) 22 (11 vs 11)	1) Repeated botulinum toxin-A injections (n=3) with occupational therapy (OT) vs OT only 2) Botulinum toxin-A injection (n=1) with OT vs intramuscular sham with OT	1)**Treatment efficacy at 12 month follow-up:** Estimated Mean Difference (EMD) $_{control - intervention}$: -0.8 (95%CI -1.5 – 0.0), p = 0.04
2) Copeland, 2014	2) Children with Cerebral palsy aged 2 to 16 yrs.	2) 41 (23 vs 18)		2) **Treatment efficacy at 1 month follow-up:** EMD $_{intervention - control}$ = 2.2 (95%CI 0.9 – 3.5), p =0.001 **Treatment efficacy at 4 month follow-up:** EMD $_{intervention - control}$ = 1.2 (95%CI 0.0-2.5), p = NS
Grade assessment				
Study design:	+4	2 Randomized Controlled Trials		
Study limitations	-1	Some limitations - Selection bias: Low in 2/2; Attrition bias low in 2/2; Performance bias high in 1/2 and low in 1/2; Detection bias: low in 1/2 and unclear in 1/2		
Consistency:	0	No important inconsistency. All studies show that treatment efficacy is higher in children receiving botulinum toxin-A. In 1 study the relation at 4 months was not significant.		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	-1	Some imprecision due to small sample sizes		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊕⊖⊖ **LOW**		
Conclusion:		**There is low quality of evidence that Botulinum Toxin-A injection (n = 1 to 3) and OT in children with Cerebral Palsy increases treatment efficacy perceived by parents as compared to treatment with OT only. It is yet unclear whether this effect sustains over a longer period of time. Long-term effect might be dependent on the amount of injections received by the patient.**		

Botulinum Toxin A injections				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Level of spasticity Modified Tardieu scale, range of scores is not reported.				
Olesh, 2010	Children with Cerebral Palsy (CP) aged 1 to 5 yrs.	22 (11 vs 11)	Repeated botulinum toxin-A injections (n=3) with occupational therapy (OT) vs OT only	**Level of spasticity forearm pronators at 12 month follow-up:** $EMD_{control - intervention}$ = 50.0 (95%CI 2.4 – 77.6), p = 0.009 **Level of spasticity wrists flexors at 12 month follow-up:** $EMD_{control - intervention}$ = 20.9 (95%CI 2.4 – 39.4), p = 0.029 **Level of spasticity elbow flexors at 12-month follow-up:** $EMD_{control - intervention}$ = 42.7 (95%CI -3.8 – 89.2), p = 0.070
Grade assessment				
Study design:	+4	1 Randomized Controlled Trial		
Study limitations	-1	Some limitations - Selection bias: Low; Attrition: bias low; Performance bias: high; Detection bias: unclear		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Results are direct. Outcomes generalizable.		
Precision:	-2	Important imprecision due to small sample size. Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence that repeated Botulinum toxin-A injections (n=3) and OT in children with Cerebral Palsy significantly decrease spasticity levels in upper limbs (forearm and wrist) as compared to treatment with OT only.**		

Botulinum Toxin A injections				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Level of motor performance Quality of Upper Extremity Skills Test (QUEST) and Peabody Development Motor Scales – Fine motor (PDMS-FM) Range of score is not reported				
Olesh, 2010	Children with Cerebral Palsy (CP) aged 1 to 5 yrs.	22 (11 vs 11)	1) Repeated botulinum toxin-A injections (n=3) with occupational therapy (OT) vs OT only	**level of motor performance assessed by QUEST[3] at 12-month follow-up:** EMD $_{control - intervention}$= -6.7 (-15.5 to 17.6), p = 0.833 **level of motor performance assessed by PDMS-FM[3] at 12-month follow-up:** EMD $_{control - intervention}$ = -5.0 (-37.6 to 27.6), p = 0.753
Grade assessment				
Study design:	+4	1 Randomized Controlled Trial		
Study limitations	-1	Some limitations - Selection bias: Low; Attrition: bias low; Performance bias: high; Detection bias: unclear		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Results are direct. Outcomes generalizable.		
Precision:	-2	Important imprecision due to small sample size. Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence that there is no significant effect of repeated botulinum toxin A injections (n = 3) and OT on motor performance in children with Cerebral Palsy as compared to treatment with OT only.**		

Botulinum Toxin A injections				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Quality of life Cerebral Palsy Quality of Life Questionnaire for children (CPQL-child), Range of score is not reported, Positive value indicates improvement in score				
1) Copeland, 2014	1) Children with Cerebral palsy aged 2 to 16 yrs.	1) 41 (23 vs 18)	1) Botulinum toxin-A injection (n=1) with OT vs intramuscular sham with OT	1) **Quality of Life at 1 month follow-up:** EMD $_{intervention - control}$ = 3.7 (95%CI -0.5 - 8.0); p= .NS **Quality of Life at 4 month follow-up :** EMD $_{intervention - control}$ = 2.0 (95%CI -2.9 – 6.8); p= NS
Grade assessment				
Study design:	+4	1 Randomized Controlled Trials		
Study limitations	0	No important limitations - Selection bias: Low; Attrition: bias low; Performance bias: low; Detection bias: low		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Results are direct. Outcomes generalizable.		
Precision:	-2	Some imprecision. Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship.		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊕⊖⊖ **LOW**		
Conclusion:		**There is low quality of evidence that there is no significant effect of botulinum toxin-A injection with OT on quality of life in children with Cerebral Palsy as compared to treatment with intramuscular sham and OT**		

5 Conclusies van evidence

5.1 Niet-medicamenteuze behandeling van neurologische symptomen

Non pharmacological treatment of neurological symptoms		
Intervention	**Conclusions of evidence**	**Quality of evidence**
Loss of neurological function		
Eyepatch/masking glasses *Optimal nutrition* *Stomach pump* *Thickening of nutrition*	Unknown effect	No studies

5.2 Medicamenteuze behandeling van neurologische symptomen

Pharmacological treatment of neurological symptoms		
Intervention	**Conclusions of evidence**	**Quality of evidence**
Epilepsy		
Midazolam (buccal, nasal, intramuscular) *Midazolam (continuous, intravenous)* *Diazepam (rectal)* *Clonazepam* *Levetiracetam* *Sodium valproate* *Carbamazepine* *Phenobarbital* *Clobazam* *Phenytoin*	Unknown effect	No studies
Dyskinesia syndromes		
Bipiridene (Akineton®) *Benzodiazepines (diazepam/midazolam)* *Baclofen*	Unknown effect	No studies
Spasticity		
Baclofen *Baclofen + tizanidine (Sirdalud®)* *Benzodiazepines (diazepam/midazolam)*	Unknown effect	No studies
Botulinum Toxin-A injections (n = 1-3) and OT *vs. OT or intramuscular sham and OT*	↑ parent-reported treatment efficacy in children with cerebral palsy after intervention; Long-term effect might be dependent on the amount of injections received by the patient	⊕⊕⊖⊖ LOW (2RCTs)
Botulinum Toxin-A injections (n = 3) and OT *vs. OT*	↓ spasticity levels of upper limbs (forearm and wrists) in children with cerebral palsy after intervention	⊕⊖⊖⊖ VERY LOW (1RCT)
Botulinum Toxin-A injections (n = 3) and OT *vs. OT*	No significant effect on motor performance in children with cerebral palsy	⊕⊖⊖⊖ VERY LOW (1RCT)
Botulinum Toxin-A injections (n = 1) and OT *vs. intramuscular sham and OT*	No significant effect on quality of life in children with cerebral palsy	⊕⊖⊖⊖ VERY LOW (1RCT)
Loss of neurological function		
Methylcellulose eyedrops *Oculentum simplex ointment*	Unknown effect	No studies

6 Aanbevelingen uit richtlijnen

6.1 Niet-medicamenteuze behandeling van neurologische symptomen

6.1.1 Epilepsie

Non pharmacological treatment of epilepsy – Child and Adult guideline	
Nederlandse Vereniging voor Neurologie. Epilepsie. 2017 (previous versions, 2013) Let op: Versie 2012 van richtlijn '***National institute for health and care Excellence (NICE).***The epilepsies, the diagnosis and management in adults and children in primary and secondary care.2019 (previous versions, 2012,2013,2015, 2018)' is als basis gebruikt voor deze richtlijn.	
Recommendation	**Level of evidence[1]**
Ketogeen dieet	
Behandel patiënten met het GLUT-1 deficiëntiesyndroom of met pyruvaat dehydrogenase deficiëntie als eerste keus met het ketogeen dieet.	Laag/Matig
Overweeg het ketogeen dieet bij kinderen, mogelijk ook volwassenen, met moeilijk instelbare epilepsie (twee of meer mislukte pogingen tot aanvalscontrole met anti-epileptica) waarbij epilepsiechirurgie geen mogelijkheid is.	Laag/Matig
Bepaal binnen twee tot vier maanden na implementatie van het ketogeen dieet of het dieet moet/kan worden voortgezet.	Laag/Matig
[1]Level of evidence: **Hoog:** Onderzoek van niveau meta-analyse van minimaal 2 onafhankelijk van elkaar uitgevoerde gerandomiseerde dubbelblind vergelijkende klinische onderzoeken of tenminste twee onafhankelijk van elkaar uitgevoerde onderzoeken **Matig:** één gerandomiseerd dubbelblind vergelijkend klinische onderzoek of ten minste twee onafhankelijk van elkaar uitgevoerde vergelijkende onderzoeken (patient-controle onderzoek, cohort onderzoek). **Laag:** één vergelijkend onderzoek of niet-vergelijkend onderzoek **Zeer laag:** Mening van deskundigen	

Non pharmacological treatment of epilepsy – Child and Adult guideline	
National institute for health and care Excellence (NICE).The epilepsies, the diagnosis and management in adults and children in primary and secondary care.2019 (previous versions, 2012,2013,2015, 2018)	
Recommendation	**Level of evidence**
Psychological methods	
No report of clinical evidence	
Psychological interventions may be used as adjunctive therapy. They have not been proven to affect seizure frequency and are not an alternative to pharmacological treatment.	Expert opinion
Psychological interventions (relaxation, cognitive behaviour therapy, and biofeedback) may be used in conjunction with AED therapy in adults where either the person or the specialist considers seizure control to be inadequate with optimal AED therapy. This approach may be associated with an improved quality of life in some people.	Expert opinion
Psychological interventions (relaxation, cognitive behaviour therapy) may be used in children and young people with drug-resistant focal epilepsy.	Expert opinion
Ketogenic diet	
Clinical evidence: *3 RCTs were identified, 2 unblinded RCTs and 1 double-blinded RCT*	
Refer children and young people with epilepsy whose seizures have not responded to appropriate AEDs to a tertiary paediatric epilepsy specialist for consideration of the use of a ketogenic diet.	Expert opinion

6.1.2 *Spasticiteit*

Non pharmacological treatment of spasticity – Child guideline	
National institute for health and care Excellence (NICE). Spasticity in children and young people with non-progressive brain disorders. 2016 (previous version 2012)	
Recommendation	**Level of evidence**
Physical therapy (physiotherapy and/or occupational therapy)	
Clinical evidence: *12 studies were identified for inclusion. The studies addressed five comparisons: Active use therapy vs. no active use therapy (3 parallel randomized controlled trials); comparisons between different forms of active use therapy (2 RCTs); Strengthening vs. usual care not including strengthening (5 parallel RCTs); Serial casting vs. usual care not including serial casting (1 cross-over RCT); Early caster after BoNT vs. delayed casting after BoNT (1 parallel RCT).* ***Key conclusions:*** *Provision of physical therapy throughout childhood and into adult life has significant resource implications. The GDG acknowledged that the evidence for effectiveness for various commonly employed physical therapy interventions (including regimens aimed at muscle strengthening, stretching and postural management) was limited. Nevertheless, the group believed, based on the rational principles underlying these regimens and their experience of using these forms of physical therapy in practice, that when employed in suitably selected children and young people they were an essential component of management.*	
General principles	
All children and young people with spasticity referred to the network team should be promptly assessed by a physiotherapist and, where necessary, an occupational therapist.	Expert opinion
Offer a physical therapy (physiotherapy and/or occupational therapy) programme tailored to the child or young person's individual needs and aimed at specific goals, such as: • enhancing skill development, function and ability to participate in everyday activities • preventing consequences such as pain or contractures.	low-high
Give children and young people and their parents or carers verbal and written (or appropriate formats) information about the physical therapy interventions needed to achieve the intended goals. This information should emphasise the balance between possible benefits and difficulties (for example, time commitment or discomfort), to enable them to participate in choosing a suitable physical therapy programme.	Expert opinion
When formulating a physical therapy programme for children and young people take into account: • the views of the child or young person and their parents or carers • the likelihood of achieving the treatment goals • possible difficulties in implementing the programme • implications for the individual child or young person and their parents or carers, including the time and effort involved and potential individual barriers.	Expert opinion
When deciding who should deliver physical therapy, take into account: • whether the child or young person and their parents or carers are able to deliver the specific therapy • what training the child or young person or their parents or carers might need • the wishes of the child or young person and their parents or carers.	Expert opinion
Ensure that any equipment or techniques used in the physical therapy programme are safe and appropriate, in particular for children or young people with any of the following: • poorly controlled epilepsy • respiratory compromise • increased risk of pulmonary aspiration • increased risk of bone fracture due to osteoporosis (for example, those who are unable to walk, malnourished or taking anti-epileptic therapy).	Expert opinion
Encourage children and young people and their parents or carers to incorporate physical therapy into daily activities (for example, standing at the sink while brushing teeth in order to stretch leg muscles).	Expert opinion
Continuing assessment	
Reassess the physical therapy programme at regular intervals to ensure that: • the goals are being achieved • the programme remains appropriate to the child or young person's needs.	Expert opinion
Other:	
Recognise the following clinical findings as possible indicators of hip displacement (hip migration greater than 30%):	Expert opinion

• pain arising from the hip • clinically important leg length difference • deterioration in hip abduction or range of hip movement • increasing hip muscle tone • deterioration in sitting or standing • increasing difficulty with perineal care or hygiene.	

6.2 Medicamenteuze behandeling van neurologische symptomen (epilepsie, bewegingsstoornissen, spasticiteit en uitvalsverschijnselen)

6.2.1 Epilepsie

Pharmacological treatment of epilepsy – Child guideline	
National institute for health and care Excellence (NICE).End of life care for infants, children and young people: planning and management. 2016	
Recommendation	**Level of evidence**
No evidence found *Key conclusions:* The Committee concluded that due to the lack of evidence, recommendations would be mainly based on Committee members' clinical experience, expert opinion and consensus regarding accepted good clinical practice.	
If a child or young person is approaching the end of life and has a seizure, look for and if possible treat or remove any potential causes, triggers or contributing factors, for example: • fever • electrolyte disturbances • drug reactions • sleep deprivation • pain • excessive environmental stimulation.	Expert opinion
If a child or young person is thought to be at increased risk of seizures (for example because they have had seizures before or because of an existing brain disorder), include seizure management in their Advance Care Plan. Think about the benefits and drawbacks of specific seizure treatments and: • take into account how any decisions could affect the choices available for place of care and place of death and • discuss this with the child or young person and their parents or carers.	Expert opinion
For children and young people who are approaching the end of life, be aware that abnormal movements (such as dystonic spasms) might be mistaken for seizures. If in doubt seek specialist advice.	Expert opinion
If a child or young person is approaching the end of life and is thought to be at increased risk of seizures, explain to them and their parents or carers: • how likely it is that they may have a seizure • what they might notice if a seizure happens • that seizures can be frightening or upsetting • what parents or carers should do if a seizure happens at home (for example placing the child or young person in a safe position).	Expert opinion
Ensure that parents or carers who have been provided with anticonvulsive therapy (such as buccal midazolam) know how and when to use it if the child or young person has a seizure at home.	Expert opinion

Pharmacological treatment of epilepsy – Child and Adult guideline	
Nederlandse Vereniging voor Neurologie. Epilepsie. 2017 (previous versions, 2013) Let op: Versie 2012 van richtlijn '***National institute for health and care Excellence (NICE).***The epilepsies, the diagnosis and management in adults and children in primary and secondary care.2019 (previous versions, 2012,2013,2015, 2018)' is als basis gebruikt voor deze richtlijn.	
Recommendation[1]	**Level of evidence**
Status epilepticus	
Convulsieve status epilepticus bij kinderen buiten het ziekenhuis	
Overweeg in plaats van diazepam rectaal, midazolam voor buccale of nasale toediening te verstrekken aan ouders / verzorgers van kinderen, indien er een indicatie is voor noodmedicatie.	Zeer laag tot matig
Gebruik een dosering van 0.2 tot 0.25 mg/kg met een maximum van 10 mg voor midazolam buccaal, nasaal of intramusculair. Dien een tweede dosering toe wanneer de eerste dosering 5 minuten na toediening nog geen resultaat heeft. Zorg er bij de tweede dosering voor dat de totale hoeveelheid het maximum van 0.5 mg/kg of 10 mg niet overschrijdt zonder adequate mogelijkheden om de vitale functies te bewaken en in te grijpen (dus op een spoedeisende hulp (SEH), intensive care (IC)). **Dien niet vaker dan twee keer noodmedicatie toe in verband met de verhoogde kans op ademdepressie.**	Zeer laag tot matig
Bespreek het gebruik van noodmedicatie, de maximale dosering en het maximale aantal toedieningen niet alleen mondeling met de ouders / verzorgers, maar geef hen deze informatie ook schriftelijk mee.	Zeer laag tot matig
Convulsieve status epilepticus op de spoedeisende hulp	
Coupeer bij een kind met een status epilepticus zo snel mogelijk met midazolam nasaal, buccaal, of intramusculair wanneer er geen aanwezige intraveneuze toegang is. Breng direct hierna een intraveneuze toegang aan.	zeer laag tot hoog
Coupeer intraveneus met midazolam of lorazepam indien er al een intraveneuze toegang bestaat.	zeer laag tot hoog
Gebruik of fenytoïne of valproaat of levetiracetam (alle intraveneus) om een voortdurende convulsieve status epilepticus te couperen.	zeer laag tot hoog
Gebruik wanneer de convulsieve status epilepticus effectief is onderdrukt en men wel intraveneus wil opladen bij voorkeur valproaat of levetiracetam omdat fenytoïne geen eerste keus middel is voor langdurende behandeling.	zeer laag tot hoog
Gebruik fenytoïne niet bij cardiale problemen, gebleken overgevoeligheid voor fenytoïne, bij falen van fenytoïne bij een eerdere status en bij een aantal specifieke epilepsiesyndromen.	zeer laag tot hoog
Wees terughoudend met valproaat bij leverziekten, mogelijke stollingsstoornissen, verdenking op een metabole ziekte en bij kinderen onder de 2 jaar vanwege het risico op het Reye syndroom.	zeer laag tot hoog
Refractaire status	
Zorg bij een refractaire status epilepticus eerst voor stabilisatie van vitale functies.	Zeer laag/laag
Waarschuw de anesthesist en/of kinderintensivist voor de kans op een refractaire status epilepticus wanneer de status niet is gestopt na toediening van twee anti-epileptica. Overweeg ondertussen nog een snel toedienbaar middel als valproaat of levetiracetam te geven.	Zeer laag/laag
Zorg voor een protocol in uw ziekenhuis. Houd u aan de doseringen en het tijdschema om het ontstaan van een refractaire status te voorkomen.	Zeer laag/laag
Bij gebruik van propofol moet de dosering binnen zekere grenzen blijven en toediening onder strikte controles plaatsvinden vanwege het risico van een propofol-infusiesyndroom.	Zeer laag/laag
Oncologie	
Gebruik geen anti-epileptica als profylaxe bij kinderen met een hersentumor vanwege onvoldoende bewijs voor effectiviteit.	Matig/zeer hoog
Maak gebruik van lamotrigine, levetiracetam of valproaat bij de behandeling van epilepsie bij patiënten met hersentumoren. Kies in tweede instantie voor gabapentine en pregabaline. Vanwege de enzyminducerende werking hebben carbamazepine, fenobarbital, fenytoïne, oxcarbazepine en topiramaat niet de voorkeur bij de behandeling van patiënten met een hersentumor.	Zeer laag
[1]Level of evidence: **Hoog:** Onderzoek van niveau meta-analyse van minimaal 2 onafhankelijk van elkaar uitgevoerde gerandomiseerde dubbelblind vergelijkende klinische onderzoeken of tenminste twee onafhankelijk van elkaar uitgevoerde onderzoeken **Matig:** één gerandomiseerd dubbelblind vergelijkend klinische onderzoek of ten minste twee onafhankelijk van elkaar uitgevoerde vergelijkende onderzoeken (patient-controle onderzoek, cohort onderzoek). **Laag:** één vergelijkend onderzoek of niet-vergelijkend onderzoek **Zeer laag:** Mening van deskundigen	

Pharmacological treatment of epilepsy – Child and adult guideline	
National institute for health and care Excellence (NICE).The epilepsies, the diagnosis and management in adults and children in primary and secondary care.2019 (previous versions, 2012,2013,2015, 2018)	
Recommendation	**Level of evidence**
Healthcare professionals should adopt a consulting style that enables the child, young person or adult with epilepsy, and their family and/or carers as appropriate, to participate as partners in all decisions about their healthcare, and take fully into account their race, culture and any specific needs. [2004]	Expert opinion
The doctor-patient relationship Doctors are not responsible for people with epilepsy, but rather they are responsible to them. This includes: • ensuring an accurate diagnosis • providing individuals with the appropriate information regarding their condition • agreeing a strategy in partnership with the individual, utilising all currently available treatment options with the goal of abolishing seizures.	Expert opinion
The diagnosis of epilepsy in children and young people should be established by a specialist paediatrician with training and expertise in epilepsy.	Low
It is recommended that all children and young people who have had a first non-febrile seizure should be seen as soon as possible by a specialist in the management of the epilepsies to ensure precise and early diagnosis and initiation of therapy as appropriate to their needs.	Low, expert opinion
A detailed history should be taken from the child, young person or adult and an eyewitness to the attack, where possible, to determine whether or not an epileptic seizure is likely to have occurred.	Low, expert opinion
Prospective recording of events, including video recording and written descriptions, can be very helpful in reaching a diagnosis.	Expert opinion
Administer buccal midazolam first-line treatment in children, young people and adults with prolonged or repeated seizures in the community. Administer rectal diazepam if preferred or if buccal midazolam is not available. If intravenous access is already established and resuscitation facilities are available, administer intravenous lorazepam. [new 2012]	Low – high, expert opinion
Depending on response to treatment, the person's situation and any personalised care plan, call an ambulance, particularly if: • the seizure is continuing 5 minutes after the emergency medication has been administered • the person has a history of frequent episodes of serial seizures or has convulsive status epilepticus, or this is the first episode requiring emergency treatment • there are concerns or difficulties monitoring the person's airway, breathing, circulation or other vital signs. [new 2012]	Expert opinion
For children, young people and adults with ongoing generalised tonic–clonic seizures (convulsive status epilepticus) who are in hospital, immediately: secure airway • give high-concentration oxygen • assess cardiac and respiratory function • check blood glucose levels and • secure intravenous access in a large vein.	Expert opinion
Administer intravenous lorazepam as first-line treatment in hospital in children, young people and adults with ongoing generalised tonic–clonic seizures (convulsive status epilepticus). Administer intravenous diazepam if intravenous lorazepam is unavailable, or use buccal midazolam if unable to secure immediate intravenous access. Administer a maximum of two doses of the first-line treatment (including pre-hospital treatment).	Moderate
If seizures continue, administer intravenous phenobarbital or phenytoin as second-line treatment in hospital in children, young people and adults with ongoing generalised tonic–clonic seizures (convulsive status epilepticus).	Low

6.2.2 Spasticiteit

Pharmacological treatment of spasticity – Child guideline	
National institute for health and care Excellence (NICE). Spasticity in children and young people with non-progressive brain disorders. 2016 (previous version 2012)	
Recommendation	**Level of evidence**
Oral drugs	

Clinical evidence: *Eight studies were identified. The studies addressed four comparisons: diazepam vs. placebo (1 parallel RCT); baclofen vs. placebo (3 cross-over RCTs); dantrolene vs. placebo (2 cross-over RCT and 1 parallel RCT); trihexyphenidyl vs. placebo (1 cross-over RCT)* *The GDG acknowledged that, as with all treatments recommended in the guideline, oral drugs should be prescribed by a relevant member of the network team. Furthermore, the use of oral drugs should be considered in the context of the child or young person's overall management programme, which is formulated in conjunction with the child or young person and their parents or carers.*	
Consider oral diazepam in children and young people if spasticity is contributing to one or more of the following: • discomfort or pain • muscle spasms (for example, night-time muscle spasms) • functional disability. Diazepam is particularly useful if a rapid effect is desirable (for example, in a pain crisis).	Expert opinion (p 125)
Consider oral baclofen if spasticity is contributing to one or more of the following: • discomfort or pain • muscle spasms (for example, night-time muscle spasms) • functional disability. Baclofen is particularly useful if a sustained long-term effect is desired (for example, to relieve continuous discomfort or to improve motor function).	Expert opinion
If oral diazepam is initially used because of its rapid onset of action, consider changing to oral baclofen if long-term treatment is indicated.	Expert opinion
Give oral diazepam treatment as a bedtime dose. If the response is unsatisfactory consider: • increasing the dose **or** • adding a daytime dose.	Expert opinion
Start oral baclofen treatment with a low dose and increase the dose stepwise over about 4 weeks to achieve the optimum therapeutic effect.	Expert opinion
Continue using oral diazepam or oral baclofen if they have a clinical benefit and are well tolerated, but think about stopping the treatment whenever the child or young person's management programme is reviewed and at least every 6 months.	Expert opinion
If adverse effects (such as drowsiness) occur with oral diazepam or oral baclofen, think about reducing the dose or stopping treatment.	Expert opinion
If the response to oral diazepam and oral baclofen used individually for 4–6 weeks is unsatisfactory, consider a trial of combined treatment using both drugs.	Expert opinion
If a child or young person has been receiving oral diazepam and/or baclofen for several weeks, ensure that when stopping these drugs the dose is reduced in stages to avoid withdrawal symptoms.	Expert opinion
In children and young people with spasticity in whom dystonia is considered to contribute significantly to problems with posture, function and pain, consider a trial of oral drug treatment, for example with trihexyphenidyl, levodopa or baclofen.	Expert opinion
Botulinum toxin (BoNT)	
Clinical evidence: *Nine studies were identified. The studies addressed four comparisons: BoNT-A and physical therapy vs. physical therapy alone (1 Cochrane review and 5 parallel RCT); BoNT-A every 4 months vs. BoNT-A every 12 months (1 parallel RCT); Electrical muscle stimulation vs. palpation of the spastic muscle group for guiding the delivery of BoNT injections (1 parallel RCT); Ultrasound versus electrical muscle stimulation for guiding the delivery of BoNT injections (1 quasi-randomised controlled trial).* *The GDG recognised that the available evidence regarding the use of BoNT-A in children and young people with spasticity was of low or moderate quality and, in many respects, complex to interpret from a clinical perspective. There was considerable variation in the patients studied, the goals of treatment,* *the mode of BoNT-A administration and especially in the specific outcomes investigated. Inevitably, the outcomes varied considerably between trials.*	
General principles	
Consider botulinum toxin type A treatment in children and young people in whom focal spasticity of the upper limb is: • impeding fine motor function • compromising care and hygiene • causing pain • impeding tolerance of other treatments, such as orthoses • causing cosmetic concerns to the child or young person.	Low/moderate, Expert opinion (p.163)
Consider botulinum toxin type A treatment where focal spasticity of the lower limb is: • impeding gross motor function • compromising care and hygiene	Low/moderate, expert opinion

• causing pain • disturbing sleep • impeding tolerance of other treatments, such as orthoses and use of equipment to support posture • causing cosmetic concerns to the child or young person.	
Consider botulinum toxin type treatment after an acquired non-progressive brain injury if rapid-onset spasticity is causing postural or functional difficulties.	Low/moderate, expert opinion
Consider a trial of botulinum toxin type A treatment in children and young people with spasticity in whom focal dystonia is causing serious problems, such as postural or functional difficulties or pain.	Low/moderate, expert opinion
Do not offer botulinum toxin type A treatment if the child or young person: • has severe muscle weakness • had a previous adverse reaction or allergy to botulinum toxin type A • is receiving aminoglycoside treatment.	Low/moderate, expert opinion

Be cautious when considering botulinum toxin type A treatment if:
• the child or young person has any of the following
  ○ a bleeding disorder, for example due to anti-coagulant therapy
  ○ generalised spasticity
  ○ fixed muscle contractures
  ○ marked bony deformity **or**
• there are concerns about the child or young person's likelihood of engaging with the post-treatment adapted physical therapy programme
	Low/moderate, expert opinion

When considering botulinum toxin type A treatment, perform a careful assessment of muscle tone, range of movement and motor function to: • inform the decision as to whether the treatment is appropriate • provide a baseline against which the response to treatment can be measured. A physiotherapist or an occupational therapist should be involved in the assessment.	Low/moderate, expert opinion

When considering botulinum toxin type A treatment, give the child or young person and their parents or carers information about:
• the possible benefits and the likelihood of achieving the treatment goals
• what the treatment entails, including:
  ○ the need for assessments before and after the treatment
  ○ the need to inject the drug into the affected muscles
  ○ the possible need for repeat injections
  ○ the benefits, where necessary, of analgesia, sedation or general anaesthesia
• the need to use serial casting or an orthosis after the treatment in some cases
• possible important adverse effects
	Low/moderate, expert opinion

Botulinum toxin type A treatment (including assessment and administration) should be provided by healthcare professionals within the network team who have expertise in child neurology and musculoskeletal anatomy.	Low/moderate, expert opinion
Delivering treatment	

Before starting treatment with botulinum toxin type A, tell children and young people and their parents or carers:
• to be aware of the following rare but serious complications of botulinum toxin type A treatment:
  ○ swallowing difficulties
  ○ breathing difficulties
• how to recognise signs suggesting these complications are present
• that these complications may occur at any time during the first week after the treatment and
that if these complications occur the child or young person should return to hospital immediately.
	Low/moderate, expert opinion

To avoid distress to the child or young person undergoing treatment with botulinum toxin type A, think about the need for: • topical or systemic analgesia or anaesthesia • sedation (see 'Sedation in children and young people', NICE clinical guideline 112).	Low/moderate, expert opinion
Consider ultrasound or electrical muscle stimulation to guide the injection of botulinum toxin type A.	Low/moderate, expert opinion
Consider injecting botulinum toxin type A into more than one muscle if this is appropriate to the treatment goal, but ensure that maximum dosages are not exceeded.	Low/moderate, expert opinion

After treatment with botulinum toxin type A, consider an orthosis to: • enhance stretching of the temporarily weakened muscle and • enable the child or young person to practice functional skills	Low/moderate, expert opinion
If an orthosis is indicated after botulinum toxin type A, but limited passive range of movement would make this difficult, consider first using serial casting to stretch the muscle. To improve the child or young person's ability to tolerate the cast, and to improve muscle stretching, delay casting until 2–4 weeks after the botulinum toxin type A treatment.	Low/moderate, expert opinion
Ensure that children and young people who receive treatment with botulinum toxin type A are offered timely access to orthotic services.	Unclear
Continuing assessment	
Perform an assessment of muscle tone, range of movement and motor function: • 6–12 weeks after injections to assess the response • 12–26 weeks after injections to inform decisions about further injections. These assessments should preferably be performed by the same healthcare professionals who undertook the baseline assessment. Consider repeat injections of botulinum toxin type A if: • the response in relation to the child or young person's treatment goal was satisfactory, and the treatment effect has worn off new goals amenable to this treatment are identified.	Low/moderate, expert opinion
Intrathecal baclofen	
Clinical evidence: *Seven studies were identified in which continuous pump-administered intrathecal baclofen (CITB)treatment was evaluated (1 parallel RCT, 4 prospective case series and 2 case-control studies)*	
General principles	
Consider treatment with continuous pump-administered intrathecal baclofen in children and young people with spasticity if, despite the use of non-invasive treatments, spasticity or dystonia are causing difficulties with any of the following: • pain or muscle spasms • posture or function • self-care (or ease of care by parents or carers).	Very low – moderate (p. 198,199)
Be aware that children and young people who benefit from continuous pump administered intrathecal baclofen typically have: • moderate or severe motor function problems (GMFCS level III, IV or V) • bilateral spasticity affecting upper and lower limbs.	Very low – moderate
Be aware of the following contraindications to treatment with continuous pump administered intrathecal baclofen: • the child or young person is too small to accommodate an infusion pump • local or systemic intercurrent infection.	Very low – moderate
Be aware of the following potential contraindications to treatment with continuous pump-administered intrathecal baclofen: • co-existing medical conditions (for example, uncontrolled epilepsy or coagulation disorders) • a previous spinal fusion procedure • malnutrition, which increases the risk of post-surgical complications (for example, infection or delayed healing) • respiratory disorders with a risk of respiratory failure.	Very low – moderate
If continuous pump-administered intrathecal baclofen is indicated in a child or young person with spasticity in whom a spinal fusion procedure is likely to be necessary for scoliosis, implant the infusion pump before performing the spinal fusion.	Very low – moderate
When considering continuous pump-administered intrathecal baclofen, balance the benefits of reducing spasticity against the risk of doing so because spasticity sometimes supports function (for example, by compensating for muscle weakness). Discuss these possible adverse effects with the child or young person and their parents or carers.	Very low – moderate
When considering continuous pump-administered intrathecal baclofen, inform children and young people and their parents or carers verbally and in writing (or appropriate formats) about: • the surgical procedure used to implant the pump • the need for regular hospital follow-up visits • the requirements for pump maintenance	Very low – moderate

the risks associated with pump implantation, pump-related complication and adverse effects that might be associated with intrathecal baclofen infusion.	

7 Overzicht conclusies van evidence en aanbevelingen uit richtlijnen

7.1 Niet-medicamenteuze behandeling van Neurologische symptomen

Non pharmacological treatment for neurological symptoms								
Treatment	Conclusions of evidence (RCTs on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children 2013 (2)	Level of evidence[1]
Epilepsy								
Ketogenic diet	Unknown effect	No studies	Treat patients with GLUT-1 deficiency syndrome or pyruvate dehydrogenase deficiency with ketogenic diet as first choice	Low, moderate (3;NP*)	Not applicable	-	No recommendation	-
			Consider the ketogenic diet in children (possibly adults) with difficulty to control epilepsy (2 or more failed seizure control attempts with ant-epileptic drugs)	Low, moderate (3;NP*, 4;NP)				
			Determine whether diet should/can be continued within 2 to 4 months	Low, moderate(3; NP*)				
Psychological interventions	Unknown effect	No studies	Psychological interventions (relaxation, cognitive behaviour therapy) may be used in children and young people with drug-resistant focal epilepsy.	Expert opinion (3;NP)	Not applicable	-	No recommendation	-
Spasticity								
Physical therapy (physiotherapy and/or occupational therapy)	Unknown effect	No studies	All children and young people with spasticity referred to the network team should be promptly assessed by a physiotherapist and, where necessary, an occupational therapist.	LOW to HIGH, expert opinion (5;NP)	Not applicable	-	No recommendation	-

			Offer a physical therapy (physiotherapy and/or occupational therapy) programme tailored to the child or young person's individual needs and aimed at specific goals, such as: enhancing skill development, function and ability to participate in everyday activities; preventing consequences such as pain or contractures.					
Loss of neurological function								
Double vision								
Eyepatch/masking glasses	Unknown effect	No studies	Not identified	-	Not identified	-	Do; strong recommendation	Expert opinion (6)
Problems with swallowing								
Optimal nutrition	Unknown effect	No studies	Not identified	-	Not identified	-	Do; strong recommendation	Expert opinion (6)
Stomach pump	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Expert opinion (6))
Thickening of nutrition	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Expert opinion (6)

Legend
NP: Non-palliative context
*: Version 2012 of the following guideline 'National institute for health and care Excellence (NICE).The epilepsies, the diagnosis and management in adults and children in primary and secondary care.' (4) is used as a base for 'Nederlandse vereniging voor neurologie. Epliepsie. 2020'(3)

[1]Level of evidence:
Level 1: Based on a systematic review or at least two randomized controlled trials of good quality
Level 2: Based on one at randomized controlled trial or at least two comparative clinical studies
Level 3: Based on one comparative study or on non-comparative studies
Level 4: Based on expert opinion

References

2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.
3. Nederlandse Vereniging voor Neurologie. Epilepsie. 2020. Available from: https://epilepsie.neurologie.nl/cmssite7/index.php?pageid=681.
4. National Institute for Health and Care Excellence. Epilepsies: diagnosis and management [Internet]. London 2019 [cited 2021 March, 1]. Available from: www.nice.org.uk/guidance/cg137.
5. National Institute for Health and Care Excellence. Spasticity in under 19s: Management. [Internet]. London: NICE; 2012 [cited 2021 March 1]. Available from: www.nice.org.uk/guidance/cg145.
6. Wolfe J, Hinds P. Textbook of Interdisciplinary Pediatric Palliative Care: Saunders; 2011.

7.2 Medicamenteuze behandeling van Neurologische symptomen

Pharmacological treatment for neurological symptoms								
Treatment	Conclusions of evidence (RCTs on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children 2013 (2)	Level of evidence[1]
Epilepsy								
Seizure treatment								
Midazolam (buccal, nasal)	Unknown effect	No studies	**Outside the hospital** Ensure that parents or carers who have been provided with anticonvulsive therapy (such as buccal midazolam) know how and when to use it if the child or young person has a seizure at home.	Expert opinion (7;P)	Not applicable	-	No recommendation	-
			Outside the hospital Consider providing midazolam (buccal or nasal) instead of diazepam (rectal) to parents or carers of children. Discuss the use of rescue medication, the maximum dose and maximum number of administration. Also provide written information	LOW – MODERATE, Expert opinion (3;NP*)				
Midazolam (buccal, nasal, intramuscular)	Unknown effect	No studies	**In the hospital** Use midazolam (buccal, nasal or intramuscular) for children with status epilepticus when intravenous access is not available. Apply intravenous access immediately afterwards.	LOW - HIGH, expert opinion (3;NP*)	Not applicable	-	Do; strong recommendation	Level 4 (6)

Diazepam (rectal)	Unknown effect	No studies	Administer rectal diazepam if preferred or if buccal midazolam is not available.	LOW – HIGH, expert opinion (4;NP)	Not applicable	-	Do; strong recommendation	Level 4 (6)
Optional treatment								
Levetiracetam	Unknown effect	No studies	Use phenytoin, valproate or levetiracetam to stop persistent convulsive status epilepticus	LOW – HIGH, expert opinion (3;NP*)	Not applicable	-	Consider; weak recommendation	Level 4 (6)
			Consider for refractory status epilepticus	LOW, expert opinion (3;NP*)				
Sodium valproate	Unknown effect	No studies	Use phenytoin, valproate or levetiracetam to stop persistent convulsive status epilepticus	LOW – HIGH, expert opinion (3;NP*)	Not applicable	-	Consider; weak recommendation	Level 4 (6)
			Be cautious with valproate in liver diseases, possible coagulation disorders, suspected metabolic disease and in children under 2 years of age (risk on reye syndrome)					
			Consider for refractory status epilepticus	LOW, expert opinion (3;NP*)				
Phenytoin	Unknown effect	No studies	Use phenytoin, valproate or levetiracetam to stop persistent convulsive status epilepticus	VERY LOW – HIGH, expert opinion (3;NP*)	Not applicable	-	Consider; weak recommendation	Level 4 (6)
			Do not use phenytoin in case of cardiac problems, proven hypersensitivity to phenytoin or in failure of phenytoin in previous status epilepticus	VERY LOW – HIGH, expert opinion (3;NP*)				
			If seizures continue, administer intravenous phenobarbital or phenytoin	LOW (4;NP)				

			as second-line treatment in hospital in children, young people and adults with ongoing generalised tonic–clonic seizures (convulsive status epilepticus).					
Phenobarbital	Unknown effect	No studies	If seizures continue, administer intravenous phenobarbital or phenytoin as second-line treatment in hospital in children, young people and adults with ongoing generalised tonic–clonic seizures (convulsive status epilepticus).	LOW (4;NP)	Not applicable	-	Consider; weak recommendation	Level 4 (6)
Midazolam (continuous, intravenous)	Unknown effect	No studies	Use midazolam or lorazepam for children with status epilepticus if there is intravenous access	VERY LOW – HIGH, expert opinion (3;NP*)	Not applicable	-	Consider; weak recommendation	Level 4 (6)
Lorazepam	Unknown effect	No studies	Use midazolam or lorazepam for children with status epilepticus if there is intravenous access	VERY LOW – HIGH, expert opinion (3;NP*)	Not applicable	-	No recommendation	-
			If intravenous access is already established and resuscitation facilities are available, administer intravenous lorazepam in children with prolonged or repeated seizures.	VERY LOW – HIGH, expert opinion (3;NP*)				
			Administer intravenous lorazepam as first-line treatment in hospital in children, young people and adults with ongoing generalised tonic–clonic seizures (convulsive status epilepticus).	Moderate (3;NP*)				

Propofol	Unknown effect	No studies	When using propofol, dosage should be kept within certain limits and administration should be under strict supervision because of risk on propofol infusion syndrome	VERY LOW – LOW, expert opinion (3;NP*)	Not applicable	-	No recommendation	-
Clonazepam	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 (6)
Clobazam	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 (6)
Carbamazepine	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 (6)
Epilepsy in children with brain tumours								
Anti-epileptic drugs	Unknown effect	No studies	Do not use as prophylaxis, due to insufficient evidence of effectiveness	MODERATE – HIGH (3;NP*)	Not applicable	-	No recommendation	-
Lamotrigine, levetiracetam, valproate	Unknown effect	No studies	Use to treat patients with brain tumours	Expert opinion (3;NP*)	Not applicable	-	No recommendation	-
Gabapentin or pregabalin	Unknown effect	No studies	Use in second instance to treat patients with brain tumours	Expert opinion (3;NP*)	Not applicable	-	No recommendation	-
Carbamazepine, phenobarbital, phenytoin, oxcarbazepine, topiramate	Unknown effect	No studies	Not preferred to treat patients with brain tumours due to enzyme inducing action	Expert opinion (3;NP*)	Not applicable	-	No recommendation	-
Dyskinesia syndromes								
Bipiridene (Akineton®)	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 (6)
Benzodiazepines (diazepam/midazolam)	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 (6)
Baclofen	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 (6)
Spasticity								
Spasms								
Benzodiazepines (diazepam/midazolam)	Unknown effect	No studies	Consider oral diazepam in children and young people if spasticity is contributing	Expert opinion (5;NP)	Not applicable	-	Consider; weak recommendation	Level 4 (6)

			to one or more of the following: discomfort or pain; muscle spasms (for example, night-time muscle spasms); functional disability. Diazepam is particularly useful if a rapid effect is desirable (for example, in a pain crisis).					
Baclofen (oral)	Unknown effect	No studies	Consider oral baclofen if spasticity is contributing to one or more of the following: discomfort or pain; muscle spasms (for example, night-time muscle spasms); functional disability. Baclofen is particularly useful if a sustained long-term effect is desired (for example, to relieve continuous discomfort or to improve motor function).		Not applicable	-	Consider; weak recommendation	Level 4 (6)
Baclofen + tizanidine (Sirdalud®)	Unknown effect	No studies	-	-	Not applicable	-	Consider; weak recommendation	Level 4 (6)
Intrathecal baclofen			Consider treatment with continuous pump-administered intrathecal baclofen in children and young people with spasticity if, despite the use of non-invasive treatments, spasticity or dystonia are causing difficulties with any of the following: pain or muscle spasms; posture or function self-care (or ease of care by parents or carers).	Very low – moderate (5;NP)	Not applicable	-	No recommendation	-

Local spasticity								
Botulinum Toxin-A injections	↑ parent-reported treatment efficacy in children with cerebral palsy after intervention; Long-term effect might be dependent on the amount of injections received by the patient	LOW, 2RCTs (8, 9)	Consider botulinum toxin type A treatment in children and young people in whom focal spasticity of the upper limb or lower limb is : impeding fine motor function; compromising care and hygiene; causing pain; impeding tolerance of other treatments, such as orthoses; causing cosmetic concerns to the child or young person; disturbing sleep (only in case of spasticity in lower limb)	Low – moderate, expert opinion (5;NP)	Not applicable	-	Consider; weak recommendation	Level 4 (6)
	↓ spasticity levels of upper limbs (forearm and wrists) in children with cerebral palsy after intervention	VERY LOW, 1RCT (8)						
	No significant effect on motor performance in children with cerebral palsy	VERY LOW, 1RCT (8)						
	No significant effect on quality of life in children with cerebral palsy	VERY LOW, 1RCT (9)						
Loss of neurological function								
Unability to close eyes								
Methylcellulose eyedrops	Unknown effect	No studies	Not identified	-	Not identified	-	Do; strong recommendation	Level 4 (6)
Oculentum simplex ointment	Unknown effect	No studies	Not identified	-	Not identified	-	Do; strong recommendation	Level 4 (6)

Legend
P: Palliative context
NP: Non-palliative context
*: Version 2012 of the following guideline 'National institute for health and care Excellence (NICE).The epilepsies, the diagnosis and management in adults and children in primary and secondary care.' (4) is used as a base for 'Nederlandse vereniging voor neurologie. Epliepsie. 2020'(3)

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2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.
3. Nederlandse Vereniging voor Neurologie. Epilepsie. 2020. Available from: https://epilepsie.neurologie.nl/cmssite7/index.php?pageid=681.
4. National Institute for Health and Care Excellence. Epilepsies: diagnosis and management [Internet]. London 2019 [cited 2021 March, 1]. Available from: www.nice.org.uk/guidance/cg137.

5. National Institute for Health and Care Excellence. Spasticity in under 19s: Management. [Internet]. London: NICE; 2012 [cited 2021 March 1]. Available from: www.nice.org.uk/guidance/cg145.
6. Wolfe J, Hinds P. Textbook of Interdisciplinary Pediatric Palliative Care: Saunders; 2011.
7. National Institute for Health and Care Excellence. End of life care for infants, children and young people with life-limiting conditions: planning and management. [Internet]. London: NICE; 2016 [cited 2021 March 1]. Available from: www.nice.org.uk/guidance/ng61.
8. Olesch CA, Greaves S, Imms C, Reid SM, Graham HK. Repeat botulinum toxin-A injections in the upper limb of children with hemiplegia: a randomized controlled trial. Dev Med Child Neurol. 2010;52(1):79-86.
9. Copeland L, Edwards P, Thorley M, Donaghey S, Gascoigne-Pees L, Kentish M, et al. Botulinum toxin A for nonambulatory children with cerebral palsy: a double blind randomized controlled trial. J Pediatr. 2014;165(1):140-6 e4.

I Pijn

Inhoudsopgave

1 Uitgangsvragen

Vraag 9A: Wat is de meest effectieve niet-medicamenteuze behandeling van pijn bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Niet-medicamenteuze behandeling van pijn
C: Geen behandeling/placebo
O: Effect op pijn en kwaliteit van leven

Vraag 9B: Wat is de meest effectieve medicamenteuze behandeling van pijn bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Medicamenteuze behandeling van pijn
C: Geen behandeling/placebo
O: Effect op pijn en kwaliteit van leven

2 Resultaten van het literatuuronderzoek

Jaar	Bibliografie	Studie karakteristieken
9A: Wat is de meest effectieve niet-medicamenteuze behandeling van pijn bij kinderen tussen 0 en 18 jaar in de palliatieve fase?*		
2010	***Joanna Briggs Institute.*** Effectiveness of non-pharmacological pain management in relieving chronic pain for children and adolescents. Best practice: evidence-based information sheets for health professionals 2010 14 (17); 1-4[1]	Richtlijn kinderen
2015	***Eccleston C et al.*** Psychological interventions for parents of children and adolescents with chronic illness. Cochrane Database of Systematic Reviews 2015 4)[2]	Systematic review of RCTs kinderen
9B: Wat is de meest effectieve medicamenteuze behandeling van pijn bij kinderen tussen 0 en 18 jaar in de palliatieve fase?*		
2016	***National institute for health and care Excellence (NICE).***End of life care for infants, children and young people: planning and management. 2016 [1]	Richtlijn kinderen
2015	***Beecham E et al.*** Pharmacological interventions for pain in children and adolescents with life-limiting conditions. Cochrane Database of Systematic Reviews 2015 3(13)	Systematic review of RCTs kinderen
2011	***Wiffen PJ et al.*** Opioids for cancer-related pain in children and adolescents. Cochrane Database of Systematic Reviews 2017 7): The Journal of Clinical Endocrinology and Metabolism 2011;96(2):355–64.	Systematic review of RCTs kinderen

[1] Aanbevelingen uit de richtlijnen over pijn bij kinderen in de palliatieve fase worden gebruikt in de overwegingen.
* Systematisch gezocht, zie: bijlage 7 zoekverantwoording – search 1

3 Evidence tabellen

3.1 Niet-medicamenteuze behandeling van Pijn

Non pharmacological treatment of pain			
Eccleston C et al. Psychological interventions for parents of children and adolescents with chronic illness. Cochrane Database of Systematic Reviews 2015 4):			
Study characteristics	**Patient characteristics**	**Outcomes / Results**	**Comments** **Risk of bias**
Type of study: Systematic review of RCTs Included studies 47 RCTs Searched databases CENTRAL, MEDLINE, EMBASE, PsychINFO Inclusion criteria *Participants* • Parents had to be referred to in the title or abstract of each study • The parent had to be the primary caregiver of the child • Children had to have one or more of the chronic illnesses: Asthma, Cancer, Diabetes Mellitus, Gynaecological disorder, inflammatory bowel diseases (IBD), Painful condition (i.e.	Number and type of participants: parents of children with chronic illness such as painful conditions (i.e. including but not exclusively limited to arthritis, back pain, complex regional pain syndrome (CRPS), fibromyalgia, headache, idiopathic pain conditions, irritable bowel syndrome (IBS), recurrent abdominal pain) cancer; diabetes; asthma; traumatic brain injury Age: Not reported Sex: Not reported Type of intervention and control *Intervention:* Four classes of psychological therapies were tested. • Cognitive Behavioural Therapy (CBT) – includes a range of strategies with the goals of modifying social/environmental and behavioural factors that may	Outcome definitions: Primary outcomes: 1) Parenting behaviour, 2)Parent mental health Secondary outcomes: 1) Child behaviour/disability, 2) Child mental health, 3)Child illness-related symptoms, family function and adverse events. Results (per outcome) Individual conditions across all psychological therapies. *Effect of all psychological interventions on parents of children with cancer.* **Parenting behaviour – post treatment** Included: 836 (I = 405/C = 431) parents of children from 5 studies Effect: Psychological had a small beneficial effect for parenting behaviour. SMD is -0.20, 95% CI -0.36 to -0.04, p = 0.01 GRADE level (risk of bias): Very low, Majority of studies have unclear or high risk of bias **Parenting behaviour – Follow-up** Included: 789 (I = 399/C=420) parents of children from 5 studies Effect: Effect was not maintained at follow-up, z = 1.39, p=0.16 GRADE level (risk of bias): Very low, Majority of studies have unclear or high risk of bias **Parent mental health – post-treatment** Included: 1010 (I = 494/ C = 516) parents of children from 9 studies Effect: There was no effect of psychological therapies on parent mental health post-treatment (Z = 1.86, p = 0.06) GRADE level (risk of bias): Very low, Majority of studies have unclear or high risk of bias **Parent mental health – follow-up** Included: 819 (I = 386, C = 403) parents of children from 6 studies Effect: Psychological therapies had a small beneficial effect for improving parent mental health (SMD = -0.18, 95%CI -0.32 to -0.04, Z = 2.58, p = 0.01 GRADE level (risk of bias): Very low, Majority of studies have unclear or high risk of bias **Child symptoms – post treatment** Included: 1 study Effect: no conclusions could be drawn. Individual psychological therapies across all conditions *Cognitive behavioural therapy* **Parenting behaviour – Post treatment** Included: 166 (I = 86, C = 80) parents of children from 4 studies Effect: Overall effect of CBT on parenting behaviour was not beneficial (z = 0.08. p = 0.94) GRADE level (risk of bias) **Parenting behaviour – follow-up** Included: 85 (I = 42, C = 43) parents of children from 2 studies Effect: Overall effect of CBT on parenting behaviour was not beneficial (z = 0.56. p = 0.58) **Parent mental health – post treatment**	Strengths: Large amount of studies included Outcomes are assessed per condition and per psychological therapy Limitations: Definitions of primary and secondary outcomes are not reported **Risk of bias** Selection bias: Low risk: 24/47 studies High risk: 0/47 studies Unclear: 23/47 studies Detection bias: Low risk: 20/47 studies High risk: 27/47 studies Unclear: 0/47 studies Attrition bias: Low risk: 15/47 studies High risk: 10/47 studies Unclear: 23/47 studies Reporting bias: Low risk: 18/47 studies High risk: 15/47 studies

headache), skin diseases, traumatic brain injury. • Children had to be in the age range: 3 months – 19 yrs. • 10 or more participants in each condition at the end of the treatment assessment. *Intervention* • Intervention had to be psychological in at least 1 treatment arm. • design = RCT, • 1 or more parents had to be treated with the intervention • Parents or child had to complete assessments at baseline and at a point in time after/during intervention *Comparison groups* • Active treatment group • Treatment-as-usual group • Waiting list control	exacerbate or cause symptoms. • Family Therapy (FT) – focus on altering patterns of interactions between family members • Problem-Solving Therapy – didactic instruction in problem-solving, followed by in-session modelling, behavioural rehearsal and performance feedback. • Multi-systemic Therapy – intensive family-community based intervention based on social ecological model and family systems theory. MST targets the child, their family and the school. *Control:* • Active treatment group (16 studies) • Treatment-as-usual group (17 studies) • Waiting list control (10 studies) • Three comparator arms (4 studies)	Included: 325 (I = 175, C = 150) parents of children from 7 studies Effect: No effect of CBT on parent mental health was identified (z = 0.66. p = 0.51) **Parent mental health – follow-up** Included: 115 (I = 67, C = 48) parents of children from 2 studies Effect: No effect of CBT on parent mental health was identified (z = 1.26. p = 0.21) **Child behaviour/disability – post-treatment** Included: 487 (I = 247, C = 240) children from 8 studies Effect: No effect of CBT was identified (z = 1.34. p = 0.18) **Child behaviour/disability – follow-up** Included: 289 (I = 150, C = 139) children from 3 studies Effect: No effect of CBT was identified (z = 0.95. p = 0.34) **Child mental health – post-treatment** Included: 439 (I = 232, C = 207) children from 5 studies Effect: No effect of CBT was identified (z = 0.21 p = 0.83) **Child mental health – follow-up** Included: 257 (I = 130, C= 127) children from 2 studies Effect: No effect of CBT was identified (z = 0.27. p = 0.78) **Child symptoms – post-treatment** Included: 754 (I = 396, C = 358) children from 12 studies Effect: Overall effect of CBT was beneficial (SMD = -0.32, 95%CI -0.53 to -0.11, p <0.01 **Child symptoms– follow-up** Included: 475 (I = 253, C = 219) children from 7 studies Effect: No effect of CBT was identified (z = 1.70. p = 0.09) **Family functioning – post-treatment** Included: 211 (I = 114, C= 97) children from 3 studies Effect: No effect of CBT was identified (z = 0.40 p = 0.69) **Family functioning – follow-up** Included: 107 (I = 60, C = 47) children from 2 studies Effect: No effect of CBT was identified (z = 0.61. p = 0.54) *Family therapy* **Parent mental health – post treatment** Included: 131 (I = 74, C = 57) parents of children from 3 studies Effect: No effect of FT on parent mental health was identified (z = 0.16. p = 0.88) **Parent mental health – follow-up** Included: Only 1 study drawn Effect: No conclusions could be drawn **Child behaviour/disability – post-treatment** Included: 107 (I = 53, C = 54) children from 2 studies Effect: Overall effect of FT was not beneficial for children with chronic condition (z = 1.44. p = 0.15) **Child symptoms – post-treatment** Included: 259 (I = 134, C = 125) children from 5 studies Effect: No beneficial effect was found, SMD -0.32 (-0.53 to -0.11) z = 0.35. p = 0.73) (z = 0.35. p = 0.73) **Child symptoms– follow-up** Included: 96(I = 48, C = 48) children from 2 studies Effect: No beneficial effect was found (z = 0.12. p = 0.91) **Family functioning** Included: 132 (I = 63, C = 69) children from 2 studies Effect: No effect of FT was identified (z = 0.45, p = 0.65)	Unclear:14/47 studies CBT – child symptoms

		Problem solving therapy **Parenting behaviour – Post treatment** Included: 832 (I = 405, C = 427) parents of children from 5 studies Effect: Small beneficial effect of PST on parenting behaviour (SMD -0.25, 95% CI -0.39 to -0.11,z = 3.59. p <0.01) **Parenting behaviour – follow-up** Included: 748 (I = 366, C = 382) parents of children from 4 studies Effect: Effect was not maintained (z = 0.1.75. p = 0.08) **Parent mental health – post treatment** Included: 907 (I = 438, C = 469) parents of children from 7 studies Effect: Small beneficial effect of PST on parent mental health (SMD -0.24, 95% CI -0.42 to -0.05,z = 2.50. p = 0.01) **Parent mental health – follow-up** Included: 778 (I = 379, C = 399) parents of children from 5 studies Effect: Small beneficial effect of PST on parent mental health (SMD -0.19, 95% CI -0.34 to -0.04,z = 2.55. p = 0.01) **Child behaviour/disability – post-treatment** Included: 260 (I = 130, C= 130) children from 5 studies Effect: No effect of PST was identified (z = 1.21. p = 0.22) **Child behaviour/disability – follow-up** Included: only 1 study included Effect: No conclusions could be drawn **Child symptoms – post-treatment** Included: 216 (I = 105, C = 111) children from 2 studies Effect: No beneficial effect of PST (z = 1.41, p = 0.59) **Child symptoms– follow-up** Included: only 1 study included Effect: No conclusions could be drawn **Family functioning – post-treatment** Included: 183 (I = 90, C = 93) children from 3 studies Effect: No effect of PST was identified (z = 0.54 p = 0.59) *Multisystem therapy* **Child behaviour/disability – post-treatment** Included: 313 I = 158, C = 155) children from 2studies Effect: No effect of MST was found at reducing child behaviour/disability (z = 0.99, p = 0.32) **Child behaviour/disability – follow-up** Included: only 1 study included Effect: No conclusions could be drawn **Child mental health– post-treatment** Included: only 1 study included Effect: No conclusions could be drawn **Child mental health– follow-up** Included: only 1 study included Effect: No conclusions could be drawn **Child symptoms – post-treatment** Included: 455 (I = 230, C = 225) children from 4 studies Effect: No beneficial effect of MST (z = 1.52, p = 0.13) **Child symptoms– follow-up** Included: 247(I = 123, C= 124) children from 2 studies Effect: No beneficial effect of MST (z = 1.47, p = 0.14)	

3.2 Medicamenteuze behandeling van Pijn

Pharmacological treatment of pain			
Beecham E et al. Pharmacological interventions for pain in children and adolescents with life-limiting conditions. Cochrane Database of Systematic Reviews 2015 3(13)			
Study characteristics	**Population**	**Main outcomes / Results**	**Conclusions** **Risk of bias**
Type of study: Systematic review of RCTs Included studies 9 studies (10 articles) Searched databases CENTRAL, MEDLINE, EMBASE, PsycINFO, CINAHL Selection criteria Inclusion: • randomised controlled trials (RCTs) (including cluster RCTs and cross-over trials), quasi-randomised studies, n of 1 studies, studies that are not randomised but include a clearly defined comparator group, and time series analyses that have investigated pharmacological treatments for pain associated with LLC in Children or Young people Exclusion:	Number and type of participants: 379 children and young people with life-limiting conditions (LLC) Age: Range: 0 – 18 years (see result section for specific range per treatment group) Sex: *(N (%)) unknown* Type of intervention and control *Intervention:* Pharmacological intervention given at any dose for any time period. Pharmacological intervention could be developed specifically to treat pain and could act as an adjuvant meaning that treatment was not primarly developed to treat pain but has pain relieving properties. *Control:*	Main outcomes **Primary outcomes** • Pain control: measured by changes in pain intensity scales or changes in physiological parameters • Safety: Adverse events **Secondary outcomes** • Changes in physical and psychological functioning and well-being measured by scales assessing quality of life and well-being quality of care. Results ***Patients with cerebral palsy*** *Intrathecal baclofen vs placebo or normal therapy* *Total participants*: 21 children with CP aged 7 to 17 • N = 4 (Bonouvrie 2011) • N = 17 (Hoving, 2007; Hoving 2009) *Intervention vs control* • Intrathecal baclofen vs placebo (Bonouvrie, 2011) • Intrathecal baclofen vs therapy as normal (Hoving, 2007 *Pain outcomes* • Pain measured using Visual Analogue Scale (0-10): Significant decrease of pain after administration of intrathecal baclofen in the intervention group compared to standard therapy in the control group. Mean Difference: 4.20, 95%CI 2.1 to 6.25 (Hoving, 2009) • Pain measured using VAS (0-10) at 6-month follow-up: Significant decrease of pain in the intervention group as compared to placebo. Mean difference: 4.20, 95%CI 2.15 to 6.25 (Hoving, 2007) • Bodily pain or discomfort measured using Child Health Questionnaire-parent form at 6-months follow-up: Decrease of pain in the intervention group. Mean difference 26.60, 95%CI 2.61 to 50.59 (Hoving, 2007). Pain measured using VAS: Decrease of pain with 2.6 points in the intervention groups. Pain scores increased in the placebo group (Bonouvrie, 2011) *Safety outcomes* Number and type of adverse effects • Nine adverse effects in 8 of 17 participant, mostly related to Cerebrospinal Fluid (CSF leakage) (Hoving, 2007) • Fourteen of 17 patients experienced a total of 28 procedure or device related adverse events, mostly related to swelling at pump site (Hoving, 2009) • 2 of 4 patients experienced CSF leakage which in discontinuation of trial in one patient (Bonouvrie, 2011) Most common adverse effect • Most common adverse effect irrespective of treatment arm was related to CSF leakage, respectively 2 patients (Bonouvrie, 2011) and 3 patients (Hoving, 2007). *Botulinum toxin A or Botulinum toxin A and occupational therapy vs placebo or occupational therapy alone* *Total participants*: 84 children with CP aged 2 to 16 • N = 41 (Copeland, 2014) • N = 43 (Russo, 2007)	**Conclusions** unable to determine the effects of pharmacological interventions for pain for CYP with LLCs. **Additional remarks** Strengths: -- Limitations: The National Institute for Health Research (NIHR) **Risk of bias** *Intrathecal baclofen vs placebo/normal therapy* *Selection bias:* Low in 2/3 and unclear in 1/3 *Attrition bias*: low in 1/3, unclear in 1/3 and high in 1/3; *Performance bias:* low in 1/3, unclear in 1/3 and high in 1/3; *Detection bias:* low in 1/3, unclear in 1/3 and high in 1/3 *Botulinum toxin A or Botulinum toxin A and occupational therapy vs placebo or OT only* Selection bias: Low in 1/2 and unclear in 1/2 Attrition bias low in 2/2 Performance bias: low in 1/2 and high in 1/2; Detection bias: low in 1/2 and high in 1/2; *Oral alendronate vs placebo*

• not relevant topic area, Adults only, not life limiting, no pain outcomes)	Other pharmacological interventions, psychological interventions, placebo, alternative dosing regimens or routes of administration	*Intervention vs control* • Botulinum Toxin A vs. placebo (Copeland, 2014) • Botulinum Toxin A with Occupational Therapy (OT) vs. OT only (Russo, 2007) *Pain outcomes* • Pain measured using the Pediatric Pain Profile at 1 month follow-up: No significant difference in pain scores between intervention and control group. Mean Difference -2.67, 95% CI -10.18 to 4.84 (Copeland, 2014) • Pain measured using the Pediatric Pain Profile at 4 month follow-up: No significant difference in pain scores between intervention and control group. Mean Difference 2.59, 95% CI -3.75 to 8.93 (Copeland, 2014) • Pain measured using VAS at 3-month follow-up (2 participants in each group): No significant difference in pain scores between intervention and control group. OR 1.05, 95%CI 0.13 to 8.24 (Russo, 2007) • Pain measured using VAS at 6-month follow-up (1 participants in each group): No significant difference in pain scores between intervention and control group. OR 1.05, 95% CI 0.06to 17.95 (Russo, 2007) *Safety outcomes* Number and type of participants with adverse events (intervention vs control) • 1 participant with epilepsy and hospital admission vs 2 participants with hospital admission due to epilepsy (Russo, 2007) • 3 participants with systemic drooling, decreased vocalization or drooling vs 1 participant (Copeland, 2014) Number and type of adverse effects (intervention vs control) • 22 adverse effects (feeling unwell) vs 0 adverse effects (Russo, 2007) • 23 patients with moderate or mild adverse effects (Copeland, 2014) Most common adverse effect Most common reported effect were seizures and respiratory symptoms ***Patients with Osteogenesis imperfecta*** <u>*Oral alendronate vs placebo*</u> *Total participants*: 159 children with OI aged 3 to 19 • N = 20 (Seikaly, 2005) • N = 139 (Ward, 2011) *Intervention vs control* • Oral alendronate vs placebo *Pain outcomes* • Pain measured by number of pain-free days per month at 12-month follow-up: Significant decrease of pain in the intervention group. Mean difference, MD-3.63, 95%CI -5.17 to -2.09 (Seikaly, 2005) • Pain measured by number of days with analgesic use for skeletal pains at 12-month follow up: Significant decrease of analgesic use in the intervention group. Mean Difference, -2.00, 95% CI -3.57 to -0.43 (Seikaly, 2005) • Pain measured by number of patients with bone pain at 24 month follow-up: In the intervention group fewer patients experienced pain in comparison to placebo (37%, 38/102 vs. 57%, 17/30). This effect was not statistically significant. OR, 0.45, 95% CI 0.20 to 1.04 (Ward, 2011) • Pain measured by number of days per week that patients experienced bone pain at 24 month follow-up: No significant difference the intervention group at baseline and follow-up (Ward, 2011). *Safety outcomes* Number and type of participants with adverse events (intervention vs control) • 2 participants vs 1 participant. This resulted in withdrawal from the study (Ward, 2011) Number and type of adverse effects • 2 of 20 participants with abdominal discomfort (Seikaly, 2005) • 50% of 139 participants experienced gastrointestinal symptoms. No difference in treatment arm (Ward, 2011) Most common adverse effect Most common reported effects were gastrointestinal symptoms.	Selection bias: Low in 1/2 and unclear in 1/2; Attrition bias: high in 1/2 and unclear in 1/2; Performance bias: low in 2/2; Detection bias: low in 1/2 and unclear in 1/2; <u>*Oral risedronate vs placebo*</u> Selection bias:Low; Attrition bias: low; Performance bias: low; Detection bias: low <u>*Intravenous pamidronate vs no treatment*</u> election bias: Unclear; Attrition bias: low; Performance bias high; Detection bias: high

		Oral risedronate vs placebo *Total participants*: unknown (bishop, 2013) *Intervention vs control:* Oral risedronate vs placebo *Pain outcomes* Pain was considered an adverse event and was measured using pain scales: When pain was reported as an adverse event there was no significant difference between the intervention of control group in the number of participants experiencing pain. OR 1.54,95% CI 0.52 to 4.56 (Bishop, 2013). No difference in pain scales was measured (discussion of Bishop, 2013) *Safety outcomes* Number of participants with adverse events (intervention vs control) No significant difference in number of adverse events between intervention and control group. OR 0.46, 95% CI 0.09 to 2.24 (Bishop, 2013) *Intravenous pamidronate vs no treatment* *Total participants*: Total participants 18 (Letocha, 2013) *Intervention vs control:* Intravenous pamidronate vs placebo *Pain outcomes* Pain measured by a 4 point self-reported pain scale (from 4 = no pain to 1 = intractable pain): No differences in self-reported bone pain were found. Mean difference: -0.11, 95% CI -0.83 to 0.61 (Letocha, 2005) *Safety outcomes* All participants experienced acute phase reactions upon the first infusion cycle of pamidronate. What these reactions were are not described; no other complications were noted (Letocha, 2005)	

Pharmacological treatment of pain			
Wiffen PJ et al. Opioids for cancer-related pain in children and adolescents. Cochrane Database of Systematic Reviews 2017 7): The Journal of Clinical Endocrinology and Metabolism 2011;96(2):355–64.			
Study characteristics	**Population**	**Outcome definitions / Main results**	**Conclusions** **Risk of bias**
Type of study: Systematic review of RCTs Included studies 0 Searched databases Cochrane Central Register of Controlled Trials(CENTRAL); MEDLINE (via Ovid); Embase (via Ovid) Selection criteria Inclusion criteria: • Type of studies: Randomised controlled trials (RCTs), with or without blinding, and participant or observer reported outcomes. • Type of participants: infants, children, and adolescents aged from birth to 17 years, who have (one or more) cancer and experience pain directly related to the condition. • Type of interventions: studies reporting interventions prescribing any opioid drug (alone or in combination) for the relief of cancer pain; by any route, in any dose, with comparison to a placebo or any active comparator. • Type of outcome measure: studies reporting pain assessments. For example measuring pain intensity and pain • relief assessed using validated tools such as numerical rating scale (NRS), visual analogue scale (VAS), Faces Pain Scale – Revised (FPS-R), Colour Analogue Scale (CAS), or any other validated rating scale. Exclusion criteria: studies of perioperative pain, short-term infection pain, short-term injury or trauma pain, acute pain, functional abdominal pain, burn pain, and musculoskeletal pains, headache and migraine, sickle cell disease acute crisis pain, mucositis, or any other chronic non-cancer related pain.	Number and type of participants: 0 Age: Not applicable Sex: Not applicable Other: Not applicable	Outcome definitions • Participant-reported pain relief of 30% or greater. • Participant-reported pain relief of 50% or greater. • GIC much or very much improved Main results There were no randomised controlled trials (RCTs) identified for inclusion.	**Conclusions** We identified no randomised controlled trials (RCTs), to support or refute the use of opioids to treat cancer pain in children and adolescents. **Additional remarks** Strengths: -- Limitations: National Institute for Health Research (NIHR), UK. **Risk of bias** Not applicable

4 Samenvatting en gradering van bewijs

4.1 Niet-medicamenteuze behandeling van Pijn

4.1.1 Geïncludeerde uitkomstmaten

Included outcomes
Child symptoms, post-treatment
Child symptoms, follow-up

4.1.2 Cognitieve gedragstherapie bij ouders van kinderen met een chronische ziekte

Cognitive behavioural therapy for parents of children with a chronic illness				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Child symptoms, post-treatment				
12 RCTs extracted from systematic review of RCTs: Eccleston, 2015	Parents of children aged 0 to 19 with a chronic illness (i.e. painful conditions, cancer, diabetes, asthma, traumatic brain injury)	Total participants 754 (396 vs 358)	Cognitive behavioural therapy for parents vs control (active treatment group, treatment-as-usual, waiting list control)	**Child symptoms – post treatment** Overall effect of CBT was beneficial (SMD = -0.32, 95%CI -0.53 to -0.11, p <0.01
Grade assessment				
Study design:	+4	12 Randomized Controlled Trials (results extracted from systematic review of RCTs: Eccleston, 2015)		
Study limitations	-2	Some limitations - Selection bias: low in 4/12 studies and unclear 8/12 studies; Attrition bias: low in 5/12, unclear in 3/12 and high in 4/12; Performance bias: unknown; Detection bias: low in 4/12 and unclear in 8/12;		
Consistency:	0	No important inconsistency, I^2 =47%		
Directness:	-1	Outcomes are direct. It is unclear whether outcomes are generalizable to all children receiving palliative care as not all chronic conditions described are life-limiting/life-threatening.		
Precision:	0	No imprecision, large sample size,		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence that cognitive behavioural therapy for parents of children with a chronic illness decreases child symptoms post-treatment as compared to treatment as usual, active control or wait-list control.**		

Cognitive behavioural therapy for parents of children with a chronic illness				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Child symptoms, follow-up				
7 RCTs extracted from systematic review of RCTs: Eccleston, 2015	Parents of children aged 0 to 19 with a chronic illness (i.e. painful conditions, cancer, diabetes, asthma, traumatic brain injury)	Total participants 475 (253 vs 219)	Cognitive behavioural therapy (CBT) for parents vs control (active treatment group, treatment-as-usual, waiting list control)	**Child symptoms– follow-up** No effect of CBT was identified. SMD -0.34 95%CI -0.73 to 0.05, z = 0.45, p = 0.65) z = 1.70. p = 0.09)

Grade assessment		
Study design:	+4	7 Randomized Controlled Trials (results extracted from systematic review of RCTs: Eccleston, 2015)
Study limitations	-2	Serious limitations - Selection bias: low in 3/7 studies and unclear 4/7 studies; Attrition bias: low in 4/7, unclear in 1/7 and high in 2/7; Performance bias: unknown; Detection bias: low in 2/7 and unclear in 5/7;
Consistency:	-1	Some inconsistency, I^2 =74%
Directness:	-1	Outcomes are direct. It is unclear whether outcomes are generalizable to all children receiving palliative care as not all chronic conditions described are life-limiting/life-threatening.
Precision:	0	No imprecision, large sample size.
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence that there is no significant effect of cognitive behavioural therapy for parents of children with a chronic illness on child symptoms at follow-up as compared to treatment as usual, active control or wait-list control.**

4.1.3 *Familie therapy bij ouders van kinderen met een chronische ziekte*

Family therapy for parents of children with a chronic illness				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Child symptoms, post-treatment				
5 RCTs extracted from systematic review of RCTs: Eccleston, 2015	Parents of children aged 0 to 19 with a chronic illness (i.e. painful conditions, cancer, diabetes, asthma, traumatic brain injury)	Total participants 259 (134 vs 125)	Family therapy for parents vs control (active treatment group, treatment-as-usual, waiting list control)	**Child symptoms – post-treatment** No effect of family therapy was found. SMD: 0.04 95%CI -0.20 to 0.29, z = 0.35. p = 0.73
Grade assessment				
Study design:	+4	5 Randomized Controlled Trials (results extracted from systematic review of RCTs: Eccleston, 2015)		
Study limitations	-2	Serious limitations - Selection bias: unclear 5/5 studies; Attrition bias: unclear in 5/5; Performance bias: unknown; Detection bias: low in 2/5 and unclear in 3/5;		
Consistency:	0	No important inconsistency, I^2 =1%		
Directness:	-1	Outcomes are direct. It is unclear whether outcomes are generalizable to all children receiving palliative care as not all chronic conditions described are life-limiting/life-threatening.		
Precision:	0	No imprecision, large sample size		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence that there is no significant effect of family therapy for parents of children with a chronic illness on child symptoms post-treatment as compared to treatment as usual, active control or wait-list control.**		

Family therapy for parents of children with a chronic illness				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Child symptoms, follow-up				
2 RCTs extracted from systematic review of RCTs: Eccleston, 2015	Parents of children aged 0 to 19 with a chronic illness (i.e. painful conditions, cancer, diabetes, asthma, traumatic brain injury)	Total participants 96 (48 vs 48)	Family therapy for parents vs control (active treatment group, treatment-as-usual, waiting list control)	**Child symptoms – follow-up** No effect of Family Therapy was identified. SMD: -0.02 95%CI -0.43 to 0.38, z = 0.12. p = 0.91

Grade assessment		
Study design:	+4	2 Randomized Controlled Trials (results extracted from systematic review of RCTs: Eccleston, 2015018)
Study limitations	-1	Some limitations - Selection bias: unclear 2/2 studies; Attrition bias: unclear in 2/2 Performance bias: unknown; Detection bias: low in 2/2;
Consistency:	0	No important inconsistency, I^2 =0%
Directness:	-1	Outcomes are direct. It is unclear whether outcomes are generalizable to all children receiving palliative care as not all chronic conditions described are life-limiting/life-threatening.
Precision:	-1	some imprecision, small sample size
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence that there is no significant effect of family therapy for parents of children with a chronic illness on child symptoms at follow-up as compared to treatment as usual, active control or wait-list control.**

4.1.4 Probleemoplossingsgerichte therapie bij ouders van kinderen met een chronische ziekte

Problem solving therapy for parents of children with a chronic illness				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Child symptoms, post-treatment				
2 RCTs extracted from systematic review of RCTs: Eccleston, 2015	Parents of children aged 0 to 19 with a chronic illness (i.e. painful conditions, cancer, diabetes, asthma, traumatic brain injury)	Total participants 216 (105 vs 111)	Problem solving therapy for parents vs control (active treatment group, treatment-as-usual, waiting list control)	**Child symptoms, post-treatment** No effect of problem solving therapy. SMD 0.19, 95%Ci -0.08 to 0.46, z = 1.41, p = 0.59
Grade assessment				
Study design:	+4	2 Randomized Controlled Trials (results extracted from systematic review of RCTs: Eccleston, 2015)		
Study limitations	-1	Some limitations - Selection bias: low in 1/2 and unclear 1/2 studies; Attrition bias: low in 1/2 and high in 1/2; Performance bias: unknown; Detection bias: low in 2/2;		
Consistency:	0	No important inconsistency, I^2 =18%		
Directness:	-1	Outcomes are direct. It is unclear whether outcomes are generalizable to all children receiving palliative care as not all chronic conditions described are life-limiting/life-threatening.		
Precision:	0	No imprecision, large sample size.		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊕⊖⊖ **LOW**		
Conclusion:		**There is low quality of evidence that there is no significant effect of problem solving therapy for parents of children with a chronic illness on child symptoms at post-treatment as compared to treatment as usual, active control or wait-list control.**		

4.1.5 Multi systemische therapie bij ouders van kinderen met een chronische ziekte

Multi-systemic therapy for parents of children with a chronic illness				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Child symptoms, post-treatment				
4 RCTs extracted from systematic review of RCTs: Eccleston, 2015	Parents of children aged 0 to 19 with a chronic illness (i.e. painful conditions, cancer, diabetes, asthma, traumatic brain injury)	Total participants 455 (130 vs 225)	Multi-systemic therapy for parents vs control (active treatment group, treatment-as-usual, waiting list control)	**Child symptoms, post-treatment** No effect of multi-systemic therapy. SMD -0.24, 95%CI -0.56 to 0.07, z = 1.52, p = 0.13
Grade assessment				
Study design:	+4	2 Randomized Controlled Trials (results extracted from systematic review of RCTs: Eccleston, 2015)		
Study limitations	-1	Some limitations - Selection bias: low in 1/4 and unclear 3/4 studies; Attrition bias: low in 3/4 and unclear in 1/4; Performance bias: unknown; Detection bias: low in 3/4 and unclear in 1/4;		
Consistency:	-1	Some inconsistency, I^2 =60%		
Directness:	-1	Outcomes are direct. It is unclear whether outcomes are generalizable to all children receiving palliative care as not all chronic conditions described are life-limiting/life-threatening.		
Precision:	0	No imprecision, large sample size		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊕⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence that there is no significant effect of multi-systemic therapy for parents of children with a chronic illness on child symptoms post-treatment as compared to treatment as usual, active control or wait-list control.**		

Multi-systemic therapy for parents of children with a chronic illness				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Child symptoms, follow-up				
2 RCTs extracted from systematic review of RCTs: Eccleston, 2015	Parents of children aged 0 to 19 with a chronic illness (i.e. painful conditions, cancer, diabetes, asthma, traumatic brain injury)	Total participants 247 (123 vs 124)	Multi-systemic therapy for parents vs control (active treatment group, treatment-as-usual, waiting list control)	**Child symptoms, follow-up** No effect of multi-systemic therapy. SMD -0.19, 95%CI -0.44 to 0.09, z = 1.47, p = 0.14)

Grade assessment		
Study design:	+4	2 Randomized Controlled Trials (results extracted from systematic review of RCTs: Eccleston, 2015)
Study limitations	-1	Some limitations - Selection bias: low in 1/2 and unclear 1/2 studies; Attrition bias: low in 1/2 and unclear in 1/2; Performance bias: unknown; Detection bias: low in 1/2 and unclear in 1/2;
Consistency:	0	No important inconsistency, I^2 =0%
Directness:	-1	Outcomes are direct. It is unclear whether outcomes are generalizable to all children receiving palliative care as not all chronic conditions described are life-limiting/life-threatening.
Precision:	0	No imprecision, large sample size
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ **LOW**
Conclusion:		**There is low quality of evidence that there is no significant effect of multi-systemic therapy for parents of children with a chronic illness on child symptoms at follow-up as compared to treatment as usual, active control or wait-list control.**

4.2 Medicamenteuze behandeling van Pijn

4.2.1 Geïncludeerde uitkomstmaten

Included outcomes
Pain, various measurements for assessment of pain
Safety, adverse events and adverse effects

4.2.2 Opioïden

Pharmacological treatment for pain		
Studies	Type and number of studies	Conclusions
Wiffen, 2011	0 randomized controlled trials	No randomised controlled trials to support or refute the use of opioids to treat cancer pain in children and adolescents were identified. Following inclusion criteria were used: randomized controlled trials with or without blinding; infants, children and adolescents aged 0 to 17; studies reporting interventions prescribing opioid drug (alone or in combination) for cancer pain; and studies reporting pain assessment.
Conclusion:	**Unknown effects of opioids to treat cancer pain in children aged 0 to 17.**	

4.2.3 Intrathecale baclofen

Intrathecal baclofen				
Studies	Type of participants	Total no. of participants	Type of intervention vs control	Outcome and Effect size
Pain				
3 RCTs extracted from systematic review of RCTs: Beecham, 2015. Included RCTs: • Bonouvrie, 2011 • Hoving, 2007 • Hoving, 2009	Children with Cerebral Palsy (CP) aged 7 to 17	Total participants 21 N = 4 (Bonouvrie 2011) N = 17 (Hoving, 2007; Hoving 2009)	Intrathecal baclofen vs placebo (Bonouvrie, 2011) Intrathecal baclofen vs therapy as normal (Hoving, 2007; Hoving 2009)	**Pain measured using Visual Analogue Scale (VAS) (0-10):** • Significant decrease of pain after administration of intrathecal baclofen in the intervention group compared to standard therapy in the control group. Mean Difference: 4.20, 95%CI 2.1 to 6.25 (Hoving, 2009) • Decrease of pain with 2.6 points in the intervention groups. Pain scores increased in the placebo group (Bonouvrie, 2011) **Pain measured using VAS (0-10) at 6-month follow-up**: Significant decrease of pain in the intervention group as compared to placebo. Mean difference: 4.20, 95%CI 2.15 to 6.25 (Hoving, 2007) **Bodily pain or discomfort measured using Child Health Questionnaire-parent form at 6-months follow-up:** Decrease of pain in the intervention group. Mean difference 26.60, 95% CI 2.61 to 50.59 (Hoving, 2007).
Grade assessment				
Study design:	+4	3 Randomized Controlled Trials (results extracted from systematic review of RCTs: Beecham, 2015)		
Study limitations	-2	Serious limitations - Selection bias: Low in 2/3 and unclear in 1/3; Attrition bias low in 1/3, unclear in 1/3 and high in 1/3; Performance bias low in 1/3, unclear in 1/3 and high in 1/3; Detection bias: low in 1/3, unclear in 1/3 and high in 1/3;		
Consistency:	0	No important inconsistency. All studies show that pain scores decreased in children receiving intrathecal baclofen.		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	-1	Some imprecision due to small sample size (n = 21)		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence that treatment with intrathecal baclofen decreases pain in children with Cerebral Palsy as compared to standard treatment or placebo.**		

Intrathecal baclofen				
Studies	Type of participants	Total no. of participants	Type of intervention vs control	Outcome and Effect size
Safety, Adverse events and adverse effects				
3 RCTs extracted from systematic review of RCTs: Beecham, 2015. Included RCTs: • Bonouvrie, 2011 • Hoving, 2007 • Hoving, 2009	Children with Cerebral Palsy (CP) aged 7 to 17	Total participants 21 N = 4 (Bonouvrie 2011) N = 17 (Hoving, 2007; Hoving 2009)	Intrathecal baclofen vs placebo (Bonouvrie, 2011) Intrathecal baclofen vs therapy as normal (Hoving, 2007; Hoving 2009)	**Number and type of adverse effects** • Nine adverse effects in 8 of 17 participant, mostly related to Cerebrospinal Fluid (CSF leakage) (Hoving, 2007) • Fourteen of 17 patients experienced a total of 28 procedure or device related adverse events, mostly related to swelling at pump site (Hoving, 2009) • 2 of 4 patients experienced CSF leakage which in discontinuation of trial in one patient (Bonouvrie, 2011) **Most common adverse effect** • Most common adverse effect irrespective of treatment arm was related to CSF leakage, respectively 2 patients (Bonouvrie, 2011) and 3 patients (Hoving, 2007)
Grade assessment				
Study design:	+4	3 Randomized Controlled Trials (results extracted from systematic review of RCTs: Beecham, 2015)		
Study limitations	-2	Serious limitations - Selection bias: Low in 2/3 and unclear in 1/3; Attrition bias low in 1/3, unclear in 1/3 and high in 1/3; Performance bias low in 1/3, unclear in 1/3 and high in 1/3; Detection bias: low in 1/3, unclear in 1/3 and high in 1/3;		
Consistency:	0	No important inconsistency.		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	-1	Some imprecision due to small sample size (n = 21)		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence that adverse effects were reported in both intervention and control group. Most common adverse effects were related to Cerebrospinal Fluid Leakage.**		

4.2.4 Botuline toxine type A injecties

Botulinum toxin A injections				
Studies	Type of participants	Total no. of participants	Type of intervention vs control	Outcome and Effect size
Pain				
N = 2 RCTs extracted from systematic review of RCTs: Beecham, 2015. Included RCTs: • Copeland, 2014 • Russo 2007	Children with CP aged 2 to 16	Total participants: 84 N = 41 (Copeland, 2014) N = 43 (Russo, 2007)	Botulinum Toxin A vs. placebo (Copeland, 2014) Botulinum Toxin A with Occupational Therapy (OT) vs. OT only (Russo, 2007)	• **Pain measured using the Pediatric Pain Profile at 1 month follow-up:** No significant difference in pain scores between intervention and control group. Mean Difference -2.67, 95% CI -10.18 to 4.84 (Copeland, 2014) • **Pain measured using the Pediatric Pain Profile at 4 month follow-up:** No significant difference in pain scores between intervention and control group. Mean Difference 2.59, 95% CI -3.75 to 8.93 (Copeland, 2014) • **Pain measured using VAS at 3-month follow-up (2 participants in each group):** No significant difference in pain scores between intervention and control group. OR 1.05, 95%CI 0.13 to 8.24 (Russo, 2007) • **Pain measured using VAS at 6-month follow-up (1 participants in each group):** No significant difference in pain scores between intervention and control group. OR 1.05, 95% CI 0.06to 17.95 (Russo, 2007)

Grade assessment		
Study design:	+4	2 Randomized Controlled Trials (results extracted from systematic review of RCTs: Beecham, 2015)
Study limitations	-2	Serious limitations - Selection bias: Low in 1/2 and unclear in 1/2; Attrition bias: Low in 2/2; Performance bias: Low in 1/2 and high in 1/2; Detection bias: Low in 1/2 and high in 1/2;
Consistency:	0	No important inconsistency. All studies show that there is no effect of treatment with Botulinum Toxin A on pain. In 1 study the relation at 4 months was not significant.
Directness:	0	Results are direct. Outcomes are generalizable.
Precision:	-1	Some imprecision due to small sample sizes
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence there is no significant effect of treatment with Botulinum Toxin A (with OT) on pain in children with Cerebral Palsy as compared to placebo or treatment with OT only.**

Botulinum toxin A injections				
Studies	Type of participants	Total no. of participants	Type of intervention vs control	Outcome and Effect size
Safety, adverse events and adverse effects				
N = 2 RCTs extracted from systematic review of RCTs: Beecham, 2015. Included RCTs: • Copeland, 2014 • Russo 2007	Children with CP aged 2 to 16	Total participants: 84 N = 41 (Copeland, 2014) N = 43 (Russo, 2007)	Botulinum Toxin A vs. placebo (Copeland, 2014) Botulinum Toxin A with Occupational Therapy (OT) vs. OT only (Russo, 2007)	**Number and type of participants with adverse events (intervention vs control)** • 1 participant with epilepsy and hospital admission vs 2 participants with hospital admission due to epilepsy (Russo, 2007) • 3 participants with systemic drooling, decreased vocalization or drooling vs 1 participant (Copeland, 2014) **Number and type of adverse effects (intervention vs control)** • 22 adverse effects (feeling unwell) vs 0 adverse effects (Russo, 2007) • 23 patients with moderate or mild adverse effects (Copeland, 2014) **Most common adverse effect** Most common reported effect were seizures and respiratory symptoms
Grade assessment				
Study design:	+4	2 Randomized Controlled Trials (results extracted from systematic review of RCTs: Beecham, 2015)		
Study limitations	-2	Serious limitations - Selection bias: Low in 1/2 and unclear in 1/2; Attrition bias: Low in 2/2; Performance bias: Low in 1/2 and high in 1/2; Detection bias: Low in 1/2 and high in 1/2;		
Consistency:	0	No important inconsistency.		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	-1	Some imprecision due to small sample sizes		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence that adverse effects were reported in both intervention and control groups. Most common adverse effects were seizures and respiratory symptoms.**		

4.2.5 Oraal alendronaat

Oral alendronate				
Studies	Type of participants	Total no. of participants	Type of intervention vs control	Outcome and Effect size
Pain				
N = 2 RCTs extracted from systematic review of RCTs: Beecham, 2015. Included RCTs: • Seikaly, 2005 (cross-over RCT) • Ward, 2011	Children with Osteogenesis imperfecta (OI) aged 3 to 19.	Total participants 159 N = 20 (Seikaly, 2005) N = 139 (Ward, 2011)	Oral alendronate vs placebo	• **Pain measured by number of pain-free days per month at 12-month follow-up:** Significant decrease of pain in the intervention group. Mean difference, MD-3.63, 95%CI -5.17 to -2.09 (Seikaly, 2005) • **Pain measured by number of days with analgesic use for skeletal pains at 12-month follow up:** Significant decrease of analgesic use in the intervention group. Mean Difference, -2.00, 95% CI -3.57 to -0.43 (Seikaly, 2005) • **Pain measured by number of patients with bone pain at 24 month follow-up:** In the intervention group fewer patients experienced pain in comparison to placebo (37%, 38/102 vs. 57%, 17/30). This effect was not statistically significant. OR, 0.45, 95% CI 0.20 to 1.04 (Ward, 2011) • **Pain measured by number of days per week that patients experienced bone pain at 24 month follow-up:** No significant difference the intervention group at baseline and follow-up (Ward, 2011).

Grade assessment		
Study design:	+4	2 Randomized Controlled Trials (results extracted from systematic review of RCTs: Beecham, 2015)
Study limitations	-1	Some limitations - Selection bias: Low in 1/2 and unclear in 1/2; Attrition bias: high in 1/2 and unclear in 1/2; Performance bias: low in 2/2; Detection bias: low in 1/2 and unclear in 1/2;
Consistency:	0	No Important inconsistency. One study shows that there is a significant decrease in pain after treatment with oral alendronate. Although treatment with oral alendronate is decreased in the other study, this effect is not considered significant.
Directness:	0	Results are direct. Outcomes are generalizable.
Precision:	-1	Some imprecision due to small study of Seikaly, 2005
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		**⊕⊕⊖⊖ LOW**
Conclusion:		**There is low quality of evidence that treatment with oral alendronate decreases pain in children with Osteogenesis Imperfecta as compared to treatment with placebo (significant in one study).**

Oral alendronate				
Studies	Type of participants	Total no. of participants	Type of intervention vs control	Outcome and Effect size
Safety, adverse events and adverse effects				
N = 2 RCTs extracted from systematic review of RCTs: Beecham, 2015. Included RCTs: • Seikaly, 2005 (cross-over RCT) • Ward, 2011	Children with Osteogenesis imperfecta (OI) aged 3 to 19.	Total participants 159 N = 20 (Seikaly, 2005) N = 139 (Ward, 2011)	Oral alendronate vs placebo	**Number and type of participants with adverse events (intervention vs control)** • 2 participants vs 1 participant. This resulted in withdrawal from the study (Ward, 2011) **Number and type of adverse effects** • 2 of 20 participants with abdominal discomfort (Seikaly, 2005) • 50% of 139 participants experienced gastrointestinal symptoms. No difference in treatment arm (Ward, 2011) **Most common adverse effect** Most common reported effects were gastrointestinal symptoms.

Grade assessment		
Study design:	+4	2 Randomized Controlled Trials (results extracted from systematic review of RCTs: Beecham, 2015)
Study limitations	-1	Some limitations - Selection bias: Low in 1/2 and unclear in 1/2; Attrition bias high in 1/2 and unclear in 1/2; Performance bias low in 2/2; Detection bias: low in 1/2 and unclear in 1/2;
Consistency:	0	No important inconsistency
Directness:	0	Results are direct. Outcomes are generalizable.
Precision:	-1	Some imprecision due to small study of Seikaly, 2005
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ **LOW**
Conclusion:		**There is low quality of evidence that adverse effects in both intervention and control groups. Most common adverse effects were gastrointestinal symptoms**

4.2.6 Oraal risedronaat

Oral risedronate				
Studies	Type of participants	Total no. of participants	Type of intervention vs control	Outcome and Effect size
Pain				
N = 1 RCTs extracted from systematic review of RCTs: Beecham, 2015. Included RCTs: • Bishop, 2013	Children with Osteogenesis imperfecta (OI)	Total participants unknown	Oral risedronate vs placebo	**Pain was considered an adverse event and was measured using pain scales:** When pain was reported as an adverse event there was no significant difference between the intervention ~~of~~ and control group in the number of participants experiencing pain: ~~,~~ OR 1.54,95% CI 0.52 to 4.56 (Bishop, 2013) No difference in pain scales was measured (discussion of Bishop, 2013)
Grade assessment				
Study design:	+4	1 Randomized Controlled Trial (results extracted from systematic review of RCTs: Beecham, 2015)		
Study limitations	0	No limitations - Selection bias: Low; Attrition bias: low; Performance bias: low; Detection bias: low		
Consistency:	0	No important inconsistency. Only 1 study performed		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	-2	Serious imprecision due to unknown sample size. Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊕⊖⊖ **LOW**		
Conclusion:		**There is low quality of evidence there is no significant effect of treatment with oral risedronate on pain in children with Osteogenesis Imperfecta as compared to treatment with placebo.**		

Oral risedronate				
Studies	Type of participants	Total no. of participants	Type of intervention vs control	Outcome and Effect size
Safety, adverse events and adverse effects				
N = 1 RCTs extracted from systematic review of RCTs: Beecham, 2015. Included RCTs: • Bishop, 2013	Osteogenesis imperfecta (OI)	Total participants unknown	Oral risedronate vs placebo	**Number of participants with adverse events (intervention vs control)** • No significant difference in number of adverse events between intervention and control group: OR 0.46, 95% CI 0.09 to 2.24 (Bishop, 2013)

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial (results extracted from systematic review of RCTs: Beecham, 2015)
Study limitations	0	No limitations - Selection bias: Low; Attrition bias: low; Performance bias: low; Detection bias: low
Consistency:	0	No important inconsistency. Only 1 study performed
Directness:	0	Results are direct. Outcomes are generalizable.
Precision:	-2	Serious imprecision due to unknown sample size. Only 1 study performed
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ **LOW**
Conclusion:		**There is low quality of evidence there is no significant effect of treatment with oral risedronate on adverse events in children with Osteogenesis Imperfecta as compared to treatment with placebo.**

4.2.7 Intraveneus pamidronaat

Oral pamidronate				
Studies	Type of participants	Total no. of participants	Type of intervention vs control	Outcome and Effect size
Pain				
N = 1 RCT extracted from systematic review of RCTs: Beecham, 2015. Included RCTs: • Letocha, 2005	Osteogenesis imperfecta (OI)	Total participants 18	Intravenous Pamidronate vs no treatment	• **Pain measured by a 4 point self-reported pain scale (from 4 = no pain to 1 = intractable pain):** No differences in self-reported bone pain were found. Mean difference: -0.11, 95% CI -0.83 to 0.61 (Letocha, 2005)
Grade assessment				
Study design:	+4	1 Randomized Controlled Trial (results extracted from systematic review of RCTs: Beecham, 2015)		
Study limitations	-2	Serious limitations - Selection bias: Unclear; Attrition bias: low; Performance bias high; Detection bias: high		
Consistency:	0	No important inconsistency. Only 1 study performed.		
Directness:	0	Results are direct. Outcomes are generalizable.		
Precision:	-2	Serious imprecision due to small sample size. Only 1 study performed		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect		
Dose-response:	0	Unclear dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**		
Conclusion:		**There is very low quality of evidence there is no significant effect of treatment with intravenous pamidronate on pain in children with Osteogenesis Imperfecta as compared to no treatment.**		

Intravenous pamidronate				
Studies	Type of participants	Total no. of participants (intervention vs control)	Type of intervention vs control	Outcome and Effect size
Safety, adverse events and adverse effects				
N = 1 RCT extracted from systematic review of RCTs: Beecham, 2015. Included RCTs: • Letocha, 2005	Osteogenesis imperfecta (OI)	Total participants 18	Intravenous Pamidronate vs no treatment	All participants experienced acute phase reactions upon the first infusion cycle of pamidronate. What these reactions were are not described; no other complications were noted (Letocha, 2005).

Grade assessment		
Study design:	+4	1 Randomized Controlled Trial (results extracted from systematic review of RCTs: Beecham, 2015)
Study limitations	-2	Serious limitations - Selection bias: Unclear; Attrition bias: low; Performance bias high; Detection bias: high
Consistency:	0	No important inconsistency. Only 1 study performed.
Directness:	0	Results are direct. Outcomes are generalizable.
Precision:	-2	Serious imprecision due to small sample size. Only 1 study performed
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ **VERY LOW**
Conclusion:		**There is very low quality of evidence that treatment with intravenous pamidronate results in acute phase reactions during the first infusion cycle in children with Osteogenesis Imperfecta.**

5 Conclusies van evidence

5.1 Niet-medicamenteuze behandeling van Pijn

Non pharmacological treatment of pain			
Intervention		**Conclusions of evidence**	**Quality of evidence**
cognitive behavioural therapy for parents	*vs. control i.e. treatment as usual, active control, wait-list control*	↓ child symptoms (post-treatment) in children with chronic illness (painful conditions, cancer, diabetes, asthma, traumatic brain injury) after intervention	⊕⊖⊖⊖ VERY LOW (12 RCTs)
		No significant effect on child symptoms (follow-up) in children with chronic illness (painful conditions, cancer, diabetes, asthma, traumatic brain injury)	⊕⊖⊖⊖ VERY LOW (7 RCTs)
family therapy for parents	*vs. control i.e. treatment as usual, active control, wait-list control*	No significant effect on child symptoms (post-treatment) in children with chronic illness (painful conditions, cancer, diabetes, asthma, traumatic brain injury)	⊕⊕⊖⊖ LOW (5 RCTs)
		No significant effect on child symptoms (follow-up) in children with chronic illness (painful conditions, cancer, diabetes, asthma, traumatic brain injury)	⊕⊖⊖⊖ VERY LOW (2 RCTs)
problem-solving therapy for parents	*vs. control i.e. treatment as usual, active control, wait-list control*	No significant effect on child symptoms (post-treatment) in children with chronic illness (painful conditions, cancer, diabetes, asthma, traumatic brain injury)	⊕⊕⊖⊖ LOW (2 RCTs)
multi-systemic therapy for parents	*vs. control i.e. treatment as usual, active control, wait-list control*	No significant effect on child symptoms (post-treatment) in children with chronic illness (painful conditions, cancer, diabetes, asthma, traumatic brain injury)	⊕⊕⊖⊖ VERY LOW (4 RCTs)
		No significant effect on child symptoms (follow-up) in children with chronic illness (painful conditions, cancer, diabetes, asthma, traumatic brain injury)	⊕⊕⊖⊖ LOW (2 RCTs)
Integrative therapies		Unknown effect	No studies

5.2 Medicamenteuze behandeling van Pijn

Pharmacological treatment of pain			
Intervention		**Conclusions of evidence**	**Quality of evidence**
Paracetamol *NSAIDs* *Tramadol* *Codeine* *Morphine* *Oxycodone* *Buprenorphine* *Corticosteroids* *Amitriptyline = TCA* *Gabapentin, pregabaline* *Phenytoin* *Carmazepine* *Valproate* *Opioids*		Unknown effect	No studies
New pharmacological interventions			
Clonidine *Dipidolor* *Fentanyl Nasal spray* *Eterocoxib en celecoxib (Cox 1 en cox 2 inhibitoren)* *Ketamine*		Unknown effect	No studies
Adjuvant pharmacological treatments			
Intrathecal baclofen	*vs. placebo or therapy as normal*	↓ pain in children with cerebral palsy after intervention Adverse effects in children with cerebral palsy in intervention and control groups. Most common adverse effects were related to Cerebrospinal Fluid Leakage.	⊕⊖⊖⊖ VERY LOW (3 RCTs)
Botulinum A injections or Botulinum A injections with OT	*vs. placebo or OT only*	No significant effect on pain in children cerebral palsy. Adverse effects in children cerebral palsy in intervention and control groups. Most common adverse effects were seizures and respiratory symptoms.	⊕⊖⊖⊖ VERY LOW (2 RCTs)
Oral alendronate	*vs. placebo*	↓ pain in children with Osteogenesis Imperfecta after intervention (no significant effect in all studies) Adverse effects in children with Osteogenesis Imperfecta in intervention and control groups. Most common adverse effects were gastrointestinal symptoms	⊕⊕⊖⊖ LOW (2 RCTs)
Oral risedronate	*vs. placebo*	No significant effect on pain in children with Osteogenesis Imperfecta No significant effect on adverse effects in children with Osteogenesis imperfecta	⊕⊕⊖⊖ LOW (1 RCT)
Intravenous pamidronate	*vs. placebo*	No significant effect on pain in children with Osteogenesis Imperfecta Adverse effects (acute phase reactions during first infusion cycle) of intervention in children with Osteogenesis Imperfecta.	⊕⊖⊖⊖ VERY LOW (1 RCT)

6 Aanbevelingen uit richtlijnen

6.1 Niet-medicamenteuze behandeling van Pijn

Non pharmacological treatment of pain – Child guideline	
Joanna Briggs Institute. Effectiveness of non-pharmocological pain management in relieving chronic pain for children and adolescents. Best practice: evidence-based information sheets for health professionals 2010 14 (17); 1-4	
Recommendation[1]	**Level of evidence**[2]
Clinical evidence: *The quality of the research was good: 4 meta-analyses were identified (Level 1), 4 RCTs (level 2) and 22 quasi-experimental studies (level 3).*	
Grade B: Relaxation programs should be considered for children and adolescents with recurrent headache pain.	Level 1
Grade B: Biofeedback treatment should be considered for children and adolescents with recurrent headache pain	Level 2
Grade B: Cognitive behavior therapy should be considered – either alone or in combination with muscle stimulation, meditation, progressive muscular relaxation training, for children and adolescents with recurrent headache pain.	Level 2 (effect of cognitive behavior therapy alone) Level 1 (effect of cognitive behavior therapy in combination with muscle stimulation, meditation etc.)

[1] **Grades of recommendation based on the JBI-developed 2006 grades of effectiveness**
A: Strong support that merits application
B: Moderate support that warrants consideration of application
C: Not supported.

[2] Level of evidence developed by the Joanna Briggs Institute Levels of Evidence and Grades of Recommendation working Party (2013)
1: Experimental Designs: Systematic review of Randomized Controlled Trials (RCTs), Systematic review of RCTs and other study designs, RCT or Pseudo-RCTs
2: Quasi-experimental Designs: Systematic review of quasi-experimental studies, Systematic review of quasi-experimental and other lower study designs, Quasi-experimental prospectively controlled study or Pre-test – post-test or historic/retrospective control group study
3: Observational analytic designs: Systematic review of comparable cohort studies, Systematic review of comparable cohort and other lower study designs, Cohort study with control group, Case – controlled study or Observational study without a control group
4: Observational descriptive studies: Systematic review of descriptive studies, Cross-sectional study, Case series, Case study
5: Expert opinion and Bench Research level: Systematic review of expert opinion, Expert consensus, Bench research/ single expert opinion

6.2 Medicamenteuze behandeling van Pijn

Pharmacological treatment of pain – Child guideline	
National institute for health and care Excellence (NICE). End of life care for infants, children and young people: planning and management. 2016	
Recommendation	**Level of evidence**
Clinical evidence: *Nine reviews were identified but none of them met the inclusion criteria. Four observational studies with uncontrolled study design were included in this review. The following outcomes were reported: pain, control of other symptoms, parents or caregivers' quality of life and adverse events.* *The overall evidence was of very low quality. This was due to the methodological flaws inherent to uncontrolled studies and the fact that data was collected retrospectively in several studies. In addition, further concerns were raised about population indirectness, as all studies included children and young people with a life-expectancy beyond 2 months.* *The recommendations were therefore mainly based on consensus within the Committee rather than on the available evidence.*	
When assessing and managing pain, be aware that various factors can contribute to it, including: • biological factors, for example musculoskeletal disorders or constipation • environmental factors, such as an uncomfortable or noisy care setting • psychological factors, such as anxiety and depression • social, emotional, religious, spiritual or cultural considerations.	Expert opinion
When assessing pain in children and young people: • use an age-appropriate approach that takes account of their stage of development and ability to communicate • try to identify what is causing or contributing to their pain, and be aware that this may not relate to the life-limiting condition • take into account the following causes of pain and distress that might have been overlooked, particularly in children and young people who cannot communicate: o neuropathic pain (for example associated with cancer) o gastrointestinal pain (for example associated with diarrhoea or constipation) o bladder pain (for example caused by urinary retention) o bone pain (for example associated with metabolic diseases) o pressure ulcers o headache (for example caused by raised intracranial pressure) o musculoskeletal pain (particularly if they have neurological disabilities) o dental pain.	Expert opinion
Be aware that pain, discomfort and distress may be caused by a combination of factors, which will need an individualised management approach.	Expert opinion
For children and young people who have pain or have had it before, regularly reassess for its presence and severity even if they are not having treatment for it.	Expert opinion
Think about non-pharmacological interventions for pain management, such as: • changes that may help them to relax, for example: • environmental adjustments (for example reducing noise) • music • physical contact such as touch, holding or massage • local hot or cold applications to the site of pain • comfort measures, such as sucrose for neonates.	Expert opinion
Consider using a stepwise approach to analgesia in children and young people, based on pain severity and persistence: • For mild pain, consider paracetamol or ibuprofen sequentially, and then in combination if needed • For moderate to severe pain, consider one of the following options: o paracetamol or ibuprofen sequentially, and then in combination if needed or o low-dose oral opioids (such as morphine), or o transmucosal opioids or o subcutaneous opioids or o intravenously infused opioids (if a central venous catheter is in place).	Very Low
If treatment with a specific opioid does not give adequate pain relief or if it causes unacceptable side effects, think about trying an alternative opioid preparation.	Very Low

When using opioids, titrate treatment to find the minimal effective dose that will relieve and prevent pain.	Very Low
Titrate treatment to provide continuous background analgesia, and prescribe additional doses for breakthrough pain if this occurs.	Very Low
In addition to background analgesia, consider giving anticipatory doses of analgesia for children and young people who have pain at predictable times (for example when changing dressings, or when moving and handling). Do not include anticipatory doses when calculating the required daily background dose of analgesia.	Very Low
Calculate opioid dosages for children and young people who are approaching the end of life using weight rather than age, because they may be underweight for their age.	Very Low
If you suspect neuropathic pain and standard analgesia is not helping, consider a trial with other medicines, such as: • gabapentin or • a low-dose tricyclic antidepressant (for example amitriptyline) or • an anti-NMDA agent (for example ketamine or methadone), used under guidance from a specialist.	Expert opinion

7 Overzicht conclusies van evidence en aanbevelingen uit richtlijnen

7.1 Niet-medicamenteuze behandeling van Pijn

Non pharmacological treatments for pain								
Treatment	Conclusions of evidence (RCTs on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children 2013 (2)	Level of evidence[1]
Non pharmacological treatments for nociceptive pain								
Psychological therapies	Unknown effect	No studies	Consider cognitive behavioural therapy (CBT) in combination with muscle stimulation, meditation and progressive muscular relaxation training (for recurrent headache pain)	Level 2 (CBT alone) Level 1 (CBT in combination other therapies) (3;NP)	Not applicable	-	Consider (for nociceptive pain); weak recommendation	Level 1 child evidence for chronic pain (4)
Integrative therapies	Unknown effect	No studies	Not identified	-	Not identified	-	Consider	-
Relaxation programmes	Unknown effect	No studies	Consider (for recurrent headache pain)	Level 1 (3;NP)	Not applicable	-	No recommendation	-
Biofeedback	Unknown effect	No studies	Consider (for recurrent headache pain)	Level 2 (3;NP)	Not applicable	-	No recommendation	-
Non pharmacological treatments for parents								
cognitive behavioural therapy for parents	↓ child symptoms (post-treatment) in children with chronic illness	VERY LOW, 12 RCTs (5;P/NP)	Not identified	-	Not identified	-	No recommendation	-
	No significant effect on child symptoms (follow-up) in children with chronic illness	VERY LOW, 7 RCTs (5;P/NP)						
family therapy for parents	No significant effect on child symptoms (post-treatment) in children with chronic illness	LOW, 5 RCTs (5;P/NP)	Not identified	-	Not identified	-	No recommendation	-
	No significant effect on child symptoms (follow-up) in children with chronic illness	VERY LOW, 2 RCTs(5;P/NP)						

problem-solving therapy for parents	No significant effect on child symptoms (post-treatment) in children with chronic illness	LOW, 2 RCTs (5;P/NP)	Not identified	-	Not identified	-	No recommendation	
	No significant effect on child symptoms (post-treatment) in children with chronic illness	VERY LOW, 4 RCTs(5;P/NP)						
multi-systemic therapy for parents	No significant effect on child symptoms (follow-up) in children with chronic illness	LOW, 2 RCTs(5;P/NP)	Not identified	-	Not identified	-	No recommendation	

Legend
P: Palliative context
NP: Non-palliative context
P/NP: Both palliative and non-palliative context
Not identified: No recommendations on specific pharmacological intervention were identified.
Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.

[1]Level of evidence:
Level 1: Based on a systematic review or at least two randomized controlled trials of good quality
Level 2: Based on one at randomized controlled trial or at least two comparative clinical studies
Level 3: Based on one comparative study or on non-comparative studies
Level 4: Based on expert opinion

References

2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.
3. Joanna Briggs Institute. Effectiveness of non-pharmacological pain management in relieving chronic pain for children and adolescents. Best Practice: evidence-based information sheets for health professionals. 2010;14(17):1-4.
4. Eccleston C, Palermo TM, Williams AC, Lewandowski A, Morley S. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. Cochrane Database Syst Rev. 2009(2):CD003968.
5. Eccleston C, Fisher E, Law E, Bartlett J, Palermo TM. Psychological interventions for parents of children and adolescents with chronic illness. Cochrane Database Syst Rev. 2015(4):CD009660.

7.2 Medicamenteuze behandeling van Pijn

Pharmacological treatment of pain								
Treatment	Conclusions of evidence (RCTs on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children 2013 (2)	Level of evidence[1]
Step 1 in pain treatment								
Paracetamol *Ibuprofen (NSAIDs)*	Unknown effect	No studies	Consider for mild pain	Expert opinion (6;P)	Not applicable	-	Do; strong recommendation	Child guideline (7)
Step 2 opioids for mild pain | Step 3 opioids for severe pain								
Codeine	Unknown effect	No studies	Not identified	-	Not identified	-	Do not give; strong recommendation	Child guideline (7)
Tramadol	Unknown effect	No studies	Not identified	-	Not identified	-	Consider for mild pain; weak recommendation	Child guideline (7)
Buprenorphine	Unknown effect	No studies	Not identified	-	Not identified	-	Consider for severe pain	Child guideline (7)
Low-dose oral opioids Transmucosal Opioids Subcutaneous opioids	Unknown effect	No studies(8)	Consider for moderate to severe pain (in combination with paracetamol/ibuprofen)	Very Low, Expert opinion (6;P)	Not applicable	-	No recommendation	-
Intravenously infused opioids	Unknown effect	No studies(8)	Consider for moderate to severe pain if a central venous catheter is in place (in combination with paracetamol/ibuprofen)	Very Low, Expert opinion (6;P)	Not applicable	-	No recommendation	-
Morphine	Unknown effect	No studies(8)	Not identified	-	Not identified	-	Do for severe pain; strong recommendation	Child guideline (7)); level 3 adult evidence (9)
Other pharmacological treatments of pain								
Oxycodone	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Unknown level of evidence
Clonidine	Unknown effect	No studies	Not identified	-	Not identified	-	No recommendation	-
Dipidolor	Unknown effect	No studies	Not identified	-	Not identified	-	No recommendation	-
Fentanyl nasal spray	Unknown effect	No studies	Not identified	-	Not identified	-	No recommendation	-
Eterocoxib en celecoxib (Cox 1 en cox 2 inhibitoren)	Unknown effect	No studies	Not identified	-	Not identified	-	No recommendation	-
Pharmacological treatments for neuropathic pain								
Gabapentin *Pregabalin*	Unknown effect	No studies	Consider for neuropathic pain if standard analgesia are not working	Expert opinion (6;P)	Not applicable	-	Consider for neuropathic pain; weak recommendation	Level 1 adult evidence (10-12)

Low-dose tricyclic antidepressants • *Amitriptyline*							Consider for neuropathic pain; weak recommendation	Level 1 adult evidence (10, 13)
Anti-NMDA agents • *Ketamine* • *Methadone*							No recommendation	-
Phenytoin *Carbamazepine* *Valproate*	Unknown effect	No studies	Not identified	-	Not identified	-	Do not give for neuropathic pain; strong recommendation	Unknown level of adult evidence (14)
Opioids	Unknown effect	No studies	Not identified	-	Not identified	-	Consider for neuropathic pain; weak recommendation	Level 1 adult evidence (10, 15)
Adjuvant pharmacological treatments for pain								
Corticosteroids	Unknown effect	No studies	Not identified	-	Not identified	-	Consider for specific situations inflammation/oedema; weak recommendation	Child guideline (7)
Intrathecal baclofen	↓ pain in children with cerebral palsy Most common adverse effects: related to Cerebrospinal Fluid Leakage	VERY LOW, 3 RCTs (16)	Not identified	-	Not identified	-	No recommendation	-
Botulinum A injections (with OT)	No significant effect on pain in children cerebral palsy Most common adverse effects: seizures and respiratory symptoms	VERY LOW, 2 RCTs (16)	Not identified	-	Not identified	-	No recommendation	-
Oral alendronate	↓ pain in children with Osteogenesis Imperfecta Most common adverse effects: gastrointestinal symptoms	LOW, 2 RCTs (16)	Not identified	-	Not identified	-	No recommendation	-
Oral risedronate	No significant effect on pain in children with Osteogenesis Imperfecta No significant effect on adverse effects in children with Osteogenesis imperfecta	LOW, 1 RCT (16)	Not identified	-	Not identified	-	No recommendation	-

Intravenous pamidronate	No significant effect on pain in children with Osteogenesis Imperfecta Adverse effects (acute phase reactions during first infusion cycle) of intervention in children with Osteogenesis Imperfecta	VERY LOW, 1 RCT (16)	Not identified	-	Not identified	-	No recommendation	-

Legend
P: Palliative context
Not identified: No recommendations on specific pharmacological treatment were identified.
Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.

[1]Level of evidence:
Level 1: Based on a systematic review or at least two randomized controlled trials of good quality
Level 2: Based on one at randomized controlled trial or at least two comparative clinical studies
Level 3: Based on one comparative study or on non-comparative studies
Level 4: Based on expert opinion

References

2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.
6. National Institute for Health and Care Excellence. End of life care for infants, children and young people with life-limiting conditions: planning and management. [Internet]. London: NICE; 2016 [cited 2021 March 1]. Available from: www.nice.org.uk/guidance/ng61.
7. World Health Organization. WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses. Geneva: World Health Organization 2012.
8. Wiffen PJ, Cooper TE, Anderson AK, Gray AL, Gregoire MC, Ljungman G, et al. Opioids for cancer-related pain in children and adolescents. Cochrane Database Syst Rev. 2017;7:CD012564.
9. Wiffen PJ, Edwards JE, Barden J, McQuay HJ. Oral morphine for cancer pain. Cochrane Database Syst Rev. 2003(4):CD003868.
10. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain. 2010;150(3):573-81.
11. Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. Cochrane Database Syst Rev. 2009(3):CD007076.
12. Moore RA, Wiffen PJ, Derry S, McQuay HJ. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2011(3):CD007938.
13. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database Syst Rev. 2007(4):CD005454.
14. Feudtner C, Kang TI, Hexem KR, Friedrichsdorf SJ, Osenga K, Siden H, et al. Pediatric palliative care patients: a prospective multicenter cohort study. Pediatrics. 2011;127(6):1094-101.
15. Eisenberg E, McNicol E, Carr DB. Opioids for neuropathic pain. Cochrane Database Syst Rev. 2006(3):CD006146.
16. Beecham E, Candy B, Howard R, McCulloch R, Laddie J, Rees H, et al. Pharmacological interventions for pain in children and adolescents with life-limiting conditions. Cochrane Database of Systematic Reviews. 2015(3).

J Reutelen in de terminale fase

Inhoudsopgave

1 Uitgangsvragen

Vraag 10A: Wat is de meest effectieve niet-medicamenteuze behandeling van reutelen bij kinderen tussen 0 en 18 jaar in de palliatieve en terminale fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve en terminale fase
I: Niet-medicamenteuze behandeling van reutelen
C: Geen behandeling/placebo
O: Effect op reutelen en kwaliteit van leven

Vraag 10B: Wat is de meest effectieve medicamenteuze behandeling van reutelen bij kinderen tussen 0 en 18 jaar in de palliatieve en terminale fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve en terminale fase
I: Medicamenteuze behandeling van reutelen
C: Geen behandeling/placebo
O: Effect op reutelen en kwaliteit van leven

2 Resultaten van het literatuuronderzoek

Jaar	Bibliografie	Studie karakteristieken
10A: Wat is de meest effectieve niet-medicamenteuze behandeling van reutelen bij kinderen tussen 0 en 18 jaar in de palliatieve fase?*		
2016	***National institute for health and care Excellence (NICE).***End of life care for infants, children and young people: planning and management. 2016[1]	Richtlijn kinderen
10B: Wat is de meest effectieve medicamenteuze behandeling van reutelen bij kinderen tussen 0 en 18 jaar in de palliatieve fase?*		
2016	***National institute for health and care Excellence (NICE).***End of life care for infants, children and young people: planning and management. 2016[1]	Richtlijn kinderen

[1]Aanbevelingen uit de richtlijn over reutelen bij kinderen in de palliatieve fase worden gebruikt in de overwegingen

* Systematisch gezocht, zie: bijlage 7 zoekverantwoording – search 1

3 Evidence tabellen

Niet van toepassing.

Uit de systematische zoekstrategie resulteerden geen gerandomiseerde studies over niet-medicamenteuze en medicamenteuze behandeling van reutelen.

4 Samenvatting en gradering van bewijs

Niet van toepassing.

Uit de systematische zoekstrategie resulteerden geen gerandomiseerde studies over niet-medicamenteuze en medicamenteuze behandeling van reutelen

5 Conclusies van evidence

5.1 Niet-medicamenteuze behandeling van Reutelen

Non pharmacological treatment of death rattle		
Intervention	**Conclusions of evidence**	**Quality of evidence**
Airway suctioning ('uitzuigen')	Unknown effect	No studies

5.2 Medicamenteuze behandeling van Reutelen

Pharmacological treatment of death rattle		
Intervention	**Conclusions of evidence**	**Quality of evidence**
Glycopyrronium en (butyl) scopalamine Atropine (eyedrops)	Unknown effect	No studies

6 Aanbevelingen uit richtlijnen

6.1 Niet-medicamenteuze en medicamenteuze behandeling van Reutelen

Pharmacological treatment and non pharmacological treatment of death rattle	
National institute for health and care Excellence (NICE). End of life care for infants, children and young people: planning and management. 2016	
Recommendation	**Level of evidence**
No evidence was found after systematic search *Key conclusions: The Committee concluded that when treating respiratory distress in children and young people approaching the end of life, it is important to be aware that contributing factors and underlying causes should be assessed and considered. Treatments could include repositioning, changes to the environment, or the management of underlying medical conditions that impact on breathing. The identified underlying cause should be addressed and treated, and regular assessment should take place to review the effectiveness of the treatment.* *Non-pharmacological management should be considered as the first-line approach for the treatment of respiratory distress. The Committee made a series of recommendations with regard to the assessment and management of altered breathing*.	

If a child or young person is approaching the end of life and has respiratory distress, breathlessness or noisy breathing, think about and if possible treat the likely contributing factors or causes. If these are likely to be caused by:
• Anxiety:
  ○ discuss why they are anxious
  ○ reassure them and manage the anxiety accordingly
  ○ consider breathing techniques and guided imagery
  ○ consider anxiolytic agents
• Physical discomfort - think about what could be causing the discomfort (for example their position) and help them with it if possible
• Environmental factors - think about environmental changes such as changing the temperature
• Accumulated airway secretions- think about repositioning, airway suctioning, physiotherapy or anti-secretory drugs
• Medical disorders (for example pneumonia, heart failure, sepsis or acidosis) - use appropriate interventions such as:
  ○ bronchodilators
  ○ nebulised saline
  ○ opioids
  ○ oxygen supplementation.
	Expert opinion

For children and young people who are approaching the end of life and have respiratory distress, breathlessness or noisy breathing that needs further assessment, consider referral to an appropriate specialist (for example a respiratory or cardiac specialist).	Expert opinion
If a child or young person is approaching the end of life and has respiratory distress, breathlessness or noisy breathing: • explain to them and to their parents or carers that these symptoms are common • discuss the likely causes or contributing factors • discuss any treatments that may help.	Expert opinion

7 Overzicht conclusies van evidence en aanbevelingen uit richtlijnen

7.1 Niet-medicamenteuze behandeling van Reutelen

Non pharmacological treatments for death rattle								
Treatment	Conclusions of evidence (RCTs on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children 2013 (2)	Level of evidence[1]
Airway suctioning	Unknown effect	No studies	Think about airway suctioning, repositioning, physiotherapy in in case of accumulated airway secretions	Expert opinion (3;P)	Not applicable	-	Consider; weak recommendation	Level 4 child evidence (4);
							No recommendation	-
Repositioning	Unknown effect	No studies					No recommendation	-

References

(1) National institute for health and care Excellence (NICE).End of life care for infants, children and young people: planning and management. 2016

Legend

P: Palliative context

Not identified: No recommendations on specific pharmacological intervention were identified.

Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.

[1]Level of evidence:

Level 1: Based on a systematic review or at least two randomized controlled trials of good quality

Level 2: Based on one at randomized controlled trial or at least two comparative clinical studies

Level 3: Based on one comparative study or on non-comparative studies

Level 4: Based on expert opinion

References

2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.

3. National Institute for Health and Care Excellence. End of life care for infants, children and young people with life-limiting conditions: planning and management. [Internet]. London: NICE; 2016 [cited 2021 March 1]. Available from: www.nice.org.uk/guidance/ng61.

4. Wolfe J, Hinds P. Textbook of Interdisciplinary Pediatric Palliative Care: Saunders; 2011.

7.2 Medicamenteuze behandeling van Reutelen

Pharmacological treatments for death rattle								
Treatment	Conclusions of evidence (RCTs on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children 2013 (2)	Level of evidence[1]
Glycopyrronium and (butyl) scopalamine	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 child evidence(4); Level 3 adult evidence (5-11)[2]
Atropine (eyedrops)	Unknown effect	No studies	Not identified	-	Not identified	-	Consider; weak recommendation	Level 4 child evidence (4)

Legend
P: Palliative context
Not identified: No recommendations on specific pharmacological intervention were identified.
Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.

[1]Level of evidence:
Level 1: Based on a systematic review or at least two randomized controlled trials of good quality
Level 2: Based on one at randomized controlled trial or at least two comparative clinical studies
Level 3: Based on one comparative study or on non-comparative studies
Level 4: Based on expert opinion
[2]Adult evidence is extracted from guidelines of pallialine.nl

References

2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.
4. Wolfe J, Hinds P. Textbook of Interdisciplinary Pediatric Palliative Care: Saunders; 2011.
5. Back IN, Jenkins K, Blower A, Beckhelling J. A study comparing hyoscine hydrobromide and glycopyrrolate in the treatment of death rattle. Palliat Med. 2001;15(4):329-36.
6. Bennett M, Lucas V, Brennan M, Hughes A, O'Donnell V, Wee B. Using anti-muscarinic drugs in the management of death rattle: evidence-based guidelines for palliative care. Palliat Med. 2002;16(5):369-74.
7. Clark K, Butler M. Noisy respiratory secretions at the end of life. Current Opinion in Supportive and Palliative Care. 2009;3(2).
8. Hughes A, Wilcock A, Corcoran R, Lucas V, King A. Audit of three antimuscarinic drugs for managing retained secretions. Palliat Med. 2000;14(3):221-2.
9. Wee B, Hillier R. Interventions for noisy breathing in patients near to death. Cochrane Database Syst Rev. 2008;2008(1):Cd005177.
10. Wildiers H, Dhaenekint C, Demeulenaere P, Clement PM, Desmet M, Van Nuffelen R, et al. Atropine, hyoscine butylbromide, or scopolamine are equally effective for the treatment of death rattle in terminal care. J Pain Symptom Manage. 2009;38(1):124-33.
11. Wildiers H, Menten J. Death rattle: prevalence, prevention and treatment. J Pain Symptom Manage. 2002;23(4):310-7.

K Vermoeidheid

Inhoudsopgave

1 Uitgangsvragen

Vraag 11A: Wat is de meest geschikte diagnostische methode voor het herkennen en beoordelen van vermoeidheid bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Diagnostische methode voor het herkennen en beoordelen van vermoeidheid.
C: -
O: Reproduceerbaarheid en validiteit

Vraag 11B: Wat is de meest effectieve niet-medicamenteuze behandeling van vermoeidheid bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Niet-medicamenteuze behandeling van vermoeidheid
C: Geen behandeling/placebo
O: Effect op vermoeidheid en kwaliteit van leven

Vraag 11C: Wat is de meest effectieve medicamenteuze behandeling van vermoeidheid bij kinderen tussen 0 en 18 jaar in de palliatieve fase?

P: Kinderen tussen 0 en 18 jaar in de palliatieve fase
I: Medicamenteuze behandeling van vermoeidheid
C: Geen behandeling/placebo
O: Effect op vermoeidheid en kwaliteit van leven

2 Resultaten van het literatuuronderzoek

Jaar	Bibliografie	Studie karakteristieken
11A: Wat is de meest geschikte diagnostische methode voor het herkennen van vermoeidheid bij kinderen tussen 0 en 18 jaar in de palliatieve fase?*		
2019	***Integraal kanker instituut Nederland.*** Vermoeidheid bij kanker in de palliatieve fase.2019 [1]	Volwassen richtlijn
11B: Wat is de meest effectieve niet-medicamenteuze behandeling van vermoeidheid bij kinderen tussen 0 en 18 jaar in de palliatieve fase?*		
2019	***Integraal kanker instituut Nederland.*** Vermoeidheid bij kanker in de palliatieve fase.2019 [1]	Volwassen richtlijn
11C: Wat is de meest effectieve medicamenteuze behandeling van vermoeidheid bij kinderen tussen 0 en 18 jaar in de palliatieve fase?*		
2019	***Integraal kanker instituut Nederland.*** Vermoeidheid bij kanker in de palliatieve fase.2019 [1]	Volwassen richtlijn

[1] Aanbevelingen uit de richtlijnen over vermoeidheid bij volwassenen in de palliatieve fase worden gebruikt in de overwegingen aangezien er geen richtlijn over vermoeidheid bij kinderen in de palliatieve fase is gevonden.
* Systematisch gezocht, zie: bijlage 7 zoekverantwoording – search 1

3 Evidence tabellen

Niet van toepassing.

Uit de systematische zoekstrategie resulteerden geen studies over diagnostische methoden voor het herkennen en beoordelen van vermoeidheid en geen gerandomiseerde studies over niet-medicamenteuze en medicamenteuze behandeling van vermoeidheid.

4 Samenvatting en gradering van bewijs

Niet van toepassing.

Uit de systematische zoekstrategie resulteerden geen studies over diagnostische methoden voor het herkennen en beoordelen van vermoeidheid en geen gerandomiseerde studies over niet-medicamenteuze en medicamenteuze behandeling van vermoeidheid

5 Conclusies van evidence

5.1 Diagnostische methoden voor het herkennen en beoordelen van vermoeidheid

Non pharmacological treatment of fatigue		
Intervention	**Conclusions of evidence**	**Quality of evidence**
Numeric rating scales *Scales used for fatigue for adults in palliative care* *PedQL Multidimensional Fatigue Scale* *PPEDiatric Functional Assessment of Chronic Illness Therapy-Fatigue (Peds FACIT-F)*	Unknown effect	No studies

5.2 Niet-medicamenteuze behandeling van vermoeidheid

Non pharmacological treatment of fatigue		
Intervention	**Conclusions of evidence**	**Quality of evidence**
Psychoeducation *Sleep hygiene* *Exercise* *Psychotherapy* *Alternative therapies* *Day programme, rhythm, regularity and rituals*	Unknown effect	No studies

5.3 Medicamenteuze behandeling van vermoeidheid

Pharmacological treatment of fatigue		
Intervention	**Conclusions of evidence**	**Quality of evidence**
Bloodtransfusion *psychostimulantia'/methylphenidate*	Unknown effect	No studies

6 Aanbevelingen uit richtlijnen

6.1 Diagnostische methoden voor het herkennen en beoordelen van vermoeidheid

Diagnostic methods for recognizing fatigue– Adult guideline	
Integraal kanker instituut Nederland. Vermoeidheid bij kanker in de palliatieve fase.2019	
Recommendation	**Level of evidence**

Bij patiënten met (vermoeidheid bij) kanker in de palliatieve fase:
• Signaleer de aanwezigheid van vermoeidheid; overweeg hiervoor de Lastmeter als signaleringsinstrument te gebruiken of maak gebruik van het Utrecht Symptoom Dagboek.
• Signaleer vermoeidheid en bespreek de gemeten vermoeidheid met de patiënt:
  o gedurende en na afloop van anti-tumor therapie;
  o op momenten dat progressie van de kanker wordt aangetoond;
  o rond de overdracht van een patiënt naar een andere setting.
• Gedurende de perioden dat de ziekte stabiel is zonder therapie, kan doorgaans volstaan worden met laagfrequente controles.
• Overweeg het gebruik van een vragenlijst voor de beoordeling van de dimensies en de mate van vermoeidheid, zoals de Multidimensionele Vermoeidheidsindex (MVI) of de Checklist Individuele Spankracht (CIS). Een score ≥35 op de subschaal ernst van vermoeidheid van de CIS wordt gehanteerd als cut-off voor ernstige vermoeidheid.
	Consensus-based, expert opinion

Bij patiënten met vermoeidheid bij kanker in de palliatieve fase: • Exploreer de vermoeidheid en de mogelijke onderliggende oorzaken bij een score voor vermoeidheid ≥4 in het Utrecht Symptoom Dagboek. • Doe altijd een volledige anamnese, inclusief heteroanamnese, gericht op de lichamelijke, cognitieve en emotionele dimensies en presentatie van vermoeidheid, de begeleidende symptomen, de mogelijke oorza(a)k(en) en de impact voor het dagelijks functioneren en de sociale interacties met naasten. • Betrek de resultaten van het signalerend onderzoek met de Lastmeter of het Utrecht Symptoom Dagboek bij de beoordeling van bijdragende lichamelijke en psychosociale oorzaken. • Beoordeel eventuele existentiële problematiek. • Overweeg het gebruik van de Hospital Anxiety and Depression Scale (HADS) of screeningslijst Vier Dimensionale Klachten Lijst (4DKL) als instrument voor de screening op angst en depressie (zie richtlijnen Angst en Depressie). • Doe altijd een lichamelijk onderzoek. • Doe op indicatie aanvullend laboratoriumonderzoek, beeldvormend onderzoek of functieonderzoek ter verdere beoordeling van een behandelbare oorzaak van vermoeidheid. • Zet alleen aanvullende diagnostiek in wanneer die haalbaar is en therapeutische consequenties heeft, in het licht van de levensverwachting, de belastbaarheid van de patiënt en zijn wensen met betrekking tot een eventuele behandeling van een onderliggende oorzaak van de vermoeidheid.	Consensus-based, expert opinion

6.2 Niet-medicamenteuze behandeling van vermoeidheid

Non pharmacological treatment of fatigue – Adult guideline	
Integraal kanker instituut Nederland. Vermoeidheid bij kanker in de palliatieve fase.2019	
Recommendation	**Level of evidence**
Voorlichting en psycho-educatie: Bij patiënten met vermoeidheid bij kanker in de palliatieve fase: • Besteed aandacht, toon begrip en erken de ervaren last van vermoeidheid bij patiënten met kanker in de palliatieve fase. • Maak vermoeidheid bespreekbaar. • Geef voorlichting over het symptoom vermoeidheid in de palliatieve fase van kanker en stem de voorlichting af op de wensen en behoeften van de patiënt en diens naasten. • Ondersteun bij de ontwikkeling van zelfinzicht van patiënten voor wat betreft de relatie tussen vermoeidheid en activiteiten(verdeling), het slaap-waak ritme, emoties en opvattingen over vermoeidheid • Stem de voorlichting af op de mate van vermoeidheid, zie paragraaf 2.1 Screening en meetinstrumenten. • Ondersteun de voorlichting met schriftelijk informatiemateriaal en attendeer de patiënt en diens naasten op relevante informatie op websites zoals: Kanker.nl en Thuisarts.nl. • De centrale zorgverlener en hoofdbehandelaar zijn ervoor verantwoordelijk dat voorlichting wordt gegeven, maar dit kan wel door een andere zorgverlener, bijvoorbeeld verpleegkundige, worden besproken. • Geef voorlichting hoe om te gaan met vermoeidheid. Bespreek met de patiënt waar hij behoefte aan heeft en geef aan wat kan helpen, zoals: o het voldoende lichamelijk actief blijven of de lichamelijke activiteiten zelfs geleidelijk uit te bouwen rekening houdend met lichamelijke beperkingen; o het hanteren van een regelmatig slaap-waak patroon; o het hanteren van een goede slaaphygiëne; o het prioriteren van activiteiten die belangrijk zijn voor de patiënt en zijn omgeving; o het aanpassen van bezigheden/activiteiten voor wat betreft de intensiteit waarmee die worden uitgevoerd; o het gelijkmatiger verdelen van activiteiten over de dag en de week zodat de patiënt het meeste profijt van zijn energie kan hebben; o het zoeken van afleiding bij ernstige vermoeidheid. • Betrek de naasten van de patiënt bij de voorlichting over en het omgaan met de vermoeidheid.	Zeer laag
Ondersteunende zorg: Bij patiënten met vermoeidheid bij kanker in de palliatieve fase: • Bepaal welke problemen gerelateerd zijn aan de vermoeidheid, de complexiteit van deze problemen en hun onderlinge samenhang (zie hoofdstuk 2. Diagnostiek). • Bespreek deze problemen met de patiënt en besluit gezamenlijk op geleide van deze onderliggende problematiek en wensen en behoeften van de patiënt naar welke zorgverleners met specifieke kennis, ervaring en vaardigheden op het gebied van vermoeidheid verwezen kan worden. De Verwijsgids Kanker kan gebruikt worden bij het vinden van aanvullende behandelings- en begeleidingsmogelijkheden. Hierbij wordt geadviseerd de zoekterm ‘vermoeidheid’ te gebruiken: o adviseer contact met lotgenoten (vaak ondersteunend door de herkenning en de erkenning van gevoelens en ervaringen), bijvoorbeeld via patiëntenverenigingen zoals Nederlandse Federatie Kankerpatiënten (NFK) of via inloophuizen. o bespreek bij vragen over activiteitenverdeling, aanpassingen in huis of het gebruik van hulpmiddelen een consult van de ergotherapeut. o bespreek bij vragen over bewegen en conditieverlies een consult van de fysiotherapeut met specifieke kennis, ervaring en vaardigheden. o bespreek bij vragen over (aanpassing van de) voeding of gewichtsverlies een consult van de diëtist. o bespreek een verwijzing voor cognitieve gedragstherapie voor vermoeidheid bij een daarin getrainde psycholoog. In de Verwijsgids Kanker wordt dit niet vermeldt, geadviseerd wordt bij de psycholoog vooraf na te gaan of deze ervaring heeft met behandeling van vermoeidheid. o bespreek een consult bij een psycholoog bij intra-psychische problematiek zoals angst, depressieve gevoelens en vragen over existentiële en levenseindevragen. o bespreek bij psychosociale, relationele, materiële en zingevingsvragen een consult bij een gezondheidszorg maatschappelijk werker. o bespreek dat bij psychosociale problematiek een consult bij een vaktherapeut overwogen kan worden wanneer de patiënt emoties hanteerbaar wil maken door ‘het doen’.	Geen literatuur

○ bespreek bij zingevings- en levenseindevragen een consult bij een geestelijk verzorger of religieus voorganger (zie de richtlijn Zingeving en spiritualiteit in de palliatieve fase). ○ bespreek bij samenhangende en/of complexe functioneringsproblemen ten gevolge van (de behandeling van) kanker een consult bij de revalidatiearts of specialist ouderengeneeskunde. ○ adviseer ondersteuning van de mantelzorg, zie: ▪ www.agora.nl ('zorg kiezen': vrijwilligers per provincie, adressen van hospices) ▪ www.vptz.nl (landelijk overzicht + contactpersonen van vrijwilligers palliatieve zorg) ▪ www.stichtingfibula.nl ▪ www.mantelzorg.nl • Vraag zo nodig advies aan een consultatieteam palliatieve zorg (IKNL of ziekenhuis) of bespreek de patiënt in een multidisciplinair team (palliatieve zorg) of een PaTz-groep (Palliatieve Thuiszorg).	
Psychosociale interventies Bij patiënten met vermoeidheid bij kanker in de palliatieve fase: • Overweeg de inzet van cognitieve gedragstherapie of mind-body interventies (bijvoorbeeld mindfulness of yoga) bij patiënten die een actieve, levensverlengende behandeling krijgen en/of in een relatief stabiele toestand zijn als psycho-educatie onvoldoende effectief is. • Verwijs naar professionals die ervaring hebben binnen de oncologie en die voorgenoemde psychosociale behandelingen voor vermoeidheid bij kanker aanbieden. Hierbij kan onder meer gebruik gemaakt worden van de digitale Verwijsgids Kanker. Hierbij wordt geadviseerd de zoekterm 'vermoeidheid' te gebruiken. Bij een verwijzing voor cognitieve gedragstherapie wordt geadviseerd vooraf na te gaan of de professional hiermee ervaring heeft, omdat dat niet specifiek wordt genoemd in de Verwijsgids	Zeer laag
Beweging/lichamelijke activiteit: Bij patiënten met vermoeidheid bij kanker in de palliatieve fase: • Adviseer patiënten dagelijks te bewegen op geleide van de individuele fysieke mogelijkheden en de adviezen in de Nederlandse Norm Gezond Bewegen. • Overweeg een verwijzing naar een fysiotherapeut voor een aerobe bewegingsinterventie in geval van vermoeidheid en functionele beperking bij inspanning in de vroege periode van ziektegerichte palliatie. • Verwijs bij voorkeur naar een fysiotherapeut met specifieke kennis, ervaring en vaardigheden die is opgenomen in de Verwijsgids Kanker. • Adviseer voeding met voldoende calorieën, eiwit en overige voedingsstoffen ter ondersteuning van de bewegingsinterventie. Specifieke voedingsadviezen zijn terug te vinden in de richtlijn Algemene Voedings- en Dieetbehandeling. Overweeg een verwijzing naar een diëtist, opgenomen in de Verwijsgids Kanker, voor ondersteuning van de beweeginterventie met gezonde en eiwitrijke voeding. • Overweeg een verwijzing naar een revalidatiearts in geval van vermoeidheid en complexe functionele beperking (meervoudige problematiek) in de vroege periode van ziektegerichte palliatie.	Zeer Laag

6.3 Medicamenteuze behandeling van vermoeidheid

Pharmacological treatment of fatigue – Adult guideline	
Integraal kanker instituut Nederland. Vermoeidheid bij kanker in de palliatieve fase.2019	
Recommendation	**Level of evidence**
Patiënten met gevorderde kanker in de palliatieve fase met matige of ernstige vermoeidheid hebben mogelijk baat bij een medicamenteuze behandeling om de klachten van vermoeidheid te verminderen en de kwaliteit van leven of het fysiek functioneren te verbeteren. Voor corticosteroïden (dexamethason, predniso(lo)n, methylprednisolon), psychostimulantia (methylfenidaat, dexamfetamine, modafinil) en antidepressiva (paroxetine, sertraline) zijn de werkzaamheid en veiligheid bij de behandeling van kanker-gerelateerde vermoeidheid in de palliatieve fase in diverse klinische studies onderzocht. Ook werd onderzocht wat het effect van deze geneesmiddelen is op de kwaliteit van leven en het functioneren in deze patiëntengroep. In de onderstaande beschrijving van studies zal indien mogelijk een onderscheid worden gemaakt in de verschillende palliatieve zorg fasen (periode van ziektegerichte-, symptoomgerichte-, en terminale palliatie).	
Corticosteroïden: Bij patiënten met vermoeidheid bij kanker in de palliatieve fase: • Overweeg behandeling met 8 mg dexamethason bij ernstige vermoeidheidsklachten in de terminale fase voor wie andere, op de oorzaak gerichte, interventies niet (meer) voorhanden zijn. • Stop de behandeling met corticosteroïden na een week indien er geen effect is opgetreden. • Weeg zorgvuldig het beoogde effect op vermoeidheid en kwaliteit van leven en mogelijke bijwerkingen af.	Zeer laag

Psychostimulantia: Bij patiënten met vermoeidheid bij kanker in de palliatieve fase: • Overweeg behandeling met methylfenidaat bij tevens aanwezige depressie en korte levensverwachting waarvoor inzet van reguliere antidepressiva niet zinvol wordt geacht. • Gebruik daarbij een startdosering van 2 dd 5 mg. Pas de dosering aan op geleide van de klachten van vermoeidheid met 10 mg/dag per 3 dagen tot een maximale dosis van 40 mg/dag. • Weeg daarbij zorgvuldig de kans op bijwerkingen af, zoals hypertensie, tachycardie en onrust. • Schrijf geen psychostimulantia voor ter vermindering van vermoeidheid bij patiënten zonder bijkomende depressieve klachten	Laag
Antidepressiva: Schrijf geen antidepressiva voor ter vermindering van vermoeidheid bij patiënten met kanker in de palliatieve fase zonder dat er sprake is van een bijkomende depressie	Zeer laag

7 Overzicht conclusies van evidence en aanbevelingen uit richtlijnen

7.1 Diagnostische methoden voor het herkennen en beoordelen van vermoeidheid

Diagnostic methods for recognizing fatigue								
Treatment	Conclusions of evidence (RCTs on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children (2013);	Level of evidence[1]
Numeric rating scales	Unknown effect	No studies	Not identified	-	Not identified	-	No recommendation	-
PedQL Multidimensial Fatigue Scale	Unknown effect	No studies	Not identified	-	Not identified	-	No recommendation	-
PPEDiatric Functional Assessment of Chronic Illness Therapy-Fatigue (Peds FACIT-F)	Unknown effect	No studies	Not identified	-	Not identified	-	No recommendation	-
Scales used for fatigue for adults in palliative care								
Lastmeter Utrecht Symptoom Dagboek	Unknown effect	No studies	Not identified	-	Use for identifying presence of fatigue	Expert opinion (2;P)	No recommendation	-
Questionnaires for assessing degree and dimensions of fatigue • Multidimensionele vermoeidheidsindex • Checklist individuele spankracht	Unknown effect	No studies	Not identified	-	Consider	Expert opinion (2;P)	No recommendation	-
HADS, Vier dimensionale klachten Lijst	Unknown effect	No studies	Not identified	-	Consider for assessing anxiety and depression	Expert opinion (2;P)	No recommendation	-

Legend
P: Palliative context
NP: Non-palliative context
P/NP: Both palliative and non-palliative conditions
Not identified: No recommendations on specific pharmacological treatment were identified.
Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.

[1]Level of evidence:
Level 1: Based on a systematic review or at least two randomized controlled trials of good quality
Level 2: Based on one at randomized controlled trial or at least two comparative clinical studies
Level 3: Based on one comparative study or on non-comparative studies
Level 4: Based on expert opinion

References

2. Integraal Kankercentrum Nederland. Vermoeidheid bij kanker in de palliatieve fase (3.0). 2019. Available from: www.pallialine.nl/vermoeidheid.

7.2 Niet-medicamenteuze behandeling van vermoeidheid

Non pharmacological treatment of fatigue								
Treatment	Conclusions of evidence	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children (2013);	Level of evidence[1]
Psycho education + information	Unknown effect	No studies	Not identified	-	Provide information on how to deal with fatigue such as, remaining sufficiently physically active; maintaining a regular sleep-wake pattern; maintaining good sleep hygiene; prioritizing activities that are important to the patients; adapting activities; spreading activities over the day; seeking distraction	Very low (2;P)	Do	Level 2 child evidence (3, 4)
Sleep hygiene							Consider	Level 4 child evidence (5); Unknown level adult evidence (5, 6)[2]
Day programme, rhythm, regularity and rituals							No recommendation	-
Exercise	Unknown effect	No studies	Not identified	-	Advise patients be physically active daily Consider referral to a physical therapist	Very low (2;P)	Consider	Level 4 child evidence (7); Level 3 adult evidence (6, 8-14)[2]
Nutrition	Unknown effect	No studies	Not identified	-	Advise nutrition with sufficient amount of calories, protein and other nutritional elements	Very low (2;P)	Consider	Level 4 child evidence (5); Level 4 adult evidence (5, 6)[2]
Psychotherapy, psychosocial interventions	Unknown effect	No studies	Not identified	-	Consider cognitive behavioural therapy if psycho-education is insufficient	Very low (2;P)	Consider	Level 4 child evidence; level 1 adult evidence (15-18)[2]
Alternative therapies	Unknown effect	No studies	Not identified	-	Not identified	-	Consider	Level 4 child evidence; Level 3 adult evidence

Legend
P: Palliative context
NP: Non-palliative context
P/NP: Both palliative and non-palliative conditions
Not identified: No recommendations on specific pharmacological treatment were identified.

Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.
[1]Level of evidence: Level 1: Based on a systematic review or at least two randomized controlled trials of good quality Level 2: Based on one at randomized controlled trial or at least two comparative clinical studies Level 3: Based on one comparative study or on non-comparative studies Level 4: Based on expert opinion [2]Adult evidence is extracted from guidelines of pallialine.nl

References

2. Integraal Kankercentrum Nederland. Vermoeidheid bij kanker in de palliatieve fase (3.0). 2019. Available from: www.pallialine.nl/vermoeidheid.
3. Davies B, Whitsett SF, Bruce A, McCarthy P. A typology of fatigue in children with cancer. Journal of Pediatric Oncology Nursing. 2002;19(1):12-21.
4. Radbruch L, Strasser F, Elsner F, Goncalves JF, Loge J, Kaasa S, et al. Fatigue in palliative care patients -- an EAPC approach. Palliat Med. 2008;22(1):13-32.
5. National Compreshensive Cancer Network. Clinical Practice Guidelines in Oncology. Cancer-related Fatigue 2009.
6. van der Mei SF. Richtlijn Vermoeidheid. 2000. In: Landelijk Oncologische Verpleegkundige Richtlijnen [Internet]. VIKC.
7. Mock V, Atkinson A, Barsevick AM, Berger AM, Cimprich B, Eisenberger MA, et al. Cancer-related fatigue. Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2007;5(10):1054-78.
8. Cramp F, Daniel J. Exercise for the management of cancer-related fatigue in adults. Cochrane Database Syst Rev. 2008(2):CD006145.
9. Headley JA, Ownby KK, John LD. The effect of seated exercise on fatigue and quality of life in women with advanced breast cancer. Oncol Nurs Forum. 2004;31(5):977-83.
10. Kangas M, Bovbjerg DH, Montgomery GH. Cancer-related fatigue: a systematic and meta-analytic review of non-pharmacological therapies for cancer patients. Psychol Bull. 2008;134(5):700-41.
11. Oldervoll LM, Loge JH, Paltiel H, Asp MB, Vidvei U, Wiken AN, et al. The effect of a physical exercise program in palliative care: A phase II study. J Pain Symptom Manage. 2006;31(5):421-30.
12. Porock D, Kristjanson LJ, Tinnelly K, Duke T, Blight J. An exercise intervention for advanced cancer patients experiencing fatigue: a pilot study. J Palliat Care. 2000;16(3):30-6.
13. Stricker CT, Drake D, Hoyer KA, Mock V. Evidence-based practice for fatigue management in adults with cancer: exercise as an intervention. Oncol Nurs Forum. 2004;31(5):963-76.
14. Temel JS, Greer JA, Goldberg S, Vogel PD, Sullivan M, Pirl WF, et al. A Structured Exercise Program for Patients with Advanced Non-small Cell Lung Cancer. Journal of Thoracic Oncology. 2009;4(5):595-601.
15. Armes J, Chalder T, Addington-Hall J, Richardson A, Hotopf M. A randomized controlled trial to evaluate the effectiveness of a brief, behaviorally oriented intervention for cancer-related fatigue. Cancer. 2007;110(6):1385-95.
16. Barsevick AM, Dudley W, Beck S, Sweeney C, Whitmer K, Nail L. A randomized clinical trial of energy conservation for patients with cancer-related fatigue. Cancer. 2004;100(6):1302-10.
17. Brunnuber K, Nash S, D Meier E, D Weissman E, Woodcock J. Putting evidence into practice: Palliative care. 2008.
18. Ream E, Richardson A, Alexander-Dann C. Supportive intervention for fatigue in patients undergoing chemotherapy: a randomized controlled trial. J Pain Symptom Manage. 2006;31(2):148-61.

7.3 Medicamenteuze behandeling van vermoeidheid

Pharmacological treatment of fatigue								
Treatment	Conclusions of evidence (RCTs on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children (2013);	Level of evidence[1,]
Bloodtransfusion	Unknown effect	No studies	Not identified	-	Not identified	-	Consider	Level 4 child evidence (19); Level 3 adult evidence (20)[2]
Psychostimulantia'/methylphenidate	Unknown effect	No studies	Not identified	-	Consider methylphenidate in case of depression and short life expectancy	Low(2;P)	Consider	Controversy in child evidence Controversy in adult evidence (21-24)[2]
					Do not use for reducing fatigue in patients without depressive complaints	Low(2;P)		
Corticosteroids	Unknown effect	No studies	Not identified	-	Consider use of dexamethasone for serious complaints of fatigue.	Very low (2;P)	No recommendation	-
Antidepressants	Unknown effect	No studies	Not identified	-	Do not give antidepressants for reducing fatigue without any additional depression	Very low (2;P)	No recommendation	-

Legend
P: Palliative context
NP: Non-palliative context
P/NP: Both palliative and non-palliative conditions
Not identified: No recommendations on specific pharmacological treatment were identified.
Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.

[1]Level of evidence:
Level 1: Based on a systematic review or at least two randomized controlled trials of good quality
Level 2: Based on one at randomized controlled trial or at least two comparative clinical studies
Level 3: Based on one comparative study or on non-comparative studies
Level 4: Based on expert opinion
[2]Adult evidence is extracted from guidelines of pallialine.nl

References

2. Integraal Kankercentrum Nederland. Vermoeidheid bij kanker in de palliatieve fase (3.0). 2019. Available from: www.pallialine.nl/vermoeidheid.
19. Wolfe J, Hinds P. Textbook of Interdisciplinary Pediatric Palliative Care: Saunders; 2011.
20. Mercadante S, Ferrera P, Villari P, David F, Giarratano A, Riina S. Effects of red blood cell transfusion on anemia-related symptoms in patients with cancer. J Palliat Med. 2009;12(1):60-3.

21. Auret KA, Schug SA, Bremner AP, Bulsara M. A randomized, double-blind, placebo-controlled trial assessing the impact of dexamphetamine on fatigue in patients with advanced cancer. J Pain Symptom Manage. 2009;37(4):613-21.
22. Breitbart W, Rosenfeld B, Kaim M, Funesti-Esch J. A randomized, double-blind, placebo-controlled trial of psychostimulants for the treatment of fatigue in ambulatory patients with human immunodeficiency virus disease. Arch Intern Med. 2001;161(3):411-20.
23. Bruera E, Valero V, Driver L, Shen L, Willey J, Zhang T, et al. Patient-controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. J Clin Oncol. 2006;24(13):2073-8.
24. Minton O, Richardson A, Sharpe M, Hotopf M, Stone P. A systematic review and meta-analysis of the pharmacological treatment of cancer-related fatigue. J Natl Cancer Inst. 2008;100(16):1155-66.

6 REFRACTAIRE SYMPTOMEN

Inhoudsopgave

1 Uitgangsvragen

1.1 Effect van palliatieve sedatie

Vraag 1A: Wat is het effect van palliatieve sedatie met andere medicatie dan midazolam (evt. in combinatie met morfine) bij kinderen tussen 0 en 18 jaar in de terminale fase op kwaliteit van leven en levensduur?

P: Kinderen tussen 0 en 18 jaar in de terminale fase
I: Palliatieve sedatie met andere medicatie dan midazolam (evt. in combinatie met morfine)
C: Palliatieve sedatie met midazolam (evt. in combinatie met morfine)
O: Mate van sedatie, kwaliteit van leven en levensduur

Vraag 1B: Wat is het effect van palliatieve sedatie met andere medicatie dan midazolam (evt. in combinatie met morfine) bij kinderen met een ernstige meervoudige beperking (EMB) tussen 0 en 18 jaar in de terminale fase op kwaliteit van leven en levensduur?

P: Kinderen met EMB tussen 0 en 18 jaar in de terminale fase
I: Palliatieve sedatie met andere medicatie dan midazolam (evt. in combinatie met morfine)
C: Palliatieve sedatie met midazolam (evt. in combinatie met morfine)
O: Mate van sedatie, kwaliteit van leven, levensduur

1.2 Effect van vocht en/of voeding onthouding

Vraag 2: Wat is het effect van vocht en/of voeding onthouding bij kinderen in de terminale fase tussen 0-18 jaar op kwaliteit van leven, levensduur en kwaliteit van leven ouders.

P: Kinderen tussen 0 en 18 jaar in de terminale fase
I: Onthouding van vocht en/of voeding
C: Geen onthouding van vocht en/of voeding.
O: Kwaliteit van leven, levensduur en kwaliteit van leven ouders

2 Resultaten van het literatuuronderzoek

Jaar	Bibliografie	Studie karakteristieken
1A: Wat is het effect van palliatieve sedatie met andere medicatie dan midazolam (evt. in combinatie met morfine) bij kinderen tussen 0 en 18 jaar in de terminale fase op kwaliteit van leven en levensduur?* **1B:** Wat is het effect van palliatieve sedatie met andere medicatie dan midazolam (evt. in combinatie met morfine) bij kinderen met een ernstige meervoudige beperking (EMB) tussen 0 en 18 jaar in de terminale fase op kwaliteit van leven en levensduur?*		
Geen literatuur gevonden		
2: Wat is het effect van vocht/voeding onthouding bij kinderen in de terminale fase tussen 0-18 jaar op kwaliteit van leven, levensduur en kwaliteit van leven ouders.*		
2016	***National institute for health and care Excellence (NICE).*** End of life care for infants, children and young people: planning and management. 2016. [1]	Richtlijn kinderen
2019	***Anderson A et al.*** Artificial nutrition and hydration for children and young people towards end of life: consensus guidelines across four specialist paediatric palliative care centres. BMJ Support Palliat Care 2019[1]	Richtlijn kinderen

[1] Aanbevelingen uit de richtlijnen over refractaire symptomen bij kinderen in de palliatieve fase worden gebruikt in de overwegingen

*Voor systematische search, zie: bijlage 7 zoekverantwoording – search 1

3 Evidence tabellen

Niet van toepassing.

Uit de systematische zoekstrategie resulteerden geen studies over het effect van vocht- en voeding onthouding en het effect van palliatieve sedatie.

4 Samenvatting en gradering van bewijs

Niet van toepassing.

Uit de systematische zoekstrategie resulteerden geen studies over het effect van vocht- en voeding onthouding en het effect van palliatieve sedatie.

5 Conclusies van evidence

5.1 Effect van palliatieve sedatie

Effect of palliative sedation		
Intervention	**Conclusions of evidence**	**Quality of evidence**
Propofol *Midazolam* *Levomepromazine*	Unknown effect	No studies

5.2 Effect van vocht en/of voeding onthouding

Effect of nutrition and hydration deprivation		
Intervention	**Conclusions of evidence**	**Quality of evidence**
(Medically assisted) nutrition *(Medically assisted) hydration* *Nutrition deprivation* *Hydration deprivation*	Unknown effect	No studies

6 Aanbevelingen uit richtlijnen

6.1 Effect van vocht en/of voeding onthouding

Effect of nutrition and hydration – child guideline	
National institute for health and care Excellence (NICE). End of life care for infants, children and young people: planning and management. 2016.	
Recommendation	**Level of evidence**
Medically-assisted hydration in infants, children and young people during end-of-life care	
No evidence found after systematic search *Key conclusions: The Committee concluded that during end of life care for infants, children or young people, while clinically assisted hydration may not be necessarily in the best interests of the child, hydration for comfort should be provided. As long as it remained in the child's best interests, fluid intake by other usual routes of administration, such as oral, tube feeding or intravenous, should be continued, with special attention given to the latter two due to the extra burden it could cause to the child or young person.*	
If a child or young person with a life-limiting condition is approaching the end of life or is dying, discuss how to manage their fluid needs with them and their parents or carers.	Expert opinion
If a child or young person is dying, encourage and support them to drink if they want to and are able.	Expert opinion
Reassess the patient's clinical condition and check their platelet count after each platelet transfusion, and give further doses if needed	Expert opinion
If a child or young person is dying, continue to provide them with lip and mouth care.	Expert opinion
If a child or young person is dying and cannot drink, discuss with them (as appropriate) and their parents or carers whether starting or continuing enteral tube or intravenous fluids is in their best interests.	Expert opinion
Be aware that enteral tube and intravenous fluids may have a significant effect on care, may be a burden for children and young people, and may mean the place of care and place of death need to be changed.	Expert opinion
If a child or young person is given enteral or intravenous fluids, review this decision regularly to make sure it continues to be in their best interests.	Expert opinion
Medically-assisted nutrition in infants, children and young people end-of-life care	
No evidence found after systematic search *Key conclusions:* The Committee concluded that during the end of life care for children or young people, while medically-assisted nutrition may not be necessarily in the best interest of the child, it was important not to withhold oral nutrition if the child is able and wishes to eat. As long as it remained in the child's best interest, intake by their other usual routes of administration, such as oral, tube feeding or intravenous, should be continued, always taking into account the benefits and possible burdens for them.	
If a child or young person is approaching the end of life or is dying, discuss how to manage their nutritional needs with them and their parents or carers.	Expert opinion
If a child or young person with a life-limiting condition is dying, encourage and support them to eat if they want to and are able.	Expert opinion
If a child or young person is dying and they are receiving enteral tube feeding or intravenous nutrition: • discuss with them (as appropriate) and their parents or carers whether continuing this is in their best interest and • review this decision regularly.	Expert opinion

Effect of nutrition and hydration– Child guideline	
Anderson A et al. Artificial nutrition and hydration for children and young people towards end of life: consensus guidelines across four specialist paediatric palliative care centres. BMJ Support Palliat Care 2019	
Recommendation	**Level of evidence[1]**
Recommendations for practice	
Recommendations are based on published guidance (2 qualitative studies and 2 systematic reviews on nutrition/hydration in adult palliative care patients) and expert opinion	
If ANH (artificial nutrition and hydration) is being considered, a trial (with a timeframe) should be discussed between members of the MDT, the child (as able) and their parents. Refer to the dietitian for feeding plan to maintain basic metabolic well-being and/or 'comfort feeds'.	C: very low
The benefit versus the risk of oral 'comfort feeds', for example, risk of choking versus ANH, should be explained to parents. Comfort feeding with very small amounts of taster food may be one approach taken by parents and professionals alike. Open and transparent discussion should be an ongoing adaptive process.	C: low
The MDT should demonstrate a 'unified' team to the parents in offering support and reassurance in decision- making. Preparation and effective communication by the MDT and between team members and parents are essential. Documentation of discussions between at least two professionals and those with parental responsibility is vital	C: low

Specialist services and professional organizations should consider running and evaluating programmes of education, training, guidance and audit about how to discuss and decide with patients and families how to manage hydration towards the end of life'.	C: very low
Parental concern about perceived discomfort or distress in their child should be addressed as part of the end-of life care symptom management plan. *Pain rating tools, for example, the revised Face, Legs, Activity, Cry, Consolability (FLACC) observational pain tool, Faces pain scale, and Numerical Rating scale, are validated to assess acute pain; however, they are not validated as a discomfort scale for ANH.*	C: low
There should be close monitoring and regular review of decision-making for initiating or withholding ANH since for some children with uncertain disease trajectories there may be several potential end-of-life episodes from which they recover.	C: very low
Additional considerations	
Indications for initiating ANH towards end of life: • Neurological impairment leading to inability to feed orally and/or risk of aspiration. • Malabsorption due to intestinal disease, gastrointestinal failure or short gut syndrome. • To relieve symptoms of hunger or thirst in children unable to maintain sufficient intake due to a progressive, life-limiting condition in the final stages of illness. For additional information, see full text	Expert opinion (including specialist dietitians)
Medically-assisted nutrition	
The role of the enteral feeding regimen is usually to attempt to alleviate symptoms of hunger and dehydration, particularly in those children who are unable to take adequate quantities of food or fluid orally. The aim of such feeding regimens is not to meet the child's full nutritional requirements and not to prevent deterioration in nutritional status at this stage of illness.	Expert opinion
Several considerations should be made when determining an optimal feeding regimen: • The route of access. • Consider NGT placement as this can be placed most easily in the home or hospice setting. However, placement of the NGT can be distressing and uncomfortable initially and can also mask the child's face. Education around its use is needed, and checking the position using an X-ray, requiring hospital review, may be needed if the appropriate pH is not obtained on the aspirate. • NJT will generally need endoscopic placement or radiological confirmation to guarantee correct positioning. In most cases an enteral feeding pump is the best option for both continuous and bolus feeding as it is easier to control the rate. However, when a feeding pump is not available, the gravity drip feed can be used as an alternative.	Expert opinion (including specialist dietitians)
If after a comprehensive MDT discussion it is agreed that enteral feeds should be started for an individual patient, we recommend the following approach: For anew patient starting feed (over the age of 1 year), it is recommended that a 1 kcal/mL feed is used**.**	Expert opinion (including specialist dietitians
If the child stabilizes or improves clinically and is considered not in the end-of-life phase, then an individualized Feeding plan should be sought from local or specialist dietetic services. The ideal feeding regimen for the patient will be determined partly by gastric function.	Expert opinion
Medically-assisted nutrition	
Before subcutaneous fluids are considered, the goals of the treatment must be addressed by the healthcare team and the parents/carers and discussed with the child (as able) with regular review. Artificial hydration may occasionally be indicated towards the end of life to satisfy thirst or alleviate symptoms of dehydration when prognosis is more than 24 hours. • The main indication for use would be to maintain hydration and to reduce sensation of thirst in those patients who are unable to sustain adequate oral or enteral fluids. Subcutaneous fluids would be contraindicated in those children who are imminently dying and for whom hydration will not improve symptom relief	Published guidance (1 guideline on artificial nutrition and hydration for adults) and expert opinion
Overnight subcutaneous infusion may meet baseline fluid requirements and relieve the burden of restricting movement during daytime. A suitable site with plentiful subcutaneous tissue (e.g., abdominal wall, upper thigh) if available is preferred, avoiding areas with skin damage, for example, oedema, lymphoedema or radiotherapy sites.	Published guidance (1 guideline on artificial nutrition and hydration for adults and 1 book on clinical nursing procedures)) and expert opinion
The formulation for subcutaneous pump volumes and flow rates is derived from adult guidelines and adapted for children by the specialist guideline group. The child's weight guides the volume of fluid deliverable over a 24-hour period. The total volume of fluid determined may be initially based on a percentage (e.g., 10%–30%) of standard intravenous fluid maintenance guidance. It is likely that significantly lower volumes are initially used and increased if tolerated.	Published guidance (1 guideline on artificial nutrition and hydration for adults and 1 book on clinical nursing

	procedures)) and expert opinion
[1] **Level of evidence adapted from GRADE** **A:** High; further research is very unlikely to change confidence in the estimate of the clinical effect. **B:** Moderate; Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **C:** Low or very low; further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain.	

7 Overzicht conclusies van evidence en aanbevelingen uit richtlijnen

7.1 Effect van palliatieve sedatie

Effect of palliative sedation								
Treatment	Conclusions of evidence (Studies on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children 2013 (2)	Level of evidence
Propofol	Unknown effect	No studies	Not identified	-	Not applicable	-	No recommendation	-
Midazolam	Unknown effect	No studies	Not identified	-	Not applicable	-	No recommendation	-
Levomepromazine	Unknown effect	No studies	Not identified	-	Not applicable	-	No recommendation	-
Legend P: Palliative context Not identified: No recommendations on specific intervention were identified. Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.								

References

2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.

7.2 Effect van vocht en voeding onthouding

Effect of nutrition and hydration								
Treatment	Conclusions of evidence (Studies on children published from 1970 to 2020)	Level of evidence	Recommendation from guidelines on children	Level of evidence	Recommendation from guidelines on adults	Level of evidence	Recommendation for children 2013 (2)	Level of evidence
Indications for artificial hydration and nutrition	Unknown effect	No studies	Neurological impairment leading to inability to feed orally and/or risk of aspiration. Malabsorption due to intestinal disease, gastrointestinal failure or short gut syndrome. To relieve symptoms of hunger or thirst in children unable to maintain sufficient intake due to a progressive, life-limiting condition in the final stages of illness.	Expert opinion (3;P)	Not applicable	-	No recommendation	-
Hydration								
Hydration			Discuss management of fluid needs with the child or young person at the end of life and their parents or carers.	Expert opinion (4;P)	Not applicable	-	No recommendation	-
			If a child or young person is dying, encourage and support them to drink if they want to and are able.	Expert opinion (4;P)				
			If a child or young person is dying, continue to provide them with lip and mouth care.	Expert opinion (4;P)				
Medically-assisted hydration	Unknown effect	No studies	indicated towards the end of life to satisfy thirst or alleviate symptoms of dehydration when prognosis is more than 24 hours. The main indication for use would be to maintain hydration and to reduce	Published guidance (2;P)	Not applicable	-	No recommendation	-

			sensation of thirst in those patients who are unable to sustain adequate oral or enteral fluids. Subcutaneous fluids would be contraindicated in those children who are imminently dying and for whom hydration will not improve symptom relief					
			Overnight subcutaneous infusion may meet baseline fluid requirements and relieve the burden of restricting movement during daytime. A suitable site with plentiful subcutaneous tissue (e.g., abdominal wall, upper thigh) if available is preferred, avoiding areas with skin damage, for example, oedema, and lymph oedema or radiotherapy sites.	Published guidance (3;P)				
			The child's weight guides the volume of fluid deliverable over a 24-hour period. The total volume of fluid determined may be initially based on a percentage (e.g., 10%–30%) of standard intravenous fluid maintenance guidance. It is likely that significantly lower volumes are initially used and increased if tolerated	Published guidance (3;P)				
			If a child or young person is dying and cannot drink, discuss with them (as appropriate) and their parents or carers whether starting or continuing enteral tube or intravenous fluids is in their best interests.	Expert opinion (4;P)				

			Be aware that enteral tube and intravenous fluids may have a significant effect on care, may be a burden for children and young people, and may mean the place of care and place of death need to be changed.	Expert opinion (4;P)				
			If a child or young person is given enteral or intravenous fluids, review this decision regularly to make sure it continues to be in their best interests.	Expert opinion (4;P)				
Hydration deprivation	Unknown effect	No studies	Not identified	-	Not identified	-	No recommendations	-
Nutrition								
Nutrition	Unknown effect	No studies	Discuss management of nutrition needs with the child or young person at the end of life and their parents or carers	Expert opinion (4;P)	Not applicable	-	No recommendation	-
			If a child or young person with a life-limiting condition is dying, encourage and support them to eat if they want to and are able.	Expert opinion (4;P)				
Comfort-feeding	Unknown effect	No studies	The benefit versus the risk of oral 'comfort feeds', for example, risk of choking versus artificial nutrition and hydration, should be explained to parents. Comfort feeding with very small amounts of taster food may be one approach taken by parents and professionals alike. Open and transparent discussion should be an ongoing adaptive process.	low (3;P)	Not applicable	-	No recommendation	-
Medically-assisted nutrition	Unknown effect	No studies	The role of the enteral feeding regimen is usually to attempt to alleviate symptoms of hunger and dehydration, particularly in those children who are unable to take adequate quantities of food or fluid	Expert opinion (3;P)	Not applicable	-	No recommendation	-

			orally. The aim of such feeding regimens is not to meet the child's full nutritional requirements and not to prevent deterioration in nutritional status at this stage of illness.					
			Several considerations should be made when determining an optimal feeding regimen: -The route of access. -Consider NGT placement as this can be placed most easily in the home or hospice setting. However, placement of the NGT can be distressing and uncomfortable initially and can also mask the child's face. -NJT will generally need endoscopic placement or radiological confirmation to guarantee correct positioning. In most cases an enteral feeding pump is the best option for both continuous and bolus feeding	Expert opinion (4;P)				
			If a child or young person is dying and they are receiving enteral tube feeding or intravenous nutrition, discuss with them (as appropriate) and their parents or carers whether continuing this is in their best interest and review this decision regularly.	Expert opinion (4;P)				
			If after a comprehensive MDT discussion it is agreed that enteral feeds should be started for an individual patient, we recommend the following approach: For a new	Expert opinion (3;P)				

			patient starting feed (over the age of 1 year), it is recommended that a 1 kcal/mL feed is used.					
			If the child stabilizes or improves clinically and is considered not in the end-of-life phase, then an individualized Feeding plan should be sought from local or specialist dietetic services.	Expert opinion (3;P)				
Nutrition deprivation	Unknown effect	No studies	Not identified	-	Not identified -		No recommendation	-

Legend
P: Palliative context
Not identified: No recommendations on specific intervention were identified.
Not applicable: Recommendations from adult guidelines are not applicable when recommendations from child guidelines were identified.

References

2. Nederlandse Vereniging voor Kindergeneeskunde. Richtlijn palliatieve zorg voor kinderen. 2013. Available from: https://www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6881317&tagtitles=Erfelijke%252ben%252baangeboren%252baandoeningen%2cIntensive%252bCare%2cNeonatologie%2cOncologie%2cSociale%252ben%252bPsychosociale%252bkindergeneeskunde%2cMetabole%252bZiekten%2cNeurologie%2cPalliatief.
3. Anderson A-K, Burke K, Bendle L, Koh M, McCulloch R, Breen M. Artificial nutrition and hydration for children and young people towards end of life: consensus guidelines across four specialist paediatric palliative care centres. BMJ Supportive & Palliative Care. 2019:bmjspcare-2019-001909.
4. National Institute for Health and Care Excellence. End of life care for infants, children and young people with life-limiting conditions: planning and management. [Internet]. London: NICE; 2016 [cited 2021 March 1]. Available from: www.nice.org.uk/guidance/ng61.