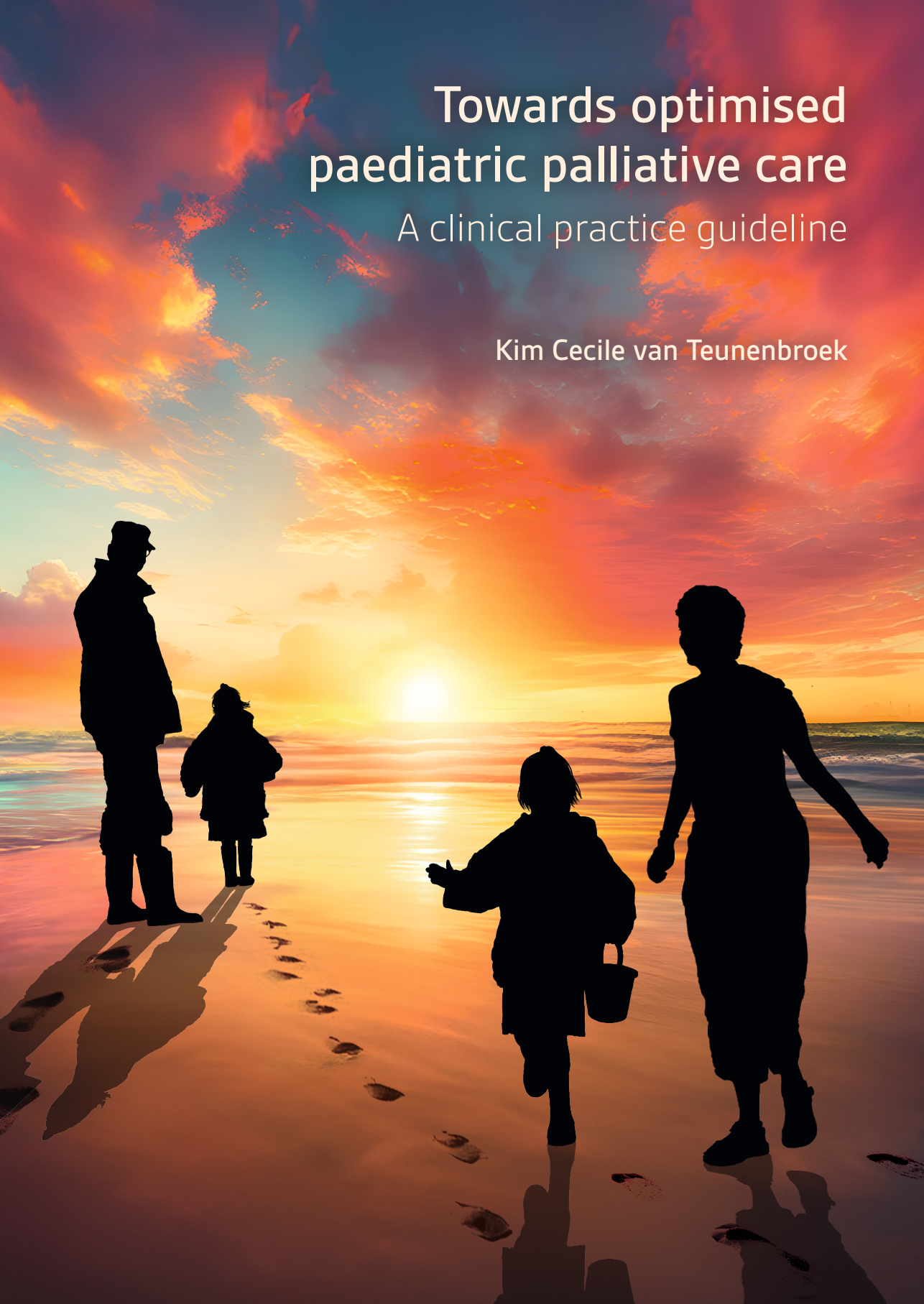


# Towards optimised paediatric palliative care

A clinical practice guideline

Kim Cecile van Teunenbroek





# **Towards optimised paediatric palliative care**

A clinical practice guideline

**Kim Cecile van Teunenbroek**

## **Colofon**

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# **Towards optimised paediatric palliative care**

## **A clinical practice guideline**

### **Richting optimalisering van kinderpalliatieve zorg**

Een richtlijn voor de klinische praktijk

(met een samenvatting in het Nederlands)

### **Proefschrift**

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Sunsets are proof that endings can often be beautiful too.

Beau Taplin



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# 1

## Introduction and thesis outline





## INTRODUCTION

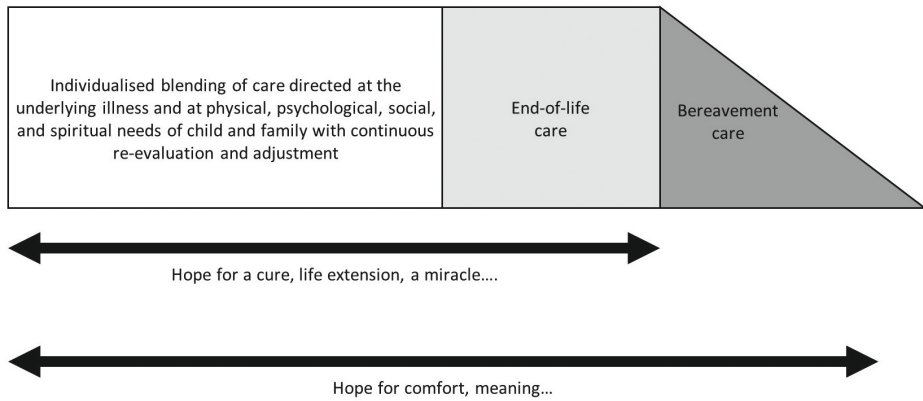
Children with life-threatening and life-limiting conditions and their families are confronted with many uncertainties, incremental losses, and difficult decisions. The impact of these conditions for children and their families involved, is immeasurable. Moreover, the death of a child has a devastating and enduring impact on parents, siblings, and others close to child and family.

Too often children with life-threatening and life-limiting conditions and their families fail to receive adequate and consistent care that meets their physical, psychological, social, and spiritual needs (1-3). Providing paediatric palliative care from the time a child's life-threatening or life-limiting condition is diagnosed can improve care and quality of life for children who survive as well as children who die (2, 4). Furthermore, it can support families of all these children during the entire disease trajectory, during end-of-life, and continuing in bereavement (2, 4).

### **Definition and scope of paediatric palliative care**

Paediatric palliative care encompasses the care for children with life-threatening or life-limiting conditions regardless of their diagnosis and stage of disease (5). According to the definition of the World Health Organisation (WHO), paediatric palliative care is the active and total care of the child's body, mind and spirit and also involves giving support to the family (6). Paediatric palliative care includes the prevention and relief of physical, psychological, social, and spiritual suffering in all children with life-threatening and life-limiting conditions and their families (4, 7). Ultimately, its goal is to achieve the best possible quality of life for these children and their families, and if the moment comes a dignified death (8).

Paediatric palliative care starts when the child is diagnosed with a life-threatening or life-limiting condition. It continues regardless of whether the child receives treatment directed at the disease. Figure 1 shows a schematic overview of the stages in paediatric palliative care which is developed by Liben et al. (2008) (8). This view towards paediatric palliative care is favoured by parents as they hope that their child's life is prolonged while wanting their child to have as much comfort as possible (8, 9). Thus, during the child's disease trajectory, both disease-directed treatment and palliative care intertwine (8, 9). During the child's end-of-life, the care will be more and more focused on improving quality of life and relief of suffering of the child but also on support for the family (8). Paediatric palliative care continues after the child's death and during bereavement, in which it is directed at improving quality of life and relieving suffering of the child's family (8).



**Figure 1.** Stages of palliative care based on the model of Liben et al. 2008 (8)

*Paediatric palliative care includes individualised integration of palliative care principles to manage expectations of life extension and comfort, both of which can be important issues throughout the child's life. End-of-life care is an important component of palliative care when the focus is almost on comfort, though hope for a miracle can persist. Bereavement care can be intense and long-lasting, gradually lessening over time.*

Thus, paediatric palliative care is provided during the child's entire disease trajectory: from diagnosis until end-of-life, after the child's death and during bereavement. Paediatric palliative care does not solely focus on end-of-life care, which is a common misconception.

To define the population which generates a need for paediatric palliative care, the terms life-threatening and life-limiting conditions are often used (4, 5, 10). Generally, four categories are distinguished: 1) children with acute life-threatening conditions from which recovery may or may not be possible, 2) children with chronic life-threatening conditions that may be cured or controlled for a long period but also may cause death, 3) children with progressive life-threatening conditions for which curative treatment is currently not possible and 4) children with irreversible but non-progressive conditions that may cause deterioration and death (4, 10, 11).

This thesis is directed at all children with a life-threatening or life-limiting condition regardless of their diagnosis and stage of disease, and their families.

### Challenges of paediatric palliative care

Paediatric palliative care comes with its own set of challenges that require specific attention and can differ significantly from palliative care for adults (12). First, the number of children living with life-threatening and life-limiting conditions is small. Life-threatening and life-limiting conditions encompass nearly four hundred diagnoses which are often extremely rare or specific to childhood (5, 12, 13). Due to this large variability of diagnoses in a small population, available knowledge is most frequently based on clinical experience rather

than scientific research (5, 12-14). Moreover, knowledge is often highly fragmented and spread across countries and even continents. As a result, there is generally limited knowledge available on how to care for children with life-threatening or life-limiting conditions.

Additionally, the timeline of children's disease trajectories differs to those of adults. In children, the period and intensity of provided palliative care can vary widely (5, 10). Provision of paediatric palliative care may be required for days, months, or years. The complexity of paediatric palliative care depends on the diagnosis and stage of disease (5, 12). Often health care providers with multiple disciplines from different lines of care and organisations are involved in the child's care (15). As a result, ensuring coordination and continuity in paediatric palliative care can be challenging.

Another challenge is that during the disease trajectory, children continue to develop physiologically, emotionally, and cognitively. In terms of physiology, children are very different from adults (16). Due to rapid changes in size, body composition and organ functioning during childhood, prescribing safe and effective dosages in children can be very challenging (6, 16). This often leads to use of inadequate doses at inappropriate intervals causing unnecessary inappropriate symptom control (6, 16). From a psycho-behavioural perspective, the child develops emotionally and cognitively and with that the child's communication and ability to comprehend the disease, treatment and prognosis continues to change. Health care providers need to understand the impact of physiological, emotional, and cognitive changes and be constantly aware and responsive to these changes.

Finally, the diagnosis of a life-threatening or life-limiting condition does not only affect the child but affects the whole family including parents, and siblings (15). Parents bear a heavy responsibility for the care of their child with often complex needs, and also siblings are especially vulnerable (12). They need support to ensure quality of life and limit psychological, social, or spiritual suffering (12). Additionally, health care providers can experience distress when caring for children with life-threatening and life-limiting diseases and might need adequate support to prevent compassion fatigue and burnout (8).

### **Availability of paediatric palliative care**

Worldwide, approximately 21 million children are living with life-threatening and life-limiting conditions and can benefit from a paediatric palliative care approach (17). Of these children, eight million have more complex symptoms and are in need for specialised paediatric palliative care (3, 17). Country-specific factors such as the financial resources that are available for paediatric palliative care, cultural attitudes toward paediatric palliative care, and the existing health care services into which paediatric palliative care must fit, vary (18). As a result, access, availability and integration of paediatric palliative care services differ significantly per country (18). The European Association of Palliative care (EAPC)

provided an overview of paediatric palliative care developments in Europe (1, 5). According to this overview, paediatric palliative care services are being developed with specialised paediatric palliative care consultants in 20 countries. Education in the specialty is available for nurses in 16 of these countries, and for doctors in 14 of these countries (1, 5). The results show that access, availability, and integration of paediatric palliative care continues to develop and grow. However, these results also show that in many countries paediatric palliative care is still not available. Worldwide, it is estimated that 95% of the children with life-threatening or life-limiting conditions have limited to zero access to paediatric palliative care (19). Thus, provision of paediatric palliative care worldwide is a huge challenge which requires attention. Especially, since the population that requires paediatric palliative care continues to grow. This is the result of continuing advances in medical care which allow children with life-threatening and life-limiting conditions to live longer and increase their survival (5, 20, 21).

### **Paediatric palliative care in the Netherlands**

In the Netherlands, approximately 5000 to 7000 children, adolescents and young adults are living with life-threatening or life-limiting conditions (22). Around 23% of these children are diagnosed with oncological diseases and 77% have complex chronic conditions that such as neonatal, neurological, or metabolic disorders (23). Annually, approximately 1000 children die due to the consequences of these conditions (23).

Over the past decades, significant progress has been made in provision of paediatric palliative care in the Netherlands (14). Initially, palliative care for children was characterised by fragmentation and was not available or easily accessible (14, 24). Professionals had difficulties to identify patients' care needs beyond medical aspects and often lacked the skills to provide the specific care required (14). This started to change when the Foundation for Children's Palliative Expertise (PAL) was established in 2007. This nationwide initiative was committed to improve palliative care for all Dutch children with life-threatening and life-limiting conditions and their families. In 2012, the first hospital-based paediatric palliative care team was established in the children's University Medical Centre (UMC) in Amsterdam (25). Currently, a total of seven paediatric palliative care teams are operational in the seven children's UMC's and national hospital for paediatric oncology. The development of these teams facilitated interdisciplinary communication and continuity of care, bridging the gap between care at the hospital and at home (26, 27). Furthermore, parents valued the involvement of paediatric palliative care teams for the provision of practical and emotional support during their child's disease trajectory (26-28).

From 2014 onwards, regional Networks for Integrated Childcare were developed. The networks are a collaboration of professionals from multiple disciplines and organisations which aim to support children with life-threatening and life-limiting conditions and their families. To coordinate all this, the Dutch Centre of Expertise in Children's Palliative care

was established by the PAL foundation in collaboration with the Dutch Association for Paediatrics.

### **Optimisation of paediatric palliative care**

To provide high quality paediatric palliative care, it is essential that the knowledge of health care providers is up to date. This is increasingly challenging since millions of scientific papers are published annually (29). As a result, health care providers are confronted with large volumes of evidence which are rarely summarised and of uncertain value. Furthermore, understanding the quantitative results of clinical research, and applying these results to patients can be very difficult. For example, biased research has frequently resulted in suboptimal medical practice (30).

In response to these challenges, the concept of evidence-based medicine was introduced in the 1990s (31, 32). Evidence-based medicine is centred around three key principles: 1) not all evidence is of equal quality, and clinical practice should be based on the best available evidence, 2) the pursuit of truth is best accomplished by evaluating the totality of evidence, and not selecting evidence that favours a particular claim, 3) clinical decision-making requires the consideration of patients' values and preferences, as evidence alone is not sufficient for effective decision-making (31, 32).

Initially, evidence-based medicine proposed to follow a relatively simple hierarchy of evidence which was based on study design (33). According to this hierarchy, randomised controlled trials (RCTs) are the highest in hierarchy, and have superiority over other study designs such as cohort studies or case-control studies (33). However, stakeholders noted that results from RCTs can also be biased. Hence, these results should not be automatically rated as high quality evidence (33, 34). All results, including results from study designs highest in hierarchy, should be critically appraised.

The rise of critically appraised evidence as a fundamental component in clinical practice, has led health care decision-makers to depend on systematic reviews to find the most trustworthy evidence that informs clinical decisions (33). Systematic reviews are designed to minimise the occurrence of bias through conducting an explicit search strategy which identifies all available evidence, selection and assessment of the methodological quality of the evidence, and reduction of random error by using quantitative evidence methods such as meta-analysis (35). Therefore, the Cochrane collaboration was established in 1993. This collaboration was an effort to enhance the quality of evidence in health care by facilitating the preparation and maintenance of systematic reviews (36).

Systematic reviews on itself are not enough to provide high quality care. Translation into clinical practice is essential. Clinical practice guidelines can facilitate in bridging this gap and are powerful and trusted instruments for health care providers to guide patient care by translating research findings into recommendations for clinical practice (37). Clinical

practice guidelines are developed according to a standard process which combines evidence from scientific literature, patient values, and clinical expertise to formulate recommendations (38) (Figure 2). Care consistent with clinical practice guidelines has led to more efficient care delivery and improved patient outcomes, as guidelines promote interventions that effectively improve patient outcomes (39-42). Furthermore, they decrease variability in care among health care providers and facilitate delivery of efficient and high quality care. Also, clinical practice guidelines are increasingly used to assist policy making in health care (39).



**Figure 2.** Components of evidence-based guideline development

In order to optimise care, it is important that clinical practice guidelines are trustworthy. Therefore, it is essential that guidelines are developed according to a standardised methodology. The Institute of Medicine recognised this and has established several criteria to ensure trustworthiness of guidelines (37). According to these criteria, guidelines should be based upon a systematic review of existing evidence and should be developed by a knowledgeable, multidisciplinary guideline development panel of experts and patient representatives. Furthermore, guidelines should consider important patient values and should be based upon an explicit transparent process which minimises bias. Moreover, the relationship between treatment options and patient outcomes should be clearly explained in guidelines and ratings of both quality of evidence and strength of recommendations should be provided. Finally, guidelines should be reconsidered and

revised as appropriate when important new evidence emerges that could affect current recommendations (37).

The importance of critically appraised evidence and the potential for clinical practice guidelines to improve clinical practice and patient outcomes, led to the development of a new approach for rating the quality of evidence and grading the strength of recommendations. This approach is called the Grades of Recommendations Assessment, Development, and Evaluation (GRADE) methodology (43). The GRADE working group began as an informal collaboration to tackle the shortcomings of grading systems. The GRADE methodology enables more consistent judgements, and communication of such judgments can support better informed choices in health care (43). The GRADE methodology uses a stepwise approach to develop clinical practice guidelines that inform decision-making (43-45).

The first step involves formulating one or more clear clinical questions for which recommendations should be provided. The second step is to identify all existing evidence by performing a systematic review. Then, the quality of existing evidence is identified for each prioritised outcome (43-45). According to the GRADE methodology, there are five factors that can lower the quality of evidence, including study limitations, inconsistency of results, indirectness of evidence, imprecision and publication bias (43-45). Furthermore, there are three factors that can increase quality of evidence including large magnitude of effect, confounding which would reduce a demonstrated effect, and a dose-response gradient. It should be noted that the GRADE methodology is mainly used to critically appraise findings from quantitative evidence (43-45). The GRADE Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual) approach was developed to give guidance for assessing how much confidence should be placed in findings from qualitative evidence (46).

After the quality of evidence is assessed and graded as high, moderate, low or very low level of evidence, recommendations can be developed (43-45). When formulating recommendations, several factors should be considered in addition to the quality of evidence. These factors include the potential harms and benefits of the recommended intervention or care, the required resources, costs, and the feasibility and acceptability to implement it into clinical practice (47). After the evidence and the other factors are carefully assessed, the recommendations are formulated and finalised. The strength of recommendations is graded as strong or moderate and are used to guide clinical decision-making (43).

The GRADE (CERQual) methodology offers a structured approach for assessing the certainty of evidence in medicine based upon predefined criteria. However, for many clinical questions, published evidence may be limited, too indirect, or does not exist (48). When evidence is lacking or of low quality, and more evidence is needed to formulate recommendations,



evidence can be carefully extrapolated from other populations via a stepwise approach. First, evidence-based guidelines should be identified that are relevant for the population of interest. The recommendations from these guidelines can be extracted to refine the considerations and inform the recommendations. Moreover, the conclusions of evidence included in the identified guidelines can be extracted if there is a need to identify the evidence base for these recommendations. If this is not possible, then recommendations can be based upon expert opinion. It is extremely important that there is consensus in order to formulate strong recommendations (48). In the absence of high quality evidence, a strong recommendation can be formulated when there is strong expert opinion that benefits clearly outweigh harms (48).

### **A clinical practice guideline for paediatric palliative care in the Netherlands**

In the Netherlands, inadequate data and scientific knowledge on paediatric palliative care impeded efforts to deliver effective paediatric palliative care, educate professionals to provide such care, and design public policies (2). Therefore, the first guideline for paediatric palliative care was developed and published in 2013 (49). This guideline aimed to improve palliative care for children with life-threatening and life-limiting conditions aged 0 to 18 years throughout the palliative trajectory (from diagnosis until end-of-life continuing in bereavement) by formulating targeted recommendations on symptom treatment, decision-making and organisation of care (49). As a result of this publication, knowledge on paediatric palliative care became widely available for the first time in the Netherlands.

Several years after the publication of the first Dutch guideline for paediatric palliative care, stakeholders expressed the need to update recommendations with new evidence from scientific literature. Furthermore, stakeholders requested to expand the guideline with recommendations on additional topics that are increasingly considered as essential to paediatric palliative care. As a result, the revised Dutch guideline for paediatric palliative care was developed and included recommendations on symptom treatment, provision of advance care planning and shared decision-making, organisation of care, and provision of psychosocial care including preloss and bereavement care.

The revised Dutch guideline for paediatric palliative care was developed according to the GRADE (CERQual) methodology. To formulate recommendations, we used different methods in accordance with the GRADE methodology. The applied methods were dependent on the specific clinical question, available evidence, and availability of additional literature such as other clinical practice guidelines, textbooks, or systematic reviews of observational, qualitative, or mixed-method studies.

For clinical questions on effectiveness of paediatric palliative care interventions, we first focused on identifying high-quality quantitative evidence by performing a systematic search for studies on paediatric palliative care interventions. For the clinical question on

barriers and facilitators to advance care planning and shared decision-making, we systematically searched for qualitative evidence. In case, we found limited or no evidence, we relied on different methods to formulate recommendations.

First, we systematically searched for evidence and recommendations in other clinical practice guidelines on paediatric palliative care. If the evidence from other clinical practice guideline was in accordance with our inclusion criteria we added it to our evidence-base. Additionally, we used the recommendations in the existing guidelines on paediatric palliative care to refine our considerations and recommendations. Second, we systematically searched for clinical practice guidelines in general paediatrics and adult palliative care. If possible, we extrapolated recommendations to our study population, children with life-threatening and life-limiting conditions. The extrapolation of recommendations was carefully performed with clinical experts from multiple disciplines and final recommendations were only approved when consensus was reached. Lastly, we used two textbooks on paediatric palliative care and systematic reviews of observational, qualitative, or mixed-method studies to refine considerations and recommendations. Inclusion of these textbooks and systematic reviews was only considered relevant for specific topics.

In situations where there was no or limited evidence, no existing paediatric palliative care guidelines, no recommendations could be extrapolated from existing general paediatrics or adult paediatric palliative care guidelines, or no other additional literature sources such as textbooks were considered relevant, recommendations were based upon clinical expertise and patient values only. This was done via a careful process in which only recommendations were made on which there was group consensus.

As the availability of evidence, and the availability and relevance of guidelines and other additional literature sources differed per clinical question and topic, different combinations of methods were used to provide recommendations on all selected topics related to paediatric palliative care. In this thesis, we will provide a thorough overview of all methods used in *chapter 2*. In *chapter 3, 4, and 5*, the evidence and recommendations are provided that resulted from the different combinations of methods in accordance with the GRADE (CERQual) methodology.

**Aim of this thesis**

The aim of this thesis is to further improve the quality of paediatric palliative care and thereby the quality of life for children aged 0 to 18 years with life-threatening and life-limiting conditions and their families by expanding and updating the Dutch clinical practice guideline for paediatric palliative care, with more attention to all four dimensions of palliative care, including the relief of physical, psychological, social, and spiritual suffering. Specific objectives are to:

1. Provide an overview of the methodology to revise the Dutch clinical practice guideline for paediatric palliative care.
2. Develop updated evidence-based recommendations on symptom treatment, provision of advance care planning and shared decision-making, and provision of psychosocial care including preloss and bereavement care.

## THESIS OUTLINE

This thesis describes the methodology of the revised Dutch clinical practice guideline for paediatric palliative care and provides an overview of the existing evidence and recommendations on topics related to paediatric palliative care.

*Chapter 2* provides an overview of the methodology that is used for the revision of the Dutch clinical practice guideline for paediatric palliative care, including a brief presentation of the identified evidence.

*Chapter 3* provides the identified evidence and evidence-based recommendations on non-pharmacological and pharmacological interventions to treat symptoms and refractory symptoms in paediatric palliative patients.

In *Chapter 4*, the identified evidence on the effectivity of advance care planning and shared-decision interventions and related barriers and facilitators is presented. Furthermore, we provide evidence-based recommendations to optimise advance care planning and shared decision-making in paediatric palliative care in the Netherlands

*Chapter 5*, we present the identified evidence and evidence-based recommendations to optimise psychosocial care including psychological interventions, psychological interventions, practical and social, support, cultural, spiritual, and religious support and preloss and bereavement care.

We conclude this thesis with *Chapter 6*, a summary and general discussion on the findings presented in this thesis including future implications.

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# 2

## Palliative care for children: methodology for the development of a national clinical practice guideline

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## **ABSTRACT**

### **Background**

Provision of paediatric palliative care for children with life-threatening or life-limiting conditions and their families is often complex. Guidelines can support professionals to deliver high quality care. Stakeholders expressed the need to update the first Dutch paediatric palliative care guideline with new scientific literature and new topics. This paper provides an overview of the methodology that is used for the revision of the Dutch paediatric palliative care guideline and a brief presentation of the identified evidence.

### **Methods**

The revised paediatric palliative care guideline was developed with a multidisciplinary guideline panel of 72 experts in paediatric palliative care and nine (bereaved) parents of children with life-threatening or life-limiting conditions. The guideline covered multiple topics related to (refractory) symptom treatment, advance care planning and shared-decision making, organisation of care, psychosocial care, and loss and bereavement. We established six main working groups that formulated 38 clinical questions for which we identified evidence by updating two existing systematic literature searches. The GRADE (CERQual) methodology was used for appraisal of evidence. Furthermore, we searched for additional literature such as existing guidelines and textbooks to deal with lack of evidence.

### **Results**

The two systematic literature searches yielded a total of 29 RCTs or systematic reviews of RCTs on paediatric palliative care interventions and 22 qualitative studies on barriers and facilitators of advance care planning and shared decision-making. We identified evidence for 14 out of 38 clinical questions. Furthermore, we were able to select additional literature (29 guidelines, two textbooks, and 10 systematic reviews) to deal with lack of evidence.

### **Conclusions**

The revised Dutch paediatric palliative care guideline addresses many topics. However, there is limited evidence to base recommendations upon. Our methodology will combine the existing evidence in scientific literature, additional literature, expert knowledge, and perspectives of patients and their families to provide recommendations.

### **Keywords**

Clinical practice guideline, evidence-based medicine, paediatric palliative care

## BACKGROUND

In the Netherlands, each year 5000 to 7000 children aged 0 to 18 years are suffering from life-threatening or life-limiting conditions (1). In 2021, 983 children, adolescents and young adults aged 0 to 20 years died due to the consequences of these conditions (2). Although these numbers seem small, the impact of these diseases for children and their families involved, is immeasurable. All these children and their families need paediatric palliative care.

Paediatric palliative care is a specialty that encompasses the care of all children with life-threatening or life-limiting conditions regardless of their diagnosis or stage of disease (3). The World Health Organization (WHO) defines paediatric palliative care as the prevention and relief of suffering of paediatric patients and their families, facing problems associated with life-threatening or life-limiting conditions (4). These problems include the physical, psychological, social and spiritual suffering of children and the psychological, social and spiritual suffering of family members (4). Thus, paediatric palliative care relates not only to the child but to the whole family (5).

Both health care providers and parents face multiple challenges in providing the best paediatric palliative care, as it is a complex trajectory where curative and palliative care intertwine. Additionally, the child continues to develop physically, emotionally and cognitively which contributes to many varieties in the child's communication skills and ability to understand the condition (5). Since the number of children living with life-threatening or life-limiting conditions is small and many conditions are extremely rare or specific to childhood, there is only limited knowledge on paediatric palliative care (5).

To ensure that all children in need of palliative care receive high quality care, clinical practice guidelines (CPGs) are needed. Care consistent with CPGs has led to more efficient care delivery and improved patient outcomes (6-8). Therefore, the Dutch multidisciplinary CPG for paediatric palliative care was developed in 2013. This CPG provides recommendations on symptom relief, decision-making and organisation of care. Several years after the development of the first national CPG, stakeholders expressed a need to update this CPG with newly published evidence and to include new topics, specifically delirium, palliative sedation, restriction of hydration and nutrition in case of palliative sedation, advance care planning, shared decision-making, psychosocial care, and loss and bereavement. As a result, the revision of the first Dutch CPG for paediatric palliative care was initiated.

This article provides an overview of the methodology for this revision of the Dutch CPG for paediatric palliative care and provides a brief presentation of the identified evidence. In subsequent manuscripts we will discuss the evidence and recommendations on (1) treatment of symptoms including refractory symptoms, (2) advance care planning, shared

decision-making, and organisation of care and (3) psychosocial care, and loss and bereavement.

## **METHODS**

### **Aim and Scope**

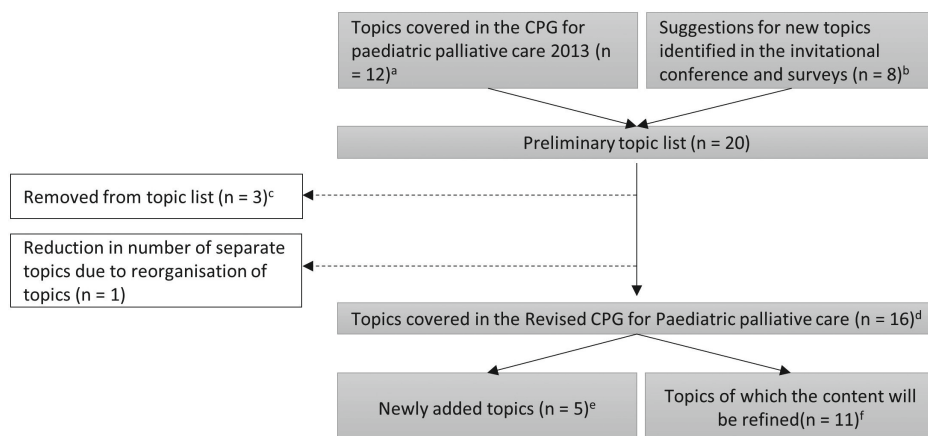
The aim of this CPG is to provide guidance on all aspects of palliative care including physical, psychological, social, and spiritual aspects, for all children aged 0 to 18 years with life-threatening or life-limiting conditions and their caregivers, brothers, and sisters (hereafter referred to as families) throughout the entire palliative trajectory (from palliative diagnosis till after end-of-life), with the ultimate goal to improve quality of paediatric palliative care. This CPG is intended for all health care providers from different specialisms who are involved in paediatric palliative care and for all children aged 0 to 18 years with life-threatening or life-limiting conditions and their families.

The guideline is an update of the first CPG for paediatric palliative care that was published in 2013, which provided recommendations on symptom relief, decision making and organisation of care.

### **Topic selection**

In 2018, an invitational conference among experts in paediatric palliative care was convened to evaluate the first CPG for paediatric palliative care and identify new topics that needed to be addressed. This formed the basis for the online survey that was conducted among 89 health care providers to prioritize new topics (Appendix A). In this survey, professionals were asked to weigh topics that should be included during the revision of the CPG on a 5-point Likert scale that ranged from not important to very important. In addition, another survey was conducted among patient representatives and mostly bereaved parents of children with life-threatening or life-limiting conditions (n=16) to indicate their priorities towards the identified topics in the invitational conference (Appendix B).

Multiple suggestions for new topics were derived from the results of the invitational conference and surveys. A preliminary topic list was generated which included topics covered in the CPG of 2013 (n=12) and the suggestions for new topics (n= 8). The core group made a final selection based on practical and financial feasibility, and priorities of professionals, and patient and parent representatives. This resulted in a final list of 16 topics of which five topics were newly added. Figure 1 shows the selection process including reasons for exclusion of topics.



**Figure 1.** Process of topic selection

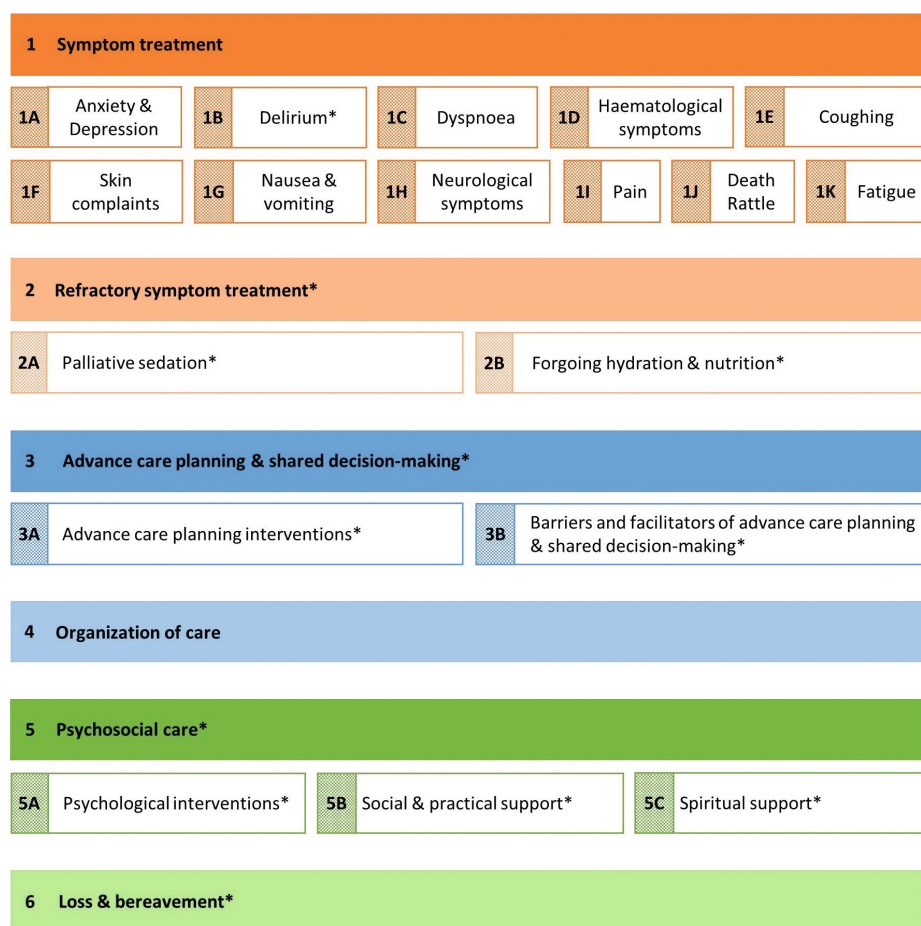
- a. Topics covered in the CPG for paediatric palliative care 2013 are: anxiety and depression; dyspnoea; haematological symptoms, coughing; skin complaints; nausea and vomiting; neurological symptoms; pain; death rattle; fatigue; decision making; and organisation of care.
- b. Suggestions for topics identified in the invitational conference and surveys are: delirium; refractory symptoms, psychosocial care, loss and bereavement, advance care planning, practicing communication skills, financing, and complementary care.
- c. Reasons for removal from topic list are: practicing communication skills and financing are outside the scope of this CPG; and complementary care will be covered in another CPG.
- d. Topics covered in the revised CPG for paediatric palliative care are: anxiety and depression; delirium, dyspnoea; haematological symptoms; coughing, skin complaints; nausea and vomiting; neurological symptoms; pain; death rattle; fatigue; refractory symptoms; advance care planning and shared decision making; organisation of care; psychosocial care; and loss and bereavement.
- e. Newly added topics are: delirium; refractory symptoms; advance care planning and shared decision making; psychosocial care; and loss and bereavement.
- f. Topics of which the content will be refined: anxiety and depression; dyspnoea; haematological symptoms; coughing; skin complaints; nausea and vomiting; neurological symptoms; pain; death rattle; fatigue; and organisation of care.

## Multidisciplinary guideline development panel

A guideline development panel was established which consisted of 72 experts in paediatric palliative care and nine (bereaved) parents (see representation of patients and their families). Professionals from various disciplines such as paediatricians, paediatric oncologists, neurologists, anaesthesiologists, nurses, psychologists, pharmacists, medical pedagogical care providers and researchers, were included in the expert panel. Each working group (WG) consisted of members with expertise knowledge relevant to the specific topic addressed (Appendix C). The WG members were selected based on their experience with paediatric palliative care, of whom some had specific certified training in paediatric palliative care. The Netherlands Comprehensive Cancer Organisation recruited the panel members. Members were either mandated by their professional associations or participated on

personal title. All members disclosed conflicts of interest at the start and end of the guideline development process.

Based on the final selection of topics, six main WGs were formed. These WGs focused on symptom treatment (WG1), refractory symptom treatment (WG2), advance care planning and shared decision-making (WG3), organisation of care (WG4), psychosocial care (WG5), and loss and bereavement (WG6). Sub-WGs were established for WGs that covered multiple topics. Figure 2 provides a full overview of the (sub)WGs. The members of the expert panel were appointed to the (sub)WGs according to their expertise. Moreover, a core group was established to ensure consistency and transparency throughout the guideline. An overview of the working structure and guideline development process is shown in appendix D and E.



**Figure 2.** Guideline working groups

\* Newly added in the revision of the Dutch Paediatric Palliative Care CPG



## **Representation of patients and their families**

Different methods were used to ensure representation of patients and their families. First, we conducted a survey to identify patient priorities for topic selection. Second, two members of the core group were dedicated to ensure the representation of patients and their families during the entire guideline process. Third, a panel consisting of nine (bereaved) parents of children with life-threatening or life-limiting conditions was established to review guideline texts and recommendations (Appendix C). We ensured the panel represented a broad spectrum of experiences regarding paediatric palliative care by including parents of children with a variety of palliative conditions, age, and stage of disease (currently receiving palliative care or deceased). The parents were recruited by the Child and Hospital Foundation and attended a short training on guideline development.

The panel reviewed the first drafts of all guideline texts and recommendations. Additionally, the panel reviewed the complete concept guideline to ensure their input was incorporated correctly. Lastly, parents were asked to share their experiences during the interactive conference for organisation of care (WG4) (see consensus-based approach).

## **Formulation of clinical questions**

Each (sub-)WG proposed several clinically relevant questions. Questions were developed according to the PICOS format, which defines the patient group, intervention, comparison to the intervention, relevant outcomes, and study design for each clinical question. The core group assessed all clinical questions carefully. If necessary, clinical questions were adjusted. The core group sent the final clinical questions to the (sub-)WGs for approval.

Below we describe the methods used to answer the clinical questions. In table 1, an overview of the methods used per WG is presented.

**Table 1.** Overview of methods used per working group

	<b>WG 1</b> Symptom treatment	<b>WG 2</b> Refractory symptom treatment	<b>WG 3</b> Advance care planning & shared-decision making	<b>WG 4</b> Organisation of care	<b>WG 5</b> Psychosocial care	<b>WG 6</b> Loss & bereavement
<b>Identification of quantitative studies</b>						
Systematic literature search to identify (SRs of) RCTs and CCTs on paediatric palliative care interventions	X	X	X	X	X	X
GRADE assessment	X	X	X	X	X	X
<b>Identification of qualitative studies</b>						
Systematic literature search to identify qualitative studies on barriers and facilitators for advance care planning and shared decision-making			X			
GRADE CERQual assessment			X			
<b>Identification of additional literature</b>						
Search for clinical practice guidelines on paediatric palliative care, general paediatrics, adult paediatric and/or palliative care	X	X	X	X	X	X
Search for textbooks on paediatric palliative care	X	X				
Search for SRs of observational, qualitative, or mixed-method studies*						X
<b>Other methods</b>						
Consensus-based approach: Ideafactory				X		

\* Studies are derived from the search for (SRs of) RCTs/CCTs on paediatric palliative care interventions

## Identification of evidence – quantitative studies

### Systematic literature search

WG1 to WG6 formulated a total 37 clinical questions related to the effect of paediatric palliative care interventions (Appendix F).

We updated the systematic literature search of the former CPG (which searched from 1970 to 2011) (9) to identify new studies on paediatric palliative care. All originally included

studies were also included in the revised CPG. We searched for studies published from January 1, 2010 to January 24, 2020 (initial search October 5, 2018; top-up search, January 24, 2020), in the databases Ovid MEDLINE and PreMEDLINE, MEDLINE (PubMed), CENTRAL and the Cochrane Database of systematic reviews using a combination of the search terms "child", "palliative care", "randomized controlled trial" and "systematic review" (Appendix G).

The following inclusion criteria were defined: (1) randomized controlled trials (RCTs), controlled clinical trials (CCTs) including at least 10 patients and systematic reviews (SRs) of RCTs, (2) study population consisting of children aged 0 to 18 with life-threatening conditions and life-limiting conditions (according to the definition of the WHO(4)); at least 75% of the study population should be aged 0 to 18 years, (3) paediatric palliative care interventions related to (a) treatment of anxiety and depression, delirium, dyspnoea, haematological symptoms, coughing, skin complaints, nausea and vomiting, pain, neurological symptoms and fatigue, (b) treatment of refractory symptoms, c) advance care planning and shared decision-making, (d) organisation of care, (e) psychosocial care, and (f) loss and bereavement. Only studies published in English or Dutch language were included. Studies that described interventions on complementary or alternative medicine were excluded (Appendix H).

We searched for eligible studies in reference lists of included studies and identified SRs, guidelines, and textbooks. Moreover, we asked WG members to provide eligible studies.

### ***Study selection***

The studies were selected through two rounds of screening, title/abstract screening, and full text screening. One independent reviewer screened the titles and/or abstracts of all citations. The full text screening was performed by one independent reviewer. In case of doubt, the citations were discussed in the core group and were included only if there was consensus. The selected citations were distributed among the WGs. When citations were relevant for multiple WGs, they were included in all relevant WGs.

### ***Summary and appraisal of evidence***

All studies were summarized in evidence tables. Evidence tables described study characteristics (study type, setting, duration and years), participant characteristics (number and diagnosis of participants, age, and sex), intervention and control characteristics, outcomes and results, and strengths, limitations, and study quality.

We determined individual study quality by assessing risk of bias according to the criteria of Cochrane Risk of Bias tool (10). This tool assesses risk of selection bias, attrition bias, detection bias and performance bias of each study. Risk of bias can be classified as either low, high, or unclear.

We categorized evidence by outcome measures in summary of findings tables for every clinical question. We then formulated conclusions of evidence for each outcome measure. We assessed the quality of the total body of evidence with the Grading Recommendation Assessment Development and Evaluation (GRADE) criteria (11). The GRADE appraisal was performed by two reviewers. Quality of evidence was downgraded if study limitations, inconsistency, indirectness, imprecision, or publication bias were present. Quality of evidence was upgraded if a dose response effect or large magnitude of effect was identified.

## **Identification of evidence – qualitative studies**

### ***Systematic literature search***

WG3 (advance care planning and shared decision-making) formulated one clinical question on barriers and facilitators of advance care planning and shared decision-making (Appendix F). We performed a systematic literature search to identify qualitative studies on barriers and facilitators for advance care planning and shared decision-making. We updated the literature search that was conducted in the guideline 'End of life care for infants, children and young people with life-limiting conditions (2016)' of the National Institute for Health and Care Excellence (NICE) (12). We searched Medline (PubMed) from January 1, 2016 to September 16, 2020 using the search terms "child", "palliative care", "advance care planning", "shared decision-making", "qualitative study" (Appendix G).

The following inclusion criteria were defined: (1) qualitative studies, mixed-methods observational studies with qualitative data and SRs of qualitative studies, (2) study population consisting of children aged 0 to 18 years old with life-threatening or life-limiting conditions, their parents and health care providers, (3) study outcomes were barriers and facilitators on advance care planning or shared decision-making. Moreover, only studies published in English or Dutch language were included (Appendix H).

We asked WG members to provide eligible studies and searched for eligible studies in identified SRs and guidelines on barriers facilitator for advance care planning and shared decision-making.

### ***Study selection***

Both title/abstract screening and full text screening were performed by two independent reviewers. One reviewer performed title/abstract screening and full text screening for all identified citations. For the second review, citations were divided among eight WG members. In case of doubt, citations were discussed in the core group and included only if there was consensus.

### ***Summary and appraisal of evidence***

All studies were summarized in evidence tables. Evidence tables described study characteristics (study type, objective, setting, duration, and years), participant characteristics

(number and diagnosis of participants, age, sex, ethnicity, religious preference, and level of education), outcomes and results, and strengths, limitations, and study quality.

We determined individual study quality by assessing the methodological limitations according to the criteria of Critical Appraisal Skills Programme (CASP) checklist tool (13). This tool assesses the aim and appropriateness of the qualitative study design, rigor in study design, sample selection, data collection, data analysis and results. Methodological limitations are classified as low, high, or unclear.

We assessed the quality the total body of evidence with the adapted GRADE Confidence in the Evidence from Reviews of Qualitative research (GRADE CERQual) methodology (14). The GRADE CERQual appraisal was performed by two reviewers. Quality of evidence was downgraded if methodological limitations were present or if there was a lack of coherence, relevance or data saturation (15). Quality of each conclusion of evidence was classified as high, moderate, low, or very low.

### Identification of additional literature

As the expectation was that the systematic searches would yield little to no evidence, we searched for additional literature.

For all WGs, we searched for guidelines on paediatric palliative care, general paediatrics, and adult palliative care. To identify relevant (inter)national guidelines on paediatric palliative care, general paediatrics, and adult palliative care, we searched multiple databases. We searched the Guideline International Network database from 2010 to January 24, 2020, using the search terms "child" and "palliative care", to identify guidelines on paediatric palliative care. Furthermore, we searched databases of the NICE, International Paediatric Oncology Guidelines in supportive care network (iPOG), the Dutch Association for Paediatrics, and Pallialine to identify guidelines on paediatric palliative care, general paediatrics, and adult palliative care. Guideline panel members were also asked to supply additional guidelines (Appendix G).

For the selection of guidelines, our first choice was to include (inter)national guidelines on paediatric palliative care. If guidelines on paediatric palliative care were not available, we included guidelines on general paediatrics if deemed relevant such as for topics related to (refractory) symptom treatment. We only included guidelines on adult palliative care, if no (relevant) guidelines on paediatric palliative care or guidelines on general paediatrics were identified (Appendix H). Throughout the guideline process, we manually checked for all selected guidelines if more recent versions were available.

In case we did not find recommendations from guidelines on paediatric palliative care, general paediatrics, or adult palliative care, we included two textbooks on paediatric palliative care to refine considerations and recommendations. Since most topics were

covered in recommendations from selected guidelines, we only used the textbooks for WG1 (symptom treatment) and WG2 (refractory symptom treatment).

Lastly, we derived SRs of observational, qualitative, or mixed-method studies from the systematic literature search on paediatric palliative care and through referencing. The inclusion of these SRs was only considered relevant for WG6 (loss and bereavement). We summarized the results of the SRs in evidence tables and translated these into conclusions of evidence. As the results of SRs included multiple studies from multiple study designs, we were not able to determine individual study quality nor the quality of the total body of evidence. The formulated conclusions were used to base recommendations upon.

### **Consensus-based approach**

We found that not all included clinical questions in the revised CPG could be appropriately answered through an evidence-based approach, as some questions were considered as highly specific to the Dutch context. In particular, WG4 (organisation of care) formulated clinical questions that focused on issues specific to the Dutch health care system and professional roles and institutions within this system (for example, methods to assist the general practitioner and other health care providers in improving continuity of paediatric palliative care at home). Therefore, an Ideafactory was organized. This is an interactive conference with a competitive element that is designed to find the best solutions for problems (formulated as questions). These solutions were used as the basis for formulating the recommendations. The methods and results will be presented in a subsequent manuscript.

### **Formulation of recommendations**

When formulating recommendations, several factors were taken into account: (1) the quality of the evidence (the higher the quality, the more likely it is to formulate a strong recommendation), (2) additional literature, (3) patient perspectives (values and needs), (4) professional perspectives (clinical expertise, values and needs), (5) acceptability (legal and ethical considerations), (6) feasibility (sufficient time, knowledge and manpower) and (7) benefits versus harms of the interventions.

For each clinical question, WG members described the relevant considerations. Decisions were made through group consensus. The strength of each recommendation was graded according to published evidence-based methods (16, 17) (appendix I). Recommendations were categorised as strong to do (green), moderate to do (yellow) or strong not to do (red). A strong recommendation reflected a high degree of certainty. Moderate recommendations have a higher degree of uncertainty, therefore factors such as the clinical expertise, the patients and family's situation and preferences, feasibility and relevant harms and benefits need to be considered.

All recommendations were supported unanimously by the core group, WG members, and parent representatives.

### **Identification of additional literature**

The search for guidelines identified 378 potential CPGs. In total, we included 29 CPGs of which 6 were paediatric palliative care CPGs, 11 were general paediatric CPGs and 12 were adult palliative care CPGs (Appendix J). Moreover, we included two textbooks on paediatric palliative care.

In addition, we included 10 SRs of observational, qualitative, or mixed-method studies on bereavement intervention components and features of communication strategies.

2

## **RESULTS**

### **Identification of quantitative studies**

For the 37 formulated clinical questions on paediatric palliative care interventions of WG1 to WG6, the updated systematic literature search yielded 5078 citations. A total of 4337 citations were excluded based on title/abstracts and 168 citations were included for full text screening. Main reasons for exclusion of full texts were wrong study design (other than RCTs, CCTs or SRs) or wrong study population (other than children in the palliative setting).

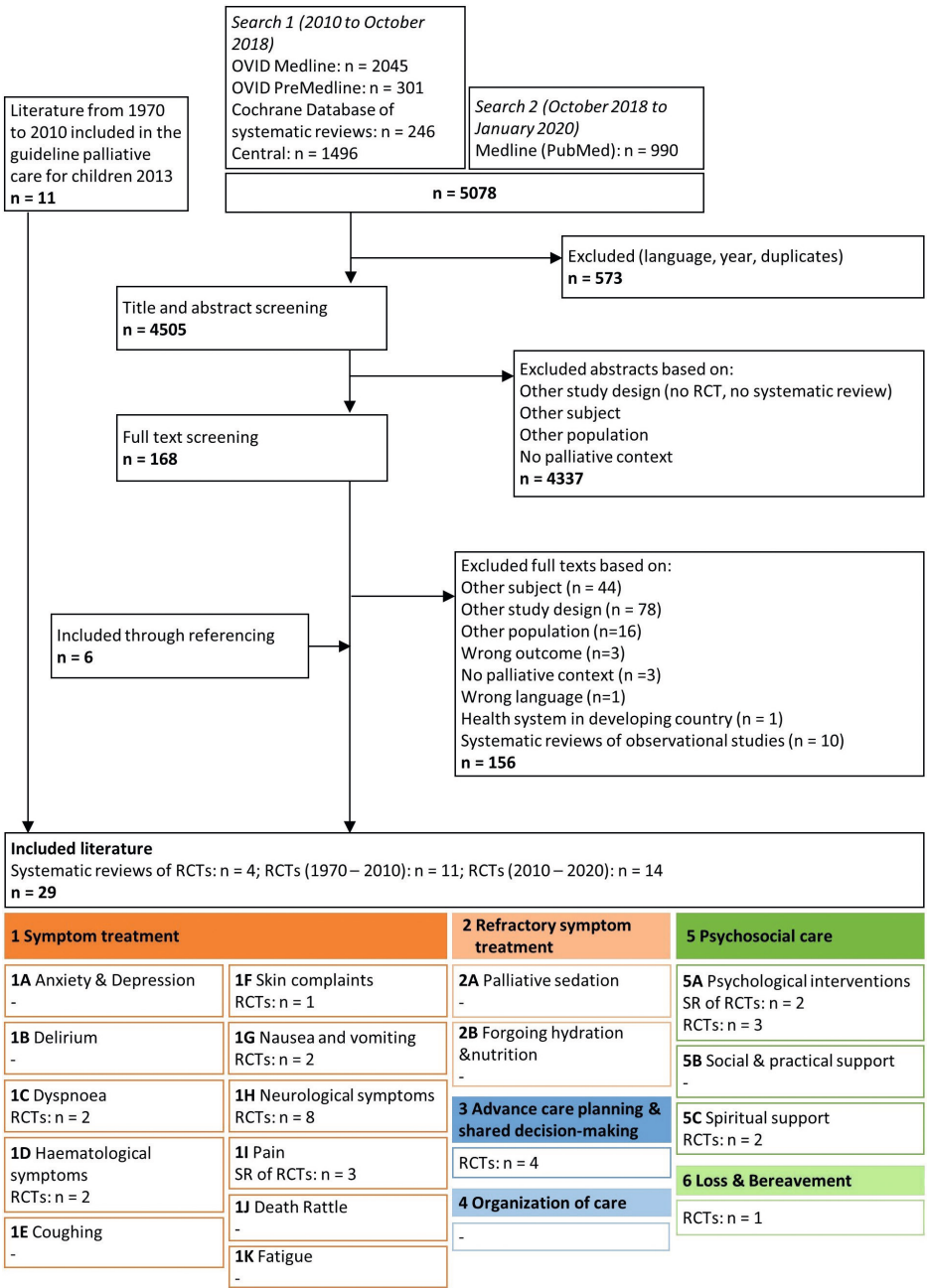
A total of 29 studies (25 RCTs and 4 SRs of RCTs) were eligible for inclusion. This included 11 RCTs that were identified in the previous CPG of 2013 and 18 newly published studies (appendix J). We subsequently categorized all 29 citations according to topic. Then, we distributed the citations among the different WGs. Figure 3 shows a flow diagram of the study selection process.

### **Identification of qualitative studies**

For the formulated clinical question on barriers and facilitators of advance care planning and shared decision-making of WG3, the updated systematic literature search yielded 1232 eligible studies. A total of 1147 citations were excluded based on title/abstract and 85 citations were included for full text screening. Main reasons for exclusion of full texts were wrong study subject (no advance care planning or shared decision-making), wrong study design, or wrong study outcome (no barriers and facilitators).

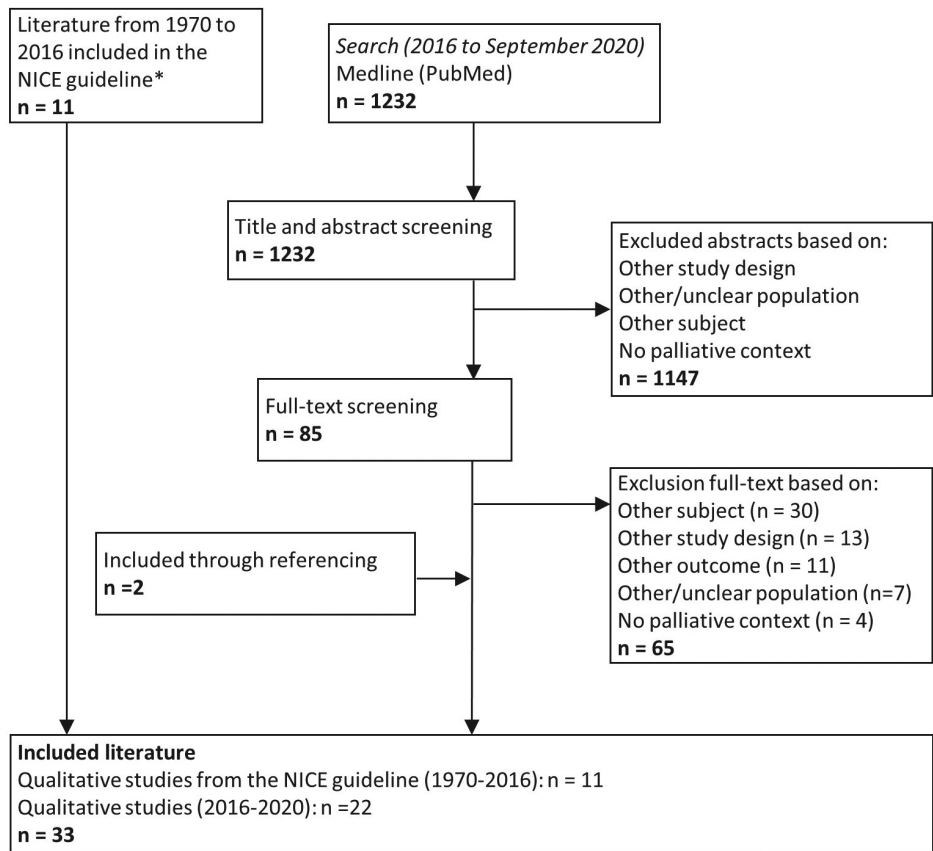
A total of 33 studies on barriers and facilitators of advance care planning and shared decision-making were included. This included 22 newly published qualitative studies and 11 qualitative studies that were identified in the search of the NICE-guideline 'End of life care for infants, children and young people with life-limiting conditions (2016)'(12) (Appendix J). We used the conclusions of evidence of the 11 included studies in the NICE guideline

and integrated these in our conclusions of evidence. Figure 4 shows a flow diagram of the selection process.



**Figure 3.** Flowchart of the selection process of quantitative studies





**Figure 4.** Flowchart of the selection process of qualitative studies

\* We only used the conclusions of evidence from the 11 identified studies in the search of the NICE guideline

**Evidence base**

Table 2 gives an overview of the selected studies from the systematic literature searches and selected additional literature per WG and clinical question. The systematic literature searches identified studies for 14 out of 38 formulated clinical questions, meaning that for 24 clinical questions the systematic literature searches identified no evidence. The number of identified studies from the systematic literature searches differed per WG and clinical question. Moreover, we were able to select additional literature, namely guidelines, textbooks, or SRs of observational, qualitative, or mixed-method studies for almost every clinical question.

**Table 2.** Selected studies per working group and clinical question

Topic/clinical question*		Selected studies from systematic literature searches	Selected additional literature
<b>WG1 Symptom treatment</b>			
1	Anxiety and depression: Non pharmacological interventions	-	4 guidelines <sup>(18-21)</sup>
2	Anxiety and depression: Pharmacological interventions	-	1 textbook <sup>(22)</sup> ; 4 guidelines <sup>(18-21)</sup>
3	Delirium: Non pharmacological interventions	-	2 guidelines <sup>(12, 23)</sup>
4	Delirium: Pharmacological interventions	-	
5	Dyspnoea: Non pharmacological interventions	2 RCTs <sup>(24, 25)</sup>	2 guidelines <sup>(20, 26)</sup>
6	Dyspnoea: Pharmacological interventions for dyspnoea	-	
7	Haematological symptoms: Pharmacological interventions for anaemia	2 RCTs <sup>(27, 28)</sup>	1 textbook <sup>(29)</sup> , 2 guidelines <sup>(30, 31)</sup>
8	Haematological symptoms: Pharmacological interventions for thrombocytopenia	-	2 guidelines <sup>(30, 32)</sup>
9	Haematological symptoms: Pharmacological interventions for haemorrhages	-	-
10	Haematological symptoms: Pharmacological interventions for thrombosis	-	-
11	Coughing: Non pharmacological interventions	-	1 guideline <sup>(33)</sup>
12	Coughing: Pharmacological interventions	-	
13	Skin complaints: Non pharmacological interventions (pressure ulcers and itching)	-	5 guidelines <sup>(34-38)</sup>
14	Skin complaints: Pharmacological interventions (pressure ulcers and itching)	1 RCT <sup>(39)</sup>	
15	Nausea vomiting: Non pharmacological interventions	1 RCT <sup>(40)</sup>	2 guidelines <sup>(41, 42)</sup>
16	Nausea vomiting: Pharmacological interventions	7 RCTs <sup>(43-49)</sup>	4 guidelines <sup>(20, 41, 42, 50)</sup>
17	Neurological symptoms: Non pharmacological interventions	-	4 guidelines <sup>(51-54)</sup>
18	Neurological symptoms: Pharmacological interventions	2 RCTs <sup>(55, 56)</sup>	5 guidelines <sup>(12, 51-54)</sup>
19	Pain: Non pharmacological interventions	1 SR of RCTs <sup>(57)</sup>	1 guideline <sup>(58)</sup>
20	Pain: Pharmacological interventions	2 SR of RCTs <sup>(59, 60)</sup>	1 guideline <sup>(12)</sup>
21	Death rattle: Non pharmacological interventions	-	2 guidelines <sup>(12, 61)</sup>
22	Death rattle: Pharmacological interventions	-	
23	Fatigue: Non pharmacological interventions	-	2 guidelines <sup>(62, 63)</sup>
24	Fatigue: Pharmacological interventions	-	1 guideline <sup>(62)</sup>

**Table 2.** Continued

Topic/clinical question*		Selected studies from systematic literature searches	Selected additional literature
WG2 Refractory symptom treatment			
25	Palliative sedation	-	2 textbooks <sup>(22, 29)</sup> , 1 guideline <sup>(64)</sup>
26	Palliative sedation in children with severe disabilities	-	-
27	Forgoing hydration and nutrition	-	2 textbooks <sup>(22, 29)</sup> , 2 guidelines <sup>(12, 65)</sup>
WG3 Advance care planning and shared decision-making			
28	Advance care planning interventions	4 RCTs <sup>(66-69)</sup>	1 guideline <sup>(12)</sup>
29	Barriers and facilitators of advance care planning and shared-decision making	22 qualitative studies <sup>(70-91)</sup> **	-
WG4 Organisation of care			
30	Organisational interventions	-	1 guidelines <sup>(12)</sup>
WG5 Psychosocial care			
31	Psychological interventions for children	1 SR of RCTs <sup>(92)</sup> , 2 RCTs <sup>(93, 94)</sup>	1 guideline <sup>(12)</sup>
32	Psychological interventions for parents, and family members	2 SRs of RCTs <sup>(57, 92)</sup> , 1 RCT <sup>(95)</sup>	
33	Social and practical support for children, parents, and family members	-	
34	Cultural, spiritual, and religious support for children, parents, and family members	2 RCTs <sup>(96, 97)</sup>	
WG6 Loss and bereavement			
35	Bereavement care interventions for children, parents, and family members	1 RCT <sup>(98)</sup>	1 guideline <sup>(12)</sup>
36	Components of bereavement care interventions		
37	Experiences and needs of parents and health care providers	-	10 SRs <sup>(99-108)</sup> , 1 guideline <sup>(12)</sup>
38	Features of communicative and affective strategies		

<sup>\*</sup> Complete clinical questions can be found in appendix D.

<sup>\*\*</sup> Conclusions of evidence from 11 studies on barriers and facilitators of ACP and shared decision making of the NICE guideline 'End of life care for infants, children and young people with life-limiting conditions (2016)' were used.

## DISCUSSION

Over the years, significant progress has been made in improving and integrating paediatric palliative care in the Netherlands (109). The first Dutch CPG for paediatric palliative care

contributed to the quality and organisation of palliative care for children with life-threatening and life-limiting conditions (109). Several years after the development of the first Dutch CPG for paediatric palliative care, health care providers, parents, and other stakeholders expressed the need for more guidance on specific topics that were not covered in the first CPG (such as palliative sedation and forgoing hydration and nutrition). This, together with the need to review evidence and build a stronger evidence-base from scientific literature, inspired the revision of the Dutch CPG for paediatric palliative care.

In this paper, we provide a complete overview of our methodology to revise the Dutch CPG for paediatric palliative care and give a brief presentation of the identified evidence. By sharing our methodology, we hope to promote transparency in CPG development and support others in developing approaches which we used to deal with expected challenges (multiple topics, lack of evidence, improve applicability and implementation) and unexpected challenges (high workload).

First, we used an evidence-based approach to revise the Dutch CPG for paediatric palliative care. We expected this would be challenging, as we chose to include a total of 38 clinical questions covering 16 topics related to paediatric palliative care. Therefore, we developed an approach that prevented unmanageable amounts of work without compromising quality. We decided to update existing systematic literature searches and mainly focus on high quality evidence. For all clinical questions on paediatric palliative care interventions, we updated the systematic literature search that was used in the first CPG to identify quantitative evidence (RCTs/CCTs and SRs of RCTs) on all paediatric palliative care interventions. For the clinical question on barriers and facilitators of advance care planning and shared decision-making, we updated the systematic literature search to identify qualitative evidence. This search was originally developed by the NICE guideline 'End of life care for infants, children and young people with life-limiting conditions: planning and management' (12). By re-using evidence from previous systematic literature searches and combine it with new identified evidence, we were able to formulate a large set of recommendations

Additionally, we developed an approach to deal with the lack of evidence. As the systematic literature search that was conducted for the first CPG identified little evidence, we expected a lack of evidence for the update as well. To deal with this challenge, we decided to search for additional literature sources to base recommendations upon. We used textbooks on paediatric palliative care, and guidelines on paediatric palliative care, general paediatrics, and adult paediatric palliative care and SRs of observational, qualitative, or mixed-method studies. Additional literature was selected according to its relevance.

Moreover, as stakeholders expressed a need for more guidance on certain topics related to paediatric palliative care, we created an approach to further improve applicability as well as implementation of this guideline. Therefore, we decided to not only focus on

physical aspects (symptom relief), decision-making, and organisation of care but also on other topics such as advance care planning, psychological, social, and spiritual support, and loss and bereavement. These topics are increasingly recognised as important within paediatric palliative care (109). Furthermore, the selected topics are based on priorities of health care providers and parents. As a result, we believe this increases the likelihood that the recommendations of this guideline will be applied in practice.

To further improve dissemination and implementation of the guideline, we collaborated with many stakeholders including health care providers from multiple disciplines and parent representatives. It has been shown that patient values improve quality of CPGs and is invaluable (110). Therefore, parent representatives have been involved in different ways throughout the entire guideline process, which ensures representation of patients and their families. Additionally, this guideline is approved by all relevant professional and patient associations in the Netherlands, meaning that these associations consider the CPG as a standard for provision of paediatric palliative care. Ultimately, we believe that this approach will lead to increased dissemination and implementation of the revised CPG among health care providers, parents, and children.

The revision of this guideline entailed a significantly greater amount of effort than we initially anticipated due to time-intensive tasks such as the selection and appraisal of evidence, and instruction and motivation of all guideline panel members. We appointed one researcher who coordinated the entire guideline development process on a fulltime basis for more than three years. This approach turned out to be very beneficial as it improved collaboration between all guideline panel members and contributed to a smooth process as issues were timely addressed. We therefore highly recommend others to adopt this approach, especially in situations where lack of time and resources might be an issue.

Unfortunately, despite our efforts to deal with (un)expected challenges, we found that there are still many knowledge gaps in paediatric palliative care for children. We identified no evidence for 24 out of 38 clinical questions, mainly including questions on (refractory) symptoms. It should be noted that we included evidence from 1970 to 2020. Therefore, it is plausible that we missed some recently published evidence. However, based on the little studies we found in a large time frame; it is plausible we miss only a small number of studies that most likely will not have a direct influence on our identified knowledge gaps. As a result, we emphasize the need for more high-quality research on paediatric palliative care interventions to further improve quality of care.

Furthermore, we acknowledge that we describe the methodology of a national CPG for paediatric palliative care. Although we use international evidence, our recommendations will be largely based on national clinical expertise and patient experiences due to identified knowledge gaps. Based on our previous experiences, we believe that the targeted recommendations we will provide in this guideline, will positively influence the further

integration of paediatric palliative care in the Netherlands. Moreover, as we used international evidence, we believe that a large proportion of provided recommendations, except recommendations that are specific for the Dutch context (organisation of care), will be applicable to other contexts and can be of great added value. Especially, since we provide a comprehensive set of recommendations for all children and their families in need of palliative care from beginning of diagnose till after the-end-life. However, country-specific factors such as availability of (non)pharmacological interventions, infrastructure, financial resources, and cultural backgrounds, should always be carefully considered before applying any recommendations in other contexts.

## **CONCLUSIONS**

We developed a transparent evidence-based methodology for the revision of the Dutch CPG for paediatric palliative care. Within this methodology, we developed approaches to deal with lack of evidence and improve applicability of the guideline by incorporating patient and family values and experiences throughout the entire guideline process. Our methodology combines existing evidence from scientific literature, additional literature, expert knowledge, and perspectives of patients and their families to formulate recommendations on all domains of paediatric palliative care (medical, psychological, social, and spiritual care). By using this methodology, we aim to develop the most comprehensive evidence-based guideline in paediatric palliative care.

## **SUPPLEMENTARY MATERIAL**

Additional files are available online (<https://doi.org/10.1186/s12904-024-01367-w>)

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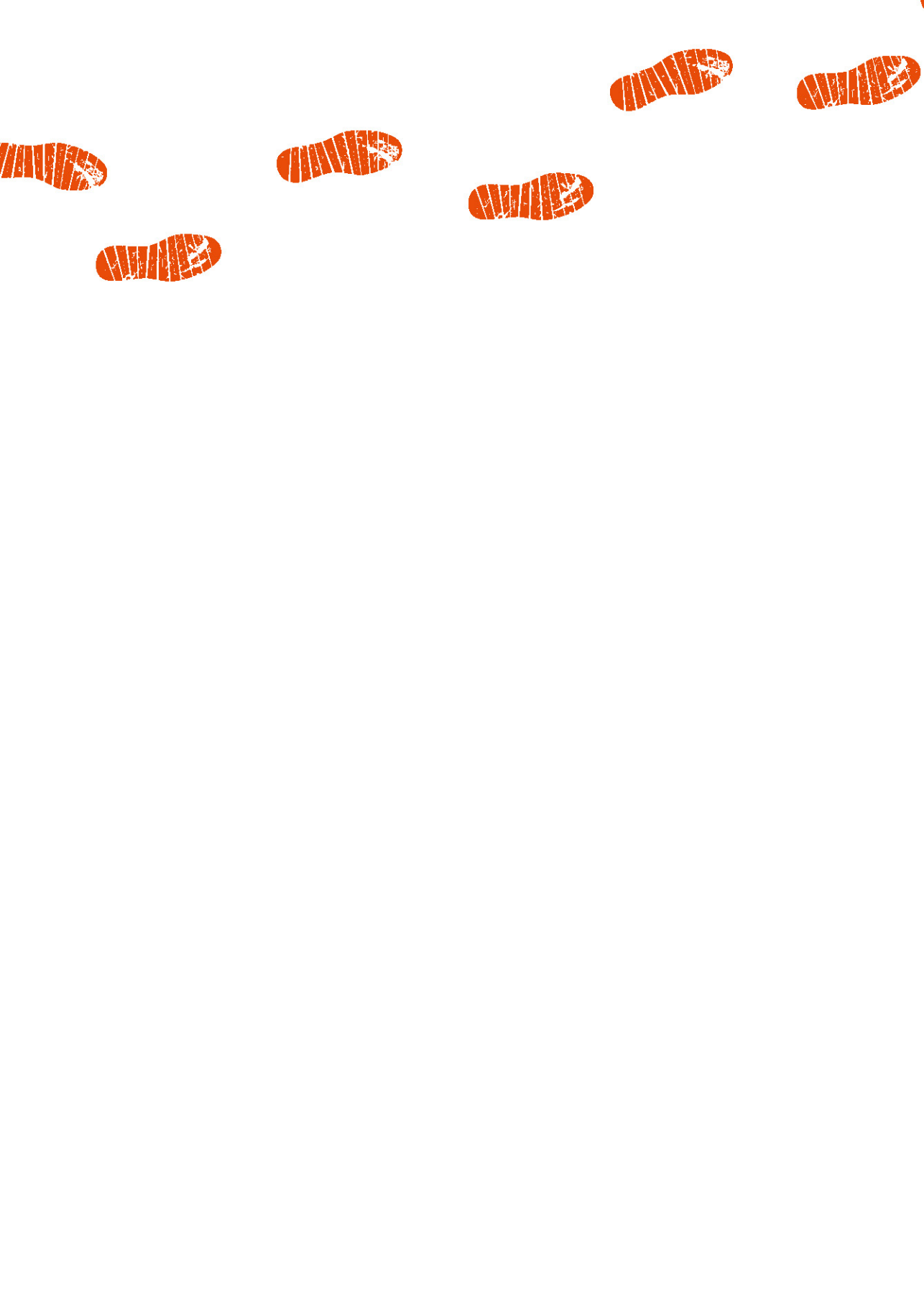
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# 3

## A Dutch paediatric palliative care guideline: a systematic review and evidence-based recommendations for symptom treatment

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## **ABSTRACT**

### **Background**

Children with life-threatening and life-limiting conditions can experience high levels of suffering due to multiple distressing symptoms that result in poor quality of life and increase risk of long-term distress in their family members. High quality symptom treatment is needed for all these children and their families, even more so at the end-of-life. In this paper, we provide evidence-based recommendations for symptom treatment in paediatric palliative patients to optimize care.

### **Methods**

A multidisciplinary panel of 56 experts in paediatric palliative care and nine (bereaved) parents was established to develop recommendations on symptom treatment in paediatric palliative care, including anxiety and depression, delirium, dyspnoea, haematological symptoms, coughing, skin complaints, nausea and vomiting, neurological symptoms, pain, death rattle, fatigue, paediatric palliative sedation and forgoing hydration and nutrition. Recommendations were based on evidence from a systematic literature search, additional literature sources (such as guidelines), clinical expertise, and patient and family values. We used the GRADE methodology for appraisal of evidence. Parents were included in the guideline panel to ensure the representation of patient and family values.

### **Results**

We included a total of 18 studies that reported on the effects of specific (non) pharmacological interventions to treat symptoms in paediatric palliative care. A few of these interventions showed significant improvement in symptom relief. This evidence could only (partly) answer eight out of 27 clinical questions. We included 29 guidelines and two textbooks as additional literature to deal with lack of evidence. In total, we formulated 221 recommendations on symptom treatment in paediatric palliative care based on evidence, additional literature, clinical expertise, and patient and family values.

### **Conclusion**

Even though available evidence on symptom-related paediatric palliative care interventions has increased, there still is a paucity of evidence in paediatric palliative care. We urge for international multidisciplinary multi-institutional collaboration to perform high-quality research and contribute to the optimization of symptom relief in palliative care for all children worldwide.

### **Keywords**

Clinical practice guideline, evidence-based medicine, paediatric palliative care, symptom treatment



## BACKGROUND

Worldwide, there are approximately 21 million children with conditions that can benefit from a palliative care approach (1). Of these children, more than eight million need specialized paediatric palliative care (1, 2). In the Netherlands, it is estimated that 7000 children, adolescents and young adults aged 0 to 20 years are living with life-threatening or life-limiting conditions and need palliative care (3). Approximately, 23% of these children are diagnosed with oncological conditions and 77% have complex chronic conditions such as neonatal, neurological, or metabolic disorders (4, 5). Annually, 1000 children die due to the consequences of these conditions (5). All these children and their families require paediatric palliative care that focuses on improving quality of life and alleviating physical, psychological, social, and spiritual suffering (6).

As all children with life-threatening or life-limiting conditions can experience multiple distressing symptoms, high quality symptom treatment is an essential component of paediatric palliative care (2). Previous international studies have reported high levels of suffering in children with cancer, complex chronic conditions, and advanced heart disease due to symptoms such as pain, dyspnoea, and fatigue (7-10). Parents reported that these symptoms, which are often amenable to treatment, are insufficiently controlled (9, 10). High levels of suffering due to symptoms decrease health-related quality of life in children and adolescents with life-threatening or life-limiting conditions (11, 12). Poor quality of life affects not only the child but the whole family including parents and siblings (8, 13). It also increases the risk of long-term distress in surviving family members (14). Clearly, there is room for improvement in easing distress due to symptoms in these children. This is even more evident at the end of life, when suffering tends to worsen and attempts to control symptoms with traditional symptom-directed interventions are more likely to be unsuccessful (10, 15).

High quality symptom treatment should be ensured for all children with life-threatening or life-limiting conditions and their families. Clinical Practice Guidelines (CPGs) are powerful instruments that can facilitate consistent, efficient, and high-quality care by translating evidence into recommendations for clinical practice (16-18). As a result, CPGs can contribute to the integration of high-quality palliative care into daily practice.

In 2013, the first Dutch CPG for Paediatric Palliative Care was published and provided the first recommendations on symptom treatment (19, 20). Almost a decade after the development of the first Dutch CPG for paediatric palliative care, stakeholders expressed the need for an update and expansion of the CPG. Most importantly, health care providers and parents requested guidance on symptom treatment including treatment of refractory symptoms at the end-of life. Additionally, recommendations needed to be updated with evidence from new scientific literature. As a result, the first Dutch CPG for Paediatric

Palliative care is revised and updated with recommendations on topics that were not covered in the first CPG (21).

The revised CPG provides recommendations on symptom treatment, advance care planning, shared decision-making, organisation of care, psychosocial care, and loss and bereavement care (21). In this paper, we present the recommendations on symptom treatment and give an overview of the most recent evidence that was used to base recommendations upon. The recommendations on advance care planning, shared decision-making, and organisation of care; and psychosocial care and loss and bereavement care will be presented in two subsequent papers.

## **METHODS**

The full methodology of the Dutch CPG for paediatric palliative care has been published in a separate paper (22).

### **Scope**

This guideline provides guidance on palliative care for all children aged 0 to 18 years with life-threatening or life-limiting conditions, their caregivers, and siblings (hereafter referred to as families) throughout the entire palliative trajectory (from palliative diagnosis till after end-of-life), with the ultimate goal to improve quality of palliative care and thereby quality of life of children and their families (6). In this paper we provide recommendations for symptom treatment.

### **Multidisciplinary guideline development panel**

The guideline development panel consisted of an expert panel of 56 professionals with expertise in paediatric palliative care and a panel of nine (bereaved) parents (Appendix A). Professionals from multiple disciplines such as psychologists, neurologists, paediatricians, nurse practitioners, dermatologists, anaesthesiologists, intensivists, physical and occupational therapists, and specialists in paediatric rehabilitation and intellectual disabilities were included in the guideline panel. Professionals were selected based on their experience with paediatric palliative care, of whom some had specific certified training in this field. Within the guideline development panel, a core group of 11 experts was established to ensure consistency throughout the guideline. The other 45 experts were appointed to working groups (WGs) that focused on symptom treatment (WG 1) and refractory symptom treatment (WG 2). WGs covered multiple topics for which sub-WGs were established. WG 1 consisted of 11 sub-WGs that focused on non-pharmacological and pharmacological interventions of anxiety and depression, delirium, dyspnoea, haematological symptoms, coughing, skin complaints, nausea and vomiting, neurological symptoms, pain, death rattle, and fatigue. WG 2 focused on paediatric palliative sedation and forgoing hydration and nutrition. All topics were selected based on priorities of health care providers and

parents (22). An overview of the working structure and guideline development process is shown in Appendix B and C.

### **Representation of patients and their families**

Different methods were used to include perspectives of children and their families (22). Two members of the core group were dedicated to ensure representation of child and family and their values during the entire guideline process. Additionally, a diverse panel consisting of nine (bereaved) parents of children with life-threatening or life-limiting conditions reviewed the first drafts of all guideline texts and recommendations and reviewed the complete concept guideline. We ensured that the panel represented a broad spectrum of experiences regarding paediatric palliative care by including parents of children with a variety of palliative conditions, age, and stage of disease (currently receiving palliative care or deceased).

### **Formulation of clinical questions**

The two WGs formulated a total of 27 clinical questions (Appendix D). WG1 formulated 24 clinical questions on the effect non-pharmacological and pharmacological interventions for symptom treatment. WG 2 formulated three clinical questions that focused on the effect of paediatric palliative sedation and the effect of forgoing hydration and nutrition.

### **Search strategy and selection criteria**

For the 27 clinical questions, we updated the literature search that was conducted for the former CPG (2013)(19) identifying randomized controlled trials (RCTs), controlled clinical trials (CCTs), or systematic reviews (SRs) of RCTs and CCTs on paediatric palliative care interventions (last update, January 24, 2020) (Appendix E). Studies were selected according to inclusion criteria related to study design (RCTs, CCTs, SRs of RCTs and CCTs), study population (children aged 0 to 18 with a life-threatening or life-limiting condition, according to the definition of the World Health Organization (6)) and study subject (paediatric palliative care interventions related to symptom treatment). Only studies published in English or Dutch language were included. Studies that described interventions on complementary or alternative medicine were excluded (Appendix F). We also searched for eligible studies in reference lists of included studies and identified SRs, guidelines, and textbooks. Moreover, we asked WG members to provide eligible studies.

### **Summary and appraisal of evidence**

To answer the clinical questions, we summarized included studies in evidence tables. We categorized evidence by outcome measures in summary of findings tables. Then, we formulated conclusions of evidence for each outcome measure. The quality of the total body of evidence was graded using the Grading of Recommendations Assessment,

Development, and Evaluation (GRADE) method (22). Study selection, summary and appraisal of evidence and formulation of conclusions was performed by one independent reviewer (22). All processes were checked by members of the core group. In case the systematic literature search would yield little to no evidence, we searched for textbooks on paediatric palliative care and existing evidence-based guidelines on general paediatrics, and paediatric and adult palliative care in several guideline databases (Appendix E). Textbooks and guidelines were included if they were deemed relevant for the topics addressed in the (sub)WGs (Appendix F). We used textbooks and recommendations from guidelines to refine considerations and recommendations for this guideline.

### **Translating evidence into recommendations**

When translating the evidence into recommendations, several factors were taken into account: (1) the quality of the evidence (the higher the quality of evidence, the more likely it is to formulate a strong recommendation), (2) additional literature including textbooks and guidelines, (3) patient and family values and needs (4) clinical expertise, (5) acceptability (legal and ethical considerations), (6) feasibility (sufficient time, knowledge, and manpower) and (7) benefits versus harms of the interventions. For each clinical question, WG members described the relevant considerations. Decisions regarding the final formulation of the recommendations were made through group consensus.

The strength of each recommendation was graded according to published evidence-based methods (appendix G)(23, 24). Recommendations were categorised as strong to do (green), moderate to do (yellow) or strong not to do (red).

## **RESULTS**

### **Identification of evidence and additional literature**

The systematic search for RCTs, CCTs and SRs of RCTs and CCTs on paediatric palliative care interventions yielded 5078 studies of which 168 were subjected to full-text screening. A total of 18 studies (three SRs of RCTs and 15 RCTs) on non-pharmacological and pharmacological interventions to treat symptoms were included (Appendix H). Furthermore, we included two textbooks, and 29 CPGs (six paediatric palliative care CPGs, 11 general paediatric CPGs and 12 adult palliative care CPGs) as additional literature to deal with lack of evidence (Appendix I).

#### ***Evidence***

The evidence tables and summary of findings tables are presented in Appendix J and K and the conclusions of evidence are shown in Table 1.

Studies reported on the effects of the following specific interventions: non-invasive ventilation (25) and high intensity training (26) for dyspnoea; erythropoietin for anaemia

(haematological symptoms) (27, 28); naloxone for pruritus (skin complaints) (29); self-hypnosis (30) and anti-emetics including ondansetron (31-33), metoclopramide (33), granisetron (34, 35), tropisetron (35), aprepitant (36), midazolam (37) and dexamethasone (37) for nausea and vomiting; botulinum toxin-A injections and occupational therapy (38, 39) for spasticity (neurological symptoms); and psychological interventions for parents including cognitive behavioural therapy, family therapy, problem-solving therapy and multi-systemic therapy (40) and adjuvant medication including intrathecal baclofen, botulinum toxin A injections, oral alendronate, oral risedronate and intravenous pamidronate (41) for pain.

A few interventions showed significant improvement in relief of symptoms or quality of life among children with life-threatening or life-limiting conditions. Non-invasive ventilation and high intensity training significantly improved exercise capacity in children with cystic fibrosis (very low quality evidence) (25, 26). One study showed that treatment with naloxone significantly decreased incidence of pruritus in children who received opioids postoperatively (very low quality evidence). Regarding nausea and vomiting, self-hypnosis significantly decreased supplemental anti-emetic medication use and anticipatory nausea in children with cancer (very low quality evidence) (30). In addition, most anti-emetic medication including ondansetron, granisetron, aprepitant, midazolam and dexamethasone significantly decreased the incidence of emetic episodes and/or nausea severity (very low to moderate quality evidence) (31-37). Concerning interventions for neurological symptoms, botulinum toxin-A injections significantly decreased spasticity levels of upper limbs and significantly increased parent-reported efficacy in children with cerebral palsy (very low to low quality evidence) (38, 39). Furthermore, cognitive behavioural therapy for parents significantly decreased child symptoms including pain in children with chronic illnesses (very low quality evidence) (40). Additionally, oral alendronate decreased pain in children with osteogenesis imperfecta (low quality evidence) (41).

For other interventions no significant effects were found. This included treatment with erythropoietin to improve anaemia in children with cancer (low quality evidence) (27, 28). Regarding pain in children with chronic illnesses, no significant effect was found for family therapy, problem-solving therapy, and multi-systemic therapy for parents which aimed to improve child symptoms (very low to low quality evidence) (40). Also, botulinum toxin A injections, oral risedronate, and intravenous pamidronate did not significantly decrease pain (very low to low quality evidence) (41). Furthermore, the effect of opioids on cancer-related pain remains unknown, as the systematic review did not identify any studies on this topic (42).

### ***Additional literature***

Because there was limited evidence on paediatric palliative care interventions, we identified additional literature. The relevant recommendations from 29 guidelines on paediatric

palliative care, general paediatrics and adult paediatric palliative care (43-71) and the textbooks (72, 73) on paediatric palliative care were used to refine considerations and recommendations.

**Table 1.** Conclusions of evidence on symptom treatment in paediatric palliative care

<b>Effect of (non) pharmacological interventions for symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions</b>	
<b>Anxiety and depression</b>	<b>Quality of evidence</b>
Unknown effect of nonpharmacological and pharmacological treatment	No studies
<b>Delirium</b>	<b>Quality of evidence</b>
Unknown effect of nonpharmacological and pharmacological treatment (preventive treatment, antipsychotics, and benzodiazepines)	No studies
<b>Dyspnoea</b>	<b>Quality of evidence</b>
Walking with non-invasive ventilation vs. walking without non-invasive ventilation in children with cystic fibrosis	⊕⊕⊕⊕ VERY LOW (1RCT) (25)
No significant effect on <i>degree of dyspnoea</i>	
↑ <i>exercise capacity</i> (walking distance; no significant effect on peripheral oxygen saturation, heart rate, respiratory rate)	
↑ <i>pulmonary function</i> (forced expiratory volume in the first second, minute volume, tidal volume, and pulmonary ribcage volume; no significant effect on other parameters)	⊕⊕⊕⊕ VERY LOW (1RCT) (26)
High intensity training vs. low intensity training in children with cystic fibrosis	
No significant effect on <i>degree of dyspnoea</i>	
↑ <i>exercise capacity</i> (inspirational muscle endurance; no significant effect on other parameters)	⊕⊕⊕⊕ VERY LOW (1RCT) (26)
No significant effect on <i>pulmonary function</i> (forced expiratory volume in the first second and forced vital capacity)	
Unknown effect of other nonpharmacological treatment (physical therapy, ventilator use, oxygen, relaxation, and distraction techniques) and pharmacological treatment (opioids, benzodiazepines, corticosteroids, dilators and mucolytics)	No studies
<b>Haematological symptoms</b>	<b>Quality of evidence</b>
Erythropoietin (Epoetin Alfa) vs. no treatment or placebo in children with cancer	⊕⊕⊕⊕ LOW (2 RCTs) (27, 28)
No significant effect on <i>haemoglobin levels</i> (in one study, haemoglobin levels did increase in the intervention group; no significant effect)	
No significant effect on the <i>number of required blood cell transfusions</i>	
Most common <i>adverse effects</i> in both intervention and control group were hypertension, fever, infection, and mucositis	⊕⊕⊕⊕ LOW (1RCT) (28)
Erythropoietin (Epoetin Alfa) vs. placebo in children with cancer	
No significant effect on <i>quality of life</i>	

Table 1. Continued

Effect of (non) pharmacological interventions for symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions	
Unknown effect of other pharmacological treatment for anaemia (vitamins, iron, and erythrocyte transfusions), pharmacological treatment for thrombocytopenia (thrombocyte transfusions), pharmacological treatment for bleeding, and pharmacological treatment for thrombosis	No studies
<b>Coughing</b>	<b>Quality of evidence</b>
Unknown effect of nonpharmacological (postural advice, physical therapy for sputum mobilization) and pharmacological treatment (non-opioids, opioids, nebulization with saline or cold steam)	No studies
<b>Skin complaints</b>	<b>Quality of evidence</b>
Naloxon infusion vs. placebo in children with post-operative opioid-induced side effects	⊕⊕⊕⊕ VERY LOW (1RCT) (29)
↓ <i>incidence of pruritus</i>	
Unknown effect of nonpharmacological treatment for pruritus and other pharmacological treatment for pruritus and pressure ulcers	No studies
<b>Nausea and vomiting</b>	<b>Quality of evidence</b>
Self-hypnosis vs. standard treatment with anti-emetics in children with cancer	⊕⊕⊕⊕ VERY LOW (1RCT) (30)
↓ <i>supplemental anti-emetic medication</i>	
no significant effect on <i>nausea and vomiting</i>	
↓ <i>anticipatory nausea</i> 1 to 2 months post diagnosis	
no significant effect on <i>anticipatory nausea</i> 4 to 6 months post diagnosis	
High dose ondansetron or low dose ondansetron vs. placebo in children with cancer	⊕⊕⊕⊕ MODERATE (1RCT) (31)
↓ <i>incidence emetic episodes</i> within 24h	
High dose ondansetron vs. low dose ondansetron	⊕⊕⊕⊕ MODERATE (2RCTs) (31, 32)
no significant effect on <i>incidence of emetic episodes</i> within 24h	
no significant effect on <i>nausea severity</i> within 24h	⊕⊕⊕⊕ VERY LOW (1RCT) (32)
High dose ondansetron + dexamethasone vs. low dose ondansetron + dexamethasone in children with cancer	⊕⊕⊕⊕ VERY LOW (1RCT) (32)
↓ <i>incidence of emetic episodes and nausea severity</i> within 24h	
Ondansetron vs. metoclopramide	⊕⊕⊕⊕ VERY LOW (1RCT) (33)
↓ <i>incidence of emetic episodes and nausea severity</i> within 24h	
↓ extrapyramidal symptoms as <i>adverse effect</i> after intervention	
Granisetron vs. ondansetron in children with cancer	⊕⊕⊕⊕ VERY LOW (1RCT) (34)
no significant effect on <i>incidence of emetic episodes and nausea severity</i> within 24h	
Most common reported <i>adverse effects</i> in both treatment groups was headache (unclear if significant difference).	

Table 1. Continued

<b>Effect of (non) pharmacological interventions for symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions</b>	
Granisetron vs. tropisetron in children with cancer	⊕⊕⊕⊕ VERY LOW (1RCT) (35)
↓ <i>incidence emetic episodes</i> and <i>nausea severity</i> within 24h	
Most common reported <i>adverse effects</i> in both treatment groups were headache and constipation.	
Aprepipant + dexamethasone + ondansetron vs. dexamethasone + ondansetron in children with cancer	⊕⊕⊕⊕ VERY LOW (1RCT) (36)
↓ <i>incidence emetic episodes</i> within 24h (unclear if significant)	
Midazolam vs. placebo; dexamethasone vs. placebo; midazolam + dexamethasone vs. placebo in children undergoing surgery	⊕⊕⊕⊕ VERY LOW (1RCT) (37)
↓ <i>incidence of emetic episodes</i> and <i>incidence of nausea</i> within 24h	
Midazolam vs. dexamethasone in children undergoing surgery	⊕⊕⊕⊕ VERY LOW (1RCT) (37)
↓ <i>incidence of emetic episodes</i> within 24h	
no significant effect on <i>incidence of nausea</i> within 24h	
<b>Neurological symptoms</b>	<b>Quality of evidence</b>
Botulinum Toxin-A injections and occupational therapy (OT) vs. OT (and intramuscular sham) in children with cerebral palsy	⊕⊕⊕⊕ LOW (2RCTs) (38, 39)
↑ <i>parent-reported treatment efficacy</i> (long-term effect might be dependent on the number of injections)	
Botulinum Toxin-A injections and OT vs. OT in children with cerebral palsy	⊕⊕⊕⊕ VERY LOW (1RCT) (38)
↓ <i>spasticity levels of upper limbs</i> (forearm and wrists)	
No significant effect on <i>motor performance</i>	
Botulinum Toxin-A injections and OT vs. intramuscular sham and OT in children with cerebral palsy	⊕⊕⊕⊕ VERY LOW (1RCT) (39)
No significant effect on <i>quality of life</i>	
Unknown effect of nonpharmacological treatment for spasticity (physical therapy and OT), and other pharmacological treatment for spasticity (baclofen, benzodiazepines)	No studies
Unknown effect of nonpharmacological treatment for epilepsy (ketogenic diet and psychological interventions) and pharmacological treatment for epilepsy (seizure treatment, seizure maintenance treatment, and refractory epilepsy treatment)	No studies
Unknown effect of (non)pharmacological for movement disorders	No studies
Unknown effect of (non)pharmacological treatment for neurological deficits (bothersome or troublesome double vision, incomplete closing of the eyes, visual hallucinations, hearing problems, swallowing difficulties, problems with talking, loss of strength and urinary retention)	No studies



Table 1. Continued

Effect of (non) pharmacological interventions for symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions	
Pain	Quality of evidence
Cognitive behavioural therapy vs. control in children with chronic illness (painful conditions, cancer, diabetes, asthma, traumatic brain injury)	⊕⊕⊕⊕ VERY LOW (12 RCTs) (40)
↓ <i>child symptoms (post-treatment)</i>	
No significant effect on <i>child symptoms (follow-up)</i>	⊕⊕⊕⊕ VERY LOW (7 RCTs) (40)
Family therapy for parents vs. control in children with chronic illness (painful conditions, cancer, diabetes, asthma, traumatic brain injury)	⊕⊕⊕⊕ LOW (5 RCTs)(40)
No significant effect on <i>child symptoms (post-treatment)</i>	
No significant effect on <i>child symptoms (follow-up)</i>	⊕⊕⊕⊕ VERY LOW (2 RCTs) (40)
Problem-solving therapy for parents vs. control in children with chronic illness (painful conditions, cancer, diabetes, asthma, traumatic brain injury)	⊕⊕⊕⊕ LOW (2 RCTs) (40)
No significant effect on <i>child symptoms (post-treatment)</i>	
Multi-systemic therapy for parents vs. control	⊕⊕⊕⊕ VERY LOW (4 RCTs) (40)
No significant effect on <i>child symptoms (post-treatment)</i>	
No significant effect on <i>child symptoms (follow-up)</i>	⊕⊕⊕⊕ LOW (2 RCTs) (40)
Intrathecal baclofen vs. placebo or therapy as normal in children with cerebral palsy	
↓ <i>pain</i>	⊕⊕⊕⊕ VERY LOW (3 RCTs) (41)
Most common <i>adverse effects</i> in both intervention and control group were related to Cerebrospinal Fluid Leakage	
Botulinum toxin A injections (with OT) vs. placebo or OT only in children with cerebral palsy	
No significant effect on <i>pain</i>	VERY LOW (2 RCTs) (41)
Most common <i>adverse effects</i> in both intervention and control group were seizures and respiratory symptoms	
Oral alendronate vs. placebo in children with osteogenesis imperfecta	
↓ <i>pain</i> (significant effect in one study)	⊕⊕⊕⊕ LOW (2 RCTs) (41)
Most common <i>adverse effects</i> in both intervention and control group were gastrointestinal symptoms.	
Oral risedronate vs. placebo in children with osteogenesis imperfecta	
No significant effect on <i>pain</i>	⊕⊕⊕⊕ LOW (1 RCT) (41)
No significant effect on <i>adverse effects</i>	

**Table 1.** Continued

<b>Effect of (non) pharmacological interventions for symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions</b>	
Intravenous pamidronate vs. placebo in children with osteogenesis imperfecta	VERY LOW (1 RCT) (41)
No significant effect on <i>pain</i>	
<i>Adverse effects</i> included acute phase reactions during first infusion cycle	
Unknown effect of other nonpharmacological treatment (psychological interventions, and complementary and alternative therapies) and other pharmacological treatment (opioids, non-opioids, and adjuvant analgesics)	No studies <sup>a</sup>
<b>Death rattle</b>	<b>Quality of evidence</b>
Unknown effect of nonpharmacological treatment (suctioning, postural advice, reducing fluid intake) and pharmacological treatment (anticholinergic agents)	No studies
<b>Fatigue</b>	<b>Quality of evidence</b>
Unknown effect of nonpharmacological treatment (psycho-education, lifestyle counselling, physical exercise, nutrition, sleep, and sleep hygiene) and pharmacological treatment	No studies
<b>Palliative sedation and forgoing hydration and/or nutrition</b>	<b>Quality of evidence</b>
Unknown effect of continuous or acute palliative sedation and forgoing hydration and/or nutrition	No studies

*a. In the systematic review of Wiffen et al., no evidence on the effect of opioids on cancer-related pain was identified (42).*

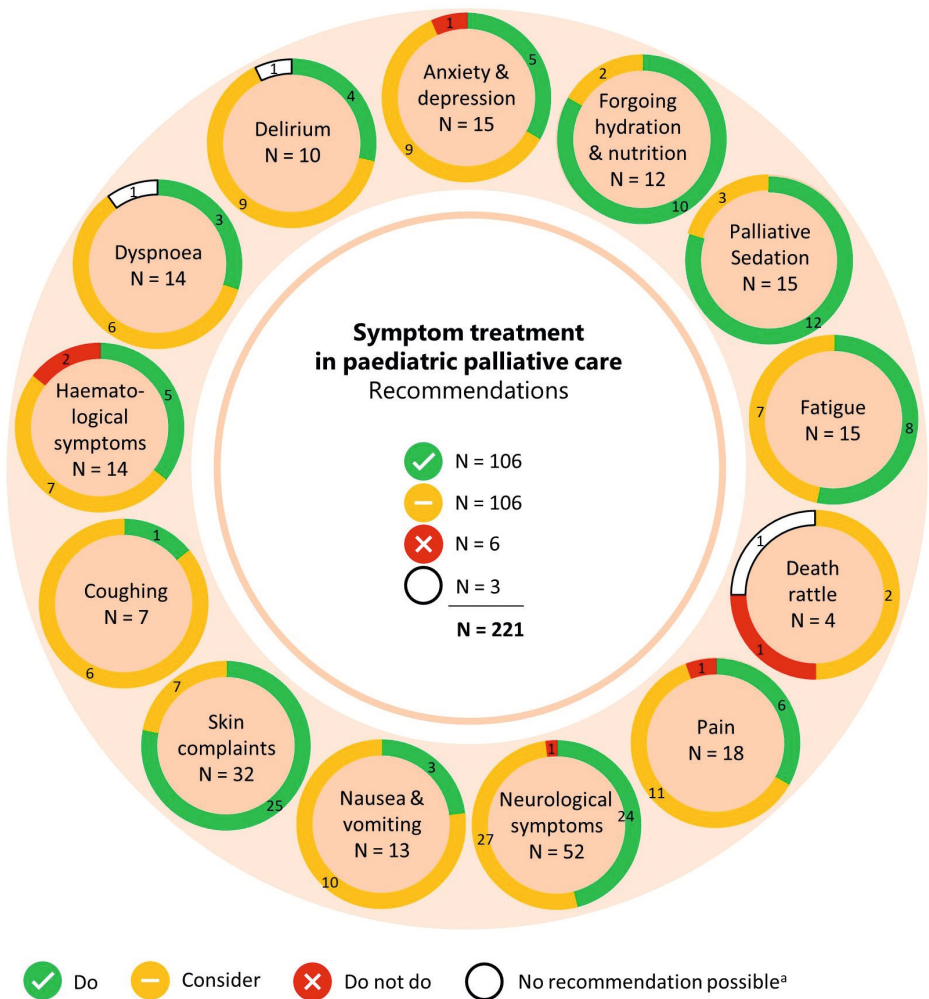
## Translating evidence into recommendations

Recommendations were based upon the evidence, additional literature, clinical expertise, patient and family values, and other considerations such as costs and availability of medication. All members of the guideline development panel agreed that quality of life and values and needs of the child and family should be the main focus of every treatment-related decision. This was the starting point in the process of formulating recommendations.

Clinical experts, patient representatives and parents identified other key aspects that frequently influenced treatment-related recommendations. In addition to the treatment effects, the expected burden of treatment on the child was considered. Physical therapy techniques, for instance, can help to relief suffering due to coughing but are physically challenging and can only be considered if the child is willing and able to perform these techniques. Moreover, the adverse effects of potential interventions were considered. For example, starting antipsychotics to treat delirium carry a high risk of adverse effects (70). Health care providers should be aware of these adverse effects of antipsychotics and monitor daily. If adverse effects occur, other medication should be considered. Finally, the child's life-expectancy or prognosis is of importance. For example, vitamins and nutritional supplements should not be given to children with anaemia if life expectancy is short.

When formulating recommendations on paediatric palliative sedation and forgoing hydration and nutrition, clinical experts and parent representatives acknowledged the importance of thoughtful communication and careful preparation of all processes related to end-of-life care. Therefore, recommendations on refractory symptom treatment covered the entire process of paediatric palliative sedation and forgoing hydration and nutrition including communication, preparation, execution, and evaluation.

We formulated a total of 221 recommendations on (non-)pharmacological treatment of anxiety and depression, delirium, dyspnoea, haematological symptoms, coughing, skin complaints, neurological symptoms, pain, death rattle, fatigue, paediatric palliative sedation and forgoing hydration and nutrition. Based on the level of evidence and other factors such as patient and family values, clinical expertise, and benefits and harms of the intervention, we formulated 106 strong recommendations to do (green), 106 weak recommendations to consider (yellow) and six strong recommendations not to do (red). In three situations, there was insufficient evidence and lack of consensus among experts to determine whether the benefits of the specific intervention outweigh potential harms. As a result, it was not possible to formulate a recommendation. In Figure 1 we provide an overview of the number of recommendations on symptom treatment per topic. All recommendations are shown in Table 2 and Table 3.



**Figure 1.** Number and strength of recommendations on symptom treatment in paediatric palliative care

*a. It was not possible to formulate a recommendation due to insufficient evidence and lack of consensus among experts.*

**Table 2.** Recommendations on symptom treatment in paediatric palliative care

<b>Recommendations on (non)pharmacological symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions (n=194)<sup>a</sup></b>	
<b>Anxiety and depression</b>	
Nonpharmacological treatment of anxiety and depression	
<b>Do</b>	Provide psychoeducation about the symptoms.
	Organize a day/week structure with attention to rituals, emotion-focused activities and activities that are "as normal as possible" (recovery-oriented).
	Involve a registered psychosocial counsellor with experience in palliative care when deploying counselling or treatment.
<b>Consider</b>	For anxiety, consider engaging experts in self-management in the form of mindfulness, relaxation, self-hypnosis, or guided fantasy.
Pharmacological treatment of anxiety and depression	
<i>Pharmacological treatment for anxiety</i>	
<b>Do</b>	Discuss the use and initiation of medication with a child psychiatrist experienced in palliative care or a paediatrician.
	When initiating medication, consider whether supporting psychotherapy is appropriate and feasible.
<b>Consider</b>	For anxiety reduction in dying children, consider intranasal midazolam.
	For acute anxiety, consider intranasal midazolam or oral lorazepam.
	For acute anxiety in pediatric delirium or psychotic dysregulation, consider antipsychotics (risperidone, haloperidol).
<i>Pharmacological treatment for depression</i>	
<b>Consider</b>	Consider use of medication in consultation with a child psychiatrist experienced in palliative care or a paediatrician.
	When using medication, consider whether supportive psychological therapy is appropriate and feasible.
	For moderate to severe depression in children 8 years and older, consider fluoxetine.
	Consider SSRIs especially for children with cancer.
	Consider methylphenidate.
<b>Do not</b>	Do not administer TCAs because of the potential for serious adverse effects and the need for determinations of blood levels.
<b>Delirium</b>	
Nonpharmacological treatment of delirium	
<b>Do</b>	Deploy, whenever possible, non-medical interventions focused on prevention, orientation, communication, matching stimuli, and safety to treat paediatric delirium.
	Involve parents in the child's care as much as possible.
	Delirium is an intense experience for all involved. Provide adequate (after) care for the child and family, environment, and caregivers (in the form of training).

Table 2. Continued

<b>Recommendations on (non)pharmacological symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions (n=194)<sup>a</sup></b>	
Pharmacological treatment of delirium	
<i>Pharmacological treatment for prevention of paediatric delirium</i>	
NA <sup>b</sup>	Opinions on the use of drug treatment for prevention of paediatric delirium, for example with antipsychotics, cannot be substantiated due to lack of evidence.
<i>Antipsychotics (haloperidol, risperidone, and quetiapine)</i>	
Consider	In children with delirium, consider treatment with medication if non-drug interventions do not have a sufficiently rapid effect.
	Depending on the adverse effects profile, drug interactions and available routes of administration, a choice may be made between risperidone or haloperidol.
	In case of non-response or adverse reaction to first administered drug (haloperidol or risperidone), consider switching drugs or administering quetiapine.
	When starting antipsychotics, be alert to side effects including extrapyramidal symptoms and prolongation of QT interval.
	For severe acute dystonia as a side effect of medication requiring treatment, consider biperidene.
<i>Benzodiazepines</i>	
Consider	In children in the terminal phase with refractory delirium, consider palliative sedation.
<b>Dyspnoea</b>	
Nonpharmacological treatment of dyspnoea	
<i>High-intensity training</i>	
NA <sup>b</sup>	High-intensity training appears to have no effect on dyspnoea compared with low-intensity training. The application of high-intensity training cannot be substantiated. Therefore, giving a recommendation is not possible. <sup>c</sup>
<i>Physical therapy techniques</i>	
Do	Provide information and advice on breathing exercises and other physical therapy techniques (see also: Coughing - physical therapy techniques for sputum mobilisation).
Consider	Consider employing a physical therapist to apply physical therapy techniques, such as breathing exercises and alternating positions (see also: Coughing - physical therapy techniques for sputum mobilisation).
<i>Non-invasive ventilation</i>	
Consider	In cases of dyspnoea due to Cystic Fibrosis, consider non-invasive ventilation. <sup>c</sup>
<i>Use of a ventilator</i>	
Consider	Consider the use of a 'hand-held' fan to cool the face.
<i>Oxygen</i>	
Consider	Consider administering oxygen as a trial treatment. Stop administering oxygen if it does not work.

Table 2. Continued

<b>Recommendations on (non)pharmacological symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions (n=194)<sup>a</sup></b>	
<i>Relaxation and distraction techniques</i>	
<b>Do</b>	Create a calm environment.
<b>Consider</b>	Consider bringing in experts for self-hypnosis.
	Consider relaxation and distraction techniques and the use of comfort talk.
Pharmacological treatment of dyspnoea	
<i>Opioids and benzodiazepines</i>	
<b>Do</b>	Give fentanyl nasal spray intranasally for rapid treatment and anxiety reduction.
	Start morphine orally, intravenously, or subcutaneously if the shortness of breath causes discomfort.
<b>Consider</b>	Consider lorazepam or midazolam (in combination with morphine) to reduce perceived discomfort, especially if anxiety is also present.
<i>Corticosteroids, dilators and mucolytics</i>	
<b>Consider</b>	In cases of dyspnoea arising from airway swelling, atelectasis, or broncho-obstruction, consider dexamethasone, other steroids, pulmonary dilators or mucolytics.
<i>Treatment of refractory dyspnoea</i>	
<b>Consider</b>	In terminally ill children with refractory dyspnoea, consider palliative sedation.
<b>Haematological symptoms</b>	
Pharmacological treatment of anaemia	
<i>Erythropoietin</i>	
<b>Do not</b>	Do not give erythropoietin in chemotherapy-associated anaemia. <sup>c</sup>
<i>Vitamins &amp; iron</i>	
<b>Do not</b>	Do not give vitamins and nutritional supplements to treat anaemia if life expectancy is short.
<i>Erythrocyte transfusions</i>	
<b>Do</b>	In children with long-term anaemia with bone marrow failure (e.g., MDS) in the palliative phase, adopt an individual transfusion policy based on perceived quality of life.
	In hematologic children with anaemia based on bone marrow failure, give erythrocyte transfusion on an individual basis at an Hb between 4.3-5.0 mmol/L or with symptoms of anaemia.

**Table 2.** Continued

<b>Recommendations on (non)pharmacological symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions (n=194)<sup>a</sup></b>	
Pharmacological treatment of thrombocytopenia	
<i>Thrombocyte transfusions</i>	
<b>Do</b>	Adhere to the platelet limits from the national transfusion guideline in palliative procedures (such as placement of an epidural catheter).
<b>Consider</b>	<p>In children with thrombocytopenia due to production disorder, consider adhering to the transfusion limits from the national transfusion guideline:</p> <ul style="list-style-type: none"> <li>• a prophylactic platelet transfusion in case of a platelet count lower than <math>10 \times 10^9/L</math>. in case of a WHO grade 2 haemorrhages, a thrombocyte transfusion in case of platelets lower than <math>30 \times 10^9/L</math>.</li> <li>• with bleeding WHO grade 3 or 4 a platelet transfusion with platelets lower than <math>100 \times 10^9/L</math>.</li> </ul> <p>Before a particular physical activity with risk of bleeding, consider a platelet transfusion</p>
Pharmacological treatment of bleeding	
<b>Do</b>	Treat nasal bleeding with local adrenaline, xylometazoline, spongostan or possibly local coagulation by ENT physician.
	Consult with a paediatric surgeon when local bleeding cannot be easily stopped.
<b>Consider</b>	<p>In bleeding due to thrombocytopathy, consider desmopressin (DDAVP).</p> <p>For persistent or severe bleeding tendency due to coagulation factor deficiency, consider vitamin K, FFP and/or recombinant factor VII.</p> <p>In thrombocytopenia and mucosal bleeding (nasal, gum bleeding, menorrhagia) anti-fibrinolytic medication to reduce bleeding tendency. Do not give fibrinolytic drugs in haematuria.</p> <p>If bleeding occurs, consider platelet transfusion: see section on platelet transfusion.</p>
Pharmacological treatment of thrombosis	
<b>Consider</b>	Consider giving a direct-acting oral anticoagulants (DOAC) for symptomatic thrombosis.
<b>Coughing</b>	
Nonpharmacological treatment of coughing	
<i>Postural advice</i>	
<b>Consider</b>	If coughing is productive, consider placing the child in a sitting or standing position.
<i>Physical therapy techniques for sputum mobilization</i>	
<b>Consider</b>	<p>Apply physical therapy techniques for sputum mobilization such as breathing exercises, air stacking, compression, cough machine 'cough assist', postural drainage, PEP, and huffing.</p> <p>Discuss with child and parents that physical therapy techniques should be discontinued if the child continues to weaken, and treatment becomes too burdensome.</p>



Table 2. Continued

Recommendations on (non)pharmacological symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions (n=194) <sup>a</sup>	
Pharmacological treatment of coughing	
<i>Non-opioids</i>	
<b>Consider</b>	If coughing is nocturnal, consider administering honey or dextromethorphan.
<i>Opioids</i>	
<b>Do</b>	Start opioids orally or parenteral if coughing causes discomfort. Here, morphine is the first choice.
<b>Consider</b>	Consider noscapine or codeine. Effect has not been demonstrated in cough.
<i>Nebulization with saline or cold steam</i>	
<b>Consider</b>	Consider nebulization with physiological or hypertonic saline or cold steam
<b>Skin complaints</b>	
Pressure ulcers	
Nonpharmacological treatment of pressure ulcers	
<b>Do</b>	Determine whether wound healing or symptom relief is the goal of treatment.
	Assess the wound for infection, pain, fragility, oedema, colour, odour, and deterioration
	Clean the wound (especially for yellow or black wounds and/or odour issues) by flushing with tap water once daily.
	Choose a wound dressing appropriate to the wound. Use the classification model in 'het WCS wondenboek' <sup>e</sup> (also available as an app) for this purpose, if necessary.
	Choose dressing materials that meet a wide range of requirements if more symptoms occur, such as odour, extreme exudate formation and bleeding tendency.
	Indicate rapidly occurring changes in the skin and respond to them promptly.
	Limit the smell of the wound by using: <ul style="list-style-type: none"> <li>• antiseptic agents</li> <li>• topical metronidazole gel</li> <li>• antimicrobial dressings</li> <li>• charcoal dressings</li> <li>• Use odour neutralizers such as cat litter or activated charcoal</li> </ul>
	If necessary, involve a (paediatric) physical therapist, occupational therapist, or medical device manufacturer in using assistive devices or making adjustments so that skin lesions are less stressed.
Pharmacological treatment of pressure ulcers	
<b>Consider</b>	Consider treatment of pain due to wounds
	Consider surgical debridement of necrotic tissue to promote wound healing and prevent/heal infections.

**Table 2.** Continued

<b>Recommendations on (non)pharmacological symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions (n=194)<sup>a</sup></b>	
Fungating wounds	
(Non)pharmacological treatment of fungating wounds	
Do	Provide clear information to child and family about fungating wounds. Explain that priority is given to the child's comfort and pay attention to the psychosocial consequences of the cancerous ulcer. Provide psychosocial and/or spiritual support if necessary.
	If possible, treat the underlying malignancy
	Clean the wound and care for it using wound dressings and locally or systemically administered medications.
	Treat factors that adversely affect the fungating wound, such as poor nutrition/hydration status, pressure spots, oedema formation.
Radiodermatitis	
(Non)pharmacological treatment of fungating wounds	
Do	Grade the degree of severity of radiodermatitis using the NCI/CTCAE table and tailor treatment accordingly.
Blisters and blister-related disorders	
(Non)pharmacological treatment of blisters and blister-related disorders	
Do	Determine the reason for blistering (exogenous or endogenous or a combination).
	Provide understandable information to child and family about the risks of fragile skin with blisters or skin with a tendency to blister.
	Prevent expansion of blistering by recognising and avoiding external factors as much as possible.
	Inspect the entire skin at least daily and record where the blistering is and where it is about to occur (often red or grey skin abnormalities).
	Make arrangements with any cooperating (multidisciplinary) healthcare provider regarding care for the prevention/treatment of blistering and consult or refer to a dermatologist/specialist in the field of blisters.
Itching	
Nonpharmacological treatment of itching	
Do	Take good care of the skin.
	Prevent skin irritation.
	Pay attention to mental well-being.
Consider	In children with itching, consider using ointments based on skin condition.
	In children with itching, consider complementary therapy, such as hypnosis.

Table 2. Continued

Recommendations on (non)pharmacological symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions (n=194) <sup>a</sup>	
Pharmacological treatment of itching	
<i>Local treatment</i>	
Do	Treat dry skin.
	In children with itching due to eczematous skin abnormalities, alternate cream with corticosteroids with a neutral cream. Preferably let cream with corticosteroids soak in for 30 min before applying oily ointment over it.
	In children with itching due to fungal infections, use topical antimycotics such as miconazole cream (2dd) or terbinafine cream (1dd).
	Use in children with itching due to bacterial infections, <ul style="list-style-type: none"> <li>• antibacterial agents such as chlorhexidine 0.5% in 70% alcohol with 1% glycerine 85% (chlorhexidine spirit FNA).</li> <li>• disinfectants such as disinfecting soaps or betadine scrub (dissolved and not applied directly to the skin, supplemented, if necessary, with fusidic acid ointment 2%).</li> <li>• hygienic measures (own towel).</li> </ul>
<i>Systemic treatment</i>	
Consider	Consider pharmacological treatment of itching depending on the cause, in accordance with the paediatric formulary.
	For itching due to cholestasis, consider stent placement for (bile) flow obstruction, naloxone (provided the child is not on opioids), colestyramine or ondansetron (be cautious in use). <sup>c</sup>
	For itching due to other causes or itching non-responsive to other agents, consider a sedative antihistamine.
<b>Nausea and vomiting</b>	
Nonpharmacological treatment of nausea and vomiting	
Do	Discuss with child and/or parents the role of nutrition and its possible change in relation to life expectancy.
	Educate about various options when fluids and nutrition are not well tolerated: <ul style="list-style-type: none"> <li>• Administering smaller portions of oral fluids.</li> <li>• Reduce total amount of nutrition.</li> <li>• Possibly administer tube feeding or parenteral fluids.</li> </ul>
	Provide relaxation and distraction, especially in situations involving anxiety.
Consider	Consider providing nutritional counselling. Involve a dietitian, if necessary.
	If the smell of food leads to symptoms, consider offering cold meals
	Consider having the child suck on ice cube, water ice, or frozen piece of fruit.
	In case of decreased gastric motility in children receiving tube feeding, consider, in consultation with an attending physician, a switch to semi-elemental nutrition or blended diet under the guidance of a dietitian.
	Consider self-hypnosis for nausea and vomiting in children with cancer. <sup>c</sup>

**Table 2.** Continued

<b>Recommendations on (non)pharmacological symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions (n=194)<sup>a</sup></b>	
Pharmacological treatment of nausea and vomiting	
<i>Nausea and vomiting with identifiable cause</i>	
<b>Consider</b>	The use of medication for nausea and vomiting requires a rational approach. Base the choice of medication on the main (probable) cause and the pharmacological properties of the medication.
<i>Nausea and vomiting with no apparent cause</i>	
<b>Consider</b>	For nausea and vomiting without identifiable cause or with insufficient effect of causative treatment, consider administration of antiemetics according to the step-by-step plan below (and deviate from the order if necessary):
Step 1	
<b>Consider</b>	Consider starting with: <ol style="list-style-type: none"> <li>1. A serotonin (5-HT<sub>3</sub>) antagonist, such as ondansetron<sup>d</sup>; and/or</li> <li>2. A dopamine (D<sub>2</sub>)-antagonist, such as domperidone or metoclopramide; and/or</li> <li>3. An antihistamine such as cyclizine.</li> </ol>
Step 2	
<b>Consider</b>	Consider adding or substituting agents from the first step with: <ol style="list-style-type: none"> <li>1. Dexamethasone.</li> <li>2. Granisetron (instead of ondansetron).</li> <li>3. Haloperidol (instead of domperidone or metoclopramide).</li> <li>4. Chlorpromazine or levomepromazine (instead of cyclizine).</li> </ol>
Step 3	
<b>Consider</b>	Consider adding: <ol style="list-style-type: none"> <li>1. Aprepitant.</li> <li>2. A cannabis preparation containing dronabinol in consultation with an expert.</li> </ol>
<b>Neurological symptoms</b>	
Epilepsy	
Nonpharmacological treatment of epilepsy	
<i>Ketogenic diet</i>	
<b>Consider</b>	In children with difficult-to-treat epilepsy, consider a ketogenic diet.
<i>Psychological interventions</i>	
<b>Consider</b>	In children with epilepsy, consider psychological interventions such as relaxation or cognitive behavioural therapy.

Table 2. Continued

Recommendations on (non)pharmacological symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions (n=194) <sup>a</sup>	
Pharmacological treatment of epilepsy	
<i>Seizure treatment</i>	
Do	In children known to have epilepsy, establish a seizure treatment plan and include any treatment restrictions.
	In children with first seizures: most seizures stop spontaneously within 2-3 minutes. After 3 minutes, give seizure treatment according to a step-by-step plan.
	Evaluate the effect after each step.
	If epilepsy cannot be controlled, consult with a pediatric neurologist.
<i>Maintenance treatment</i>	
Do	Initiate maintenance treatment with antiepileptic drugs if there are multiple seizures or if a seizure is highly likely to recur. Always do this in consultation with a pediatric neurologist.
Do not	Do not start preventive maintenance treatment with antiepileptic drugs in children with neurological disorders of the brain who do not have epileptic seizures
<i>Treatment of refractory epilepsy</i>	
Consider	In the case of a refractory form of epilepsy from which the child suffers, consider administration of intravenous anaesthetics.
Movement disorders	
Nonpharmacological treatment for movement disorders	
<i>Treatment aimed at reducing impairments due to movement disorders</i>	
Consider	Check for movement disorder luxating factors such as physical discomfort, constipation, bladder retention, inadequate rest, pain, and anxiety.
	Consider low-level consultation with a (pediatric) physical therapist, occupational therapist, or pediatric rehabilitation physician.
	Consider using assistive devices to help the child sit, stand or lie down as optimally as possible.
Pharmacological treatment for movement disorders	
Consider	In acute status dystonicus, consider biperiden. For other acute movement disorders, consult readily with a pediatric neurologist with expertise in movement disorders.
	In dystonia, consider treatment with baclofen, clonazepam, trihexyphenidyl or gabapentin.
	In focal dystonia, consider botulinum toxin A injections in consultation with a pediatric rehabilitation physician.
	In persistent status dystonia, consider a deep-brain stimulator (surgical).

**Table 2.** Continued

<b>Recommendations on (non)pharmacological symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions (n=194)<sup>a</sup></b>	
Spasticity	
Nonpharmacological treatment for spasticity	
<i>Physical therapy and/or occupational therapy</i>	
<b>Do</b>	Advise the child on optimal supported posture (in standing, sitting, and lying down) to promote the child's movement and performance of daily activities and prevent complications of spasticity.
<b>Consider</b>	Consider using assistive devices and orthoses/ splints to prevent complications due to spasticity and to support movement.
	Consider referral to a physical therapist, occupational therapist or rehabilitation physician for treatment and advice focused on (coping with the limitations due to) spasticity.
Pharmacological treatment for spasticity	
<i>Baclofen (oral/intrathecal)</i>	
<b>Do</b>	Consult with a pediatric neurologist or pediatric rehabilitation physician for drug options for treatment of spasticity.
<b>Consider</b>	Consider treatment with baclofen (oral) or in combination with Tizanidine.
	Consider an intrathecal baclofen pump.
<i>Benzodiazepines</i>	
<b>Do</b>	Consult with pediatric neurologist or pediatric rehabilitation physician for medication options for treatment of spasticity.
<b>Consider</b>	For acute painful muscle spasms, consider diazepam.
	Consider midazolam when there is a need for sedation or treatment of epilepsy.
<i>Botulinum toxin type A injections</i>	
<b>Consider</b>	In cases of localized spasticity, consider botulinum toxin type A injection in consultation with the rehabilitation physician. <sup>c</sup>
Neurological deficits	
Nonpharmacological and pharmacological treatment of neurological deficits	
<i>Bothersome or troublesome double vision</i>	
<b>Do</b>	Pay attention how the child should be approached.
<b>Consider</b>	Consider an eye patch or taping a lens.
<i>Incomplete closing of the eyes</i>	
<b>Do</b>	Drop methyl cellulose eye drops during the day.
	For sleeping, use oculentum simplex ointment and a watch glass plaster.
<b>Consider</b>	If redness of the eye occurs, consider more frequent drops and/or ointments, both with and without antibiotics.

Table 2. Continued

<b>Recommendations on (non)pharmacological symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions (n=194) <sup>a</sup></b>	
<i>Visual hallucinations</i>	
<b>Do</b>	Advise children to close their eyes briefly and then open them again.
	Provide good room lighting; this may reduce the likelihood of developing visual hallucinations.
<b>Consider</b>	Consider referral to a vision expertise centre to get targeted advice for how to deal with the visual problems.
<i>Hearing problems</i>	
<b>Do</b>	Make it known that you are present by touching or looking at the child.
	Talk calm and clearly.
	Avoid excessive ambient noise.
	Use visual support through text, pictures, or gestures.
<b>Consider</b>	Consider hearing aids or solo aids depending on the child's condition.
	Consider referral to an expertise centre on hearing problems to obtain practical advice on the management of hearing problems.
<i>Swallowing difficulties</i>	
<b>Do</b>	Provide optimal nutrition in terms of consistency; consider thickening beverages.
	Offer drinking with a straw or from an appropriate drinking cup.
	Provide breaks between sips to prevent choking.
	Monitor administration of medication and adjust the form of administration as needed.
<b>Consider</b>	Consider involving a speech therapist or occupational therapist for swallowing advice.
	To prevent aspiration or for adequate intake, consider a tube.
<i>Problems with talking</i>	
<b>Do</b>	Be alert to changes in communication abilities.
	Make best use of support in communication.
<b>Consider</b>	Consider guidance from a speech therapist (possibly along with an occupational therapist) for advice on supportive communication devices appropriate to the child's abilities.
<i>Loss of strength</i>	
<b>Consider</b>	Consider guidance from a (pediatric) physical therapist, occupational therapist, pediatric neurologist and/or pediatric rehabilitation physician.
<i>Urinary retention</i>	
<b>Do</b>	Be alert for spinal cord injury or other neurological symptoms in cases of urinary retention.
<b>Consider</b>	Consider placement of an indwelling catheter or intermittent catheterization.

**Table 2.** Continued

<b>Recommendations on (non)pharmacological symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions (n=194)<sup>a</sup></b>	
<b>Pain</b>	
Nonpharmacological treatment of pain	
<i>Complementary and alternative therapies</i>	
<b>Consider</b>	Consider the use of complementary therapies.
<i>Psychological interventions for children</i>	
<b>Consider</b>	Consider the use of psychological therapies for children. <sup>c</sup>
<i>Psychological interventions for parents</i>	
<b>Consider</b>	Consider cognitive behavioural therapy for parents. <sup>c</sup>
Pharmacological treatment of pain	
<i>Stepwise pain management</i>	
<b>Do</b>	Treat pain according to a set (time) schedule, through the most appropriate route and adapted to the child.
	Follow a stepwise approach to pain management, such as the WHO ladder.
	For complex pain problems, involve a pediatric palliative care team and/or a pain team.
<b>Do not</b>	Do not use codeine in children.
Step 1 - Non-opioids	
<b>Do</b>	Administer in case of mild to moderate pain, paracetamol, ibuprofen or a combination of paracetamol and ibuprofen.
Step 2 - opioids for severe pain	
<b>Do</b>	Administer morphine as first choice in case of severe pain.
<b>Consider</b>	In case of severe pain, consider administering opioids in consultation with a pediatric palliative care team and/or pain team, for example fentanyl, hydromorphone, oxycodone, or methadone.
Step 3- Adjuvant analgesics	
<b>Consider</b>	For specific conditions e.g., inflammation or oedema, consider corticosteroids.
	Consider administration of clonidine or ketamine. Consult with a pediatric palliative care team and/or pain team first.
<i>Neuropathic pain</i>	
<b>Do</b>	If neuropathic pain is suspected and standard analgesia is not efficient enough, involve a specialist from a pediatric palliative care team and/or pain team.
<b>Consider</b>	In case of neuropathic pain, consider tricyclic antidepressants such as amitriptyline.
	In case of neuropathic pain, consider anticonvulsants such as gabapentin.



Table 2. Continued

Recommendations on (non)pharmacological symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions (n=194) <sup>a</sup>	
<i>Adjuvant analgesia</i>	
Consider	In children with spastic palsy, consider implanting a baclofen pump. <sup>c</sup>
	In children with osteogenesis imperfecta, consider administering bisphosphonates. <sup>c</sup>
	If classical pain management is ineffective or pain is located at a specific site, consult early with an experienced pain team about the possibilities of an invasive pain management technique.
<b>Death rattle</b>	
Nonpharmacological treatment of death rattle	
<i>Suctioning</i>	
Do not	Avoid suctioning in the case of death rattle in the terminal phase given the additional discomfort.
<i>Postural advice</i>	
Consider	Consider lateral position and adjusting head positions when feasible.
<i>Reduce fluid intake</i>	
NA <sup>b</sup>	Recommendations to adjust the amount of fluid administered to prevent death rattle or facilitate coughing cannot be given due to lack of evidence. There appears to be no reason to include death rattle as a factor in determining terminal fluid management.
Pharmacological treatment of death rattle	
<i>Anticholinergic agents</i>	
Consider	Standard medication does not seem appropriate. Should relatives wish to do so, anticholinergic agents ((butyl)scopolamine, glycopyrronium, and atropine) may be considered.
<b>Fatigue</b>	
Nonpharmacological treatment of fatigue	
<i>Psycho education</i>	
Do	Provide psycho education focused on fatigue and strategies for coping with fatigue to the child and parents.
Consider	Consider referral to a health care provider or psychologist with expertise in treating fatigue.
<i>Lifestyle counselling focused on fatigue.</i>	
Do	Offer lifestyle advice aimed at fatigue in the areas of diet, exercise, and sleep.
	Emphasize the importance of balancing physical, mental activities, relaxation, and rest in a day.
Consider	In case of physical fatigue, cognitive fatigue, or functional limitations, consider referral to an occupational therapist for an intervention aimed at optimizing the balance between load and load capacity.

**Table 2.** Continued

<b>Recommendations on (non)pharmacological symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions (n=194)<sup>a</sup></b>	
<i>Physical exercise</i>	
<b>Do</b>	Advise the child to move daily (out of bed) according to individual (physical) capabilities (including bedridden children).
	If desired and physically possible, offer the child an exercise/training program supervised by the (pediatric) physical therapist.
<b>Consider</b>	Consider consultation or referral to a rehabilitation physician for an integrated (multidisciplinary) approach to fatigue and functional (physical) limitations.
<i>Nutrition</i>	
<b>Do</b>	Recommend nutrition with enough calories, protein, and other nutrients to support energy needs during (exercise) intervention.
<b>Consider</b>	Consider diagnosis and treatment of nutritional deficiencies because they may contribute to fatigue.
	Consider referral to a dietitian.
<i>Sleep and sleep hygiene</i>	
<b>Do</b>	Offer advice on sleep hygiene to create optimal conditions for good sleep.
<b>Consider</b>	Consider offering the child and parents, e-health interventions focused on fatigue.
<i>Pharmacological treatment of fatigue</i>	
<b>Do</b>	Keep in mind that there is no scientific evidence for drug treatment of fatigue. If there is any effect at all, the effect often wears off quickly.
<b>Consider</b>	Consider treatment with methylphenidate, for children with fatigue with limited life expectancy, or if treatment options are ineffective or if the aforementioned measures are not feasible. Keep in mind possible side effects.

- a. This table shows the recommendations on (non)pharmacological treatment of symptoms. We also formulated recommendations on diagnosis and evaluation of symptoms for which we did not systematically search in scientific literature. These recommendations are available on request.
- b. Not applicable, it was not possible to formulate a recommendation due to insufficient evidence and lack of consensus among experts.
- c. For this recommendation, very low to low quality evidence was identified.
- d. For this recommendation, moderate quality evidence was identified.
- e. Only available in Dutch.

**Table 3.** Recommendations on refractory symptom treatment in paediatric palliative care

<b>Recommendations on refractory symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions (n=27)</b>	
<b>Palliative sedation</b>	
Education and communication on palliative sedation	
<b>Do</b>	Introduce palliative sedation early during Advance Care Planning conversations in preparation for the last stage of life and at the child's dying stage.
	Check with the multidisciplinary team that all conditions for palliative sedation are met.
	Consult experts and/or paediatric palliative care teams about communication about palliative sedation and the implementation of palliative sedation.
	When palliative sedation has been decided upon, discuss the process of palliative sedation with the child, parents and/or loved ones. Pay attention to purpose of palliative sedation, course of the dying process, implementation of palliative sedation, and agreements between child, parents, and caregivers.
Effect of continuous palliative sedation	
<b>Do</b>	Use the step-by-step plan for the recommended agents and corresponding dosage schedule in continuous palliative sedation.
	If symptom-oriented medication (e.g., morphine) is given continuously parenterally, continue the symptom-oriented medication and the medication for the purpose of continuous palliative sedation via a separate pump to prevent unwanted increase in symptom-oriented medication when the dosage of sedatives is increased.
	In children with alcohol abuse, drug use and/or higher doses of psychopharmaceuticals (including chronic use of benzodiazepines with the indication of antiepileptic drugs), consult with paediatric palliative care team prior to palliative sedation.
	If in doubt or questions about necessary dosages, consult with a pediatric palliative care team.
<b>Consider</b>	In case of no or little effect of subcutaneous administration of midazolam and/or levomepromazine, consider switching to intravenous administration.
	When administering medication intravenously, consider administering boluses slowly over several minutes because of the risk of apnoea with some agents.
Effect of acute palliative sedation	
<b>Do</b>	Deploy acute palliative sedation when all of the following criteria are present: <ul style="list-style-type: none"> <li>• an acute life-threatening complication that cannot be treated causally or symptomatically.</li> <li>• the complication leads to unbearable suffering.</li> <li>• the child is expected to die within minutes/hours due to the complication.</li> </ul>
	Anticipate if acute complications are expected during the palliative phase by: <ul style="list-style-type: none"> <li>• discussing the possibility in advance with child, parents and/or loved ones.</li> <li>• creating a plan (available to all involved) for acute sedation if needed.</li> </ul>

**Table 3.** Continued

<b>Recommendations on refractory symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions (n=27)</b>	
Evaluation of palliative sedation	
<b>Do</b>	Evaluate the effect of palliative sedation after 30 minutes using comfort score and/or FLACC score and also pain score if pain is among the refractory symptoms. If in doubt whether the effect is sufficient, consider increasing the dose.
	If in doubt about medication/doses used, consult readily with a paediatric palliative care team.
<b>Consider</b>	In case of no or little effect of subcutaneous administration of midazolam and/or levomepromazine, consider switching to intravenous administration.
<b>Forgoing hydration and nutrition</b>	
<b>Do</b>	Include decision-making about not starting or discontinuing (artificial) fluids and/or nutrition in Advance Care Planning conversations.
	In preparation for the last phase of life, communicate with parents on the topic of (artificial) fluid and/or nutrition abstinence.
	Clarify with child (if possible) and parents that not starting, reducing, or discontinuing (artificial) fluids and/or nutrition at the end of life is part of the natural process.
	With refractory symptoms, weigh the pros and cons of not starting or discontinuing (artificial) fluids and/or nutrition.
	Reduce or discontinue (artificial) fluids and/or nutrition if the child experiences discomfort as a result. Continue to confirm that not starting or discontinuing (artificial) fluids and/or nutrition is in the child's best interest and that the child is not suffering extra.
	Discuss the joint assessment of signs of discomfort, whether based on a specific scale or not, and agree how to deal with it.
	In case of discomfort due to thirst/hunger, discuss to initiate additional sedation.
	Continue to give the child good lip and mouth care.
	Prepare parents for the changing appearance of the child.
	Document the policy around (artificial) fluids and/or feeding in the medical record and individual care plan.
<b>Consider</b>	Consider comfort feeding if (artificial) fluids and/or nutrition are not started or discontinued.
	Consider organizing training for caregivers on the responsibility and communication around not starting or discontinuing (artificial) fluids and/or nutrition in the terminal phase.

## DISCUSSION

Optimal treatment to relieve symptoms in children with life-threatening or life-limiting conditions is intense and challenging. Although progress has been made in improving and integrating paediatric palliative care in the Netherlands (4), health care providers, parents and other stakeholders have urged for more guidance to relieve physical suffering and ease distress in these children and their families. We responded to this need by developing

recommendations on symptom treatment, including anxiety and depression, delirium, dyspnoea, haematological symptoms, coughing, skin complaints, nausea and vomiting, neurological symptoms, pain, death rattle, fatigue, paediatric palliative sedation and forgoing hydration and nutrition, as part of the revised Dutch CPG for paediatric palliative care. With these recommendations we aim to optimize symptom treatment in paediatric palliative care in the Netherlands. Furthermore, these recommendations can be used in other countries to optimize symptom treatment on a global scale.

This study has multiple strengths. First of all, the selection of symptoms was based upon priorities of clinical experts and parents (22). This approach allowed us to provide recommendations on the symptoms that were most relevant to children with life-threatening or life-limiting conditions and their families. Furthermore, in this way, we were able to provide recommendations for a diverse group of children without limiting to a specific diagnosis. It should be noted that the selection of symptoms does not cover the full range of symptoms that may occur in paediatric palliative care. Still, our selection of symptoms is most comprehensive in comparison to other international guidelines on paediatric palliative care (66). Additionally, we introduce the first evidence-based recommendations on paediatric palliative sedation in Europe.

Second, our recommendations on symptom treatment are based on an evidence-based methodology, meaning that we systematically searched for RCTs, CCTs and SRs of RCTs and CCTs in scientific literature. We identified 18 studies reporting on effectivity of several non-pharmacological and pharmacological interventions to treat symptoms. We found that since the development of the first Dutch guideline in 2013, the number of studies on paediatric palliative care interventions has increased (19, 22). However, after allocating the studies to the relevant clinical questions, we concluded that the evidence could only (partly) answer eight out of 27 clinical questions. Also, the total body of evidence was rated as low to very low quality, mainly due to imprecision of effects (as a result of small number of participants) and potential risk of bias. For the other 19 clinical questions on effects of symptom treatment, we did not find evidence. Therefore, we developed a strategy to deal with this lack of evidence and included additional literature: 29 guidelines on paediatric palliative care, general paediatrics, and adult palliative care, and two textbooks on paediatric palliative care.

Finally, our recommendations are carefully developed according to a transparent and comprehensive guideline methodology (22). We closely collaborated with experts in paediatric palliative care from multiple disciplines and parents. The transparency and the interactive relationship between all stakeholders increased validity and trustworthiness of our guideline process and recommendations.

The recommendations within this guideline are based on national clinical expertise, patient perspectives, and international evidence. We believe that these targeted recommendations

on symptom treatment will be largely applicable to other contexts and can give guidance for symptom treatment in other countries as well. However, country-specific factors such as availability of non-pharmacological and pharmacological interventions, infrastructure, financial resources, and cultural backgrounds, should always be carefully considered before applying any recommendations in other contexts.

Unfortunately, we identified multiple gaps in knowledge for non-pharmacological and pharmacological interventions to treat symptoms (Table 4). Even though evidence on paediatric palliative care has increased there is still paucity in evidence on non-pharmacological and pharmacological interventions to treat symptoms (19, 74). However, it should be noted that these knowledge gaps are based on our search that focused on paediatric palliative care only. Extrapolating evidence from general paediatrics might fill some knowledge gaps for treatment of symptoms. On the other hand, it is acknowledged that paediatric palliative care requires expertise that is often lacking in general paediatrics (75). Extrapolating study results from general paediatrics is not always appropriate, so caution is needed when applying this evidence.

It is clear that more research is required to relieve symptom-related suffering and to ease distress in children and family members. Future research should focus on international, multidisciplinary, and multi-institutional collaboration to reach higher numbers of participants, to broaden the scope of study questions and also improve study quality. In this way, we can strengthen the evidence base of our guideline and contribute to the optimization symptom treatment in paediatric palliative care. Additionally, attention should be given to facilitate implementation of knowledge and guidelines in paediatric palliative care for the purpose of achieving sufficient symptom relief in children with life-threatening and life-limiting conditions (75). Furthermore, it should be noted that other factors such as access to financial resources and the organizational infrastructure of paediatric palliative care impact the quality of palliative care and differ among countries (2, 76). These factors should be addressed to achieve optimal symptom treatment in paediatric palliative care on a global scale.

**Table 4.** Knowledge gaps for symptom treatment in paediatric palliative care

Current knowledge gaps
<p>Effects of non-pharmacological interventions in palliative care for children aged 0 to 18 years with life-threatening and life-limiting conditions to treat:</p> <ul style="list-style-type: none"> <li>• Anxiety and depression (e.g., psycho education, mindfulness, relaxation, and self-hypnosis)</li> <li>• Delirium (e.g., interventions focused on prevention, orientation, and communication)</li> <li>• Dyspnoea (e.g., high intensity training, non-invasive ventilation, physical therapy, ventilator use, oxygen, and relaxation and distraction techniques)</li> <li>• Coughing (e.g., postural advice, and physical therapy for sputum mobilisation)</li> <li>• Skin complaints (e.g., psycho-education, and general skincare)</li> <li>• Nausea and vomiting (e.g., relaxation and distraction techniques, nutritional advice, self-hypnosis)</li> <li>• Neurological symptoms: <ul style="list-style-type: none"> <li>– Epilepsy (e.g., ketogenic diet, and psychological interventions)</li> <li>– Spasticity (e.g., physical therapy, and occupational therapy)</li> <li>– Movement disorders</li> <li>– Neurological deficits (e.g., bothersome or troublesome double vision, incomplete closing of the eyes, visual hallucination, hearing problems, swallowing difficulties, and problems with talking.</li> </ul> </li> <li>• Pain (e.g., psychological interventions for children, complementary and alternative therapies, psychological interventions for parents)</li> <li>• Death rattle (e.g., airway suctioning, and postural advice)</li> <li>• Fatigue (e.g., psycho education, lifestyle counselling, physical exercise, nutritional advice, and sleep hygiene)</li> </ul> <p>Effects of pharmacological interventions in palliative care for children aged 0 to 18 years with life-threatening and life-limiting conditions to treat:</p> <ul style="list-style-type: none"> <li>• Anxiety and depression (e.g., benzodiazepines, antipsychotics, and selective serotonin reuptake inhibitors)</li> <li>• Delirium (e.g., antipsychotics, and benzodiazepines)</li> <li>• Dyspnoea (e.g., opioids, benzodiazepines, corticosteroids, dilators, and mucolytics)</li> <li>• Haematological symptoms <ul style="list-style-type: none"> <li>– Anaemia (e.g., erythropoietin, vitamins, iron, erythrocyte transfusions)</li> <li>– Thrombocytopenia (e.g., thrombocyte transfusions)</li> <li>– Bleeding (e.g., adrenaline, xylometazoline, and antifibrinolytic medication)</li> <li>– Thrombosis (e.g., direct-acting oral anticoagulants)</li> </ul> </li> <li>• Coughing (e.g., non-opioids, opioids, nebulization with saline or cold steam)</li> <li>• Skin complaints: <ul style="list-style-type: none"> <li>– Pruritus (e.g., naloxone, and antihistamine)</li> <li>– Pressure ulcers (e.g., pain treatment, and surgical debridement of necrotic tissues)</li> </ul> </li> <li>• Nausea and vomiting: (e.g., metoclopramide, granisetron, tropisetron, dexamethasone, aprepitant, midazolam)</li> <li>• Neurological symptoms: <ul style="list-style-type: none"> <li>– Epilepsy: (e.g., seizure treatment, seizure maintenance treatment, refractory epilepsy treatment)</li> <li>– Spasticity: (e.g., botulinum toxin A injections, baclofen, benzodiazepines)</li> <li>– Movement disorders (e.g., biperiden, baclofen)</li> <li>– Neurological deficits such as bothersome or troublesome double vision, incomplete closing of the eyes, visual hallucination, hearing problems, swallowing difficulties, problems with talking.</li> </ul> </li> </ul>

**Table 4.** Continued

Current knowledge gaps
<ul style="list-style-type: none"><li>• Pain (e.g., opioids, non-opioids, and adjuvant analgesics)</li><li>• Death rattle (e.g., anticholinergic agents)</li><li>• Fatigue: (e.g., methylphenidate)</li></ul> <p>Effects of paediatric palliative sedation on depth of sedation, quality of life and lifespan in children aged 0 to 18 years with life-threatening and life-limiting conditions or with a (very) severe multiple (intellectual) disability at the end-of-life.</p> <p>Effects of forgoing hydration and nutrition on quality of life, lifespan, and parental quality of life in children aged 0 to 18 years with life-threatening and life-limiting conditions at the end of life.</p>

With these recommendations, we aim to limit symptom-related suffering and ease distress in children with life-threatening and life-limiting conditions and their families. Our methodology allowed us to provide evidence-based recommendations on a comprehensive selection of symptoms in close collaboration with experts in paediatric palliative care, and parents. Even though available evidence on symptom-related paediatric palliative care interventions has increased, there still is a paucity in evidence on non-pharmacological and pharmacological interventions to treat symptoms in paediatric palliative care. We urge for international multidisciplinary multi-institutional collaboration to perform high-quality research and to contribute to the optimization of symptom relief for all children with life-threatening or life-limiting conditions worldwide.

**SUPPLEMENTARY MATERIAL**

Additional files are available online (<https://doi.org/10.1186/s12904-023-01293-3>)



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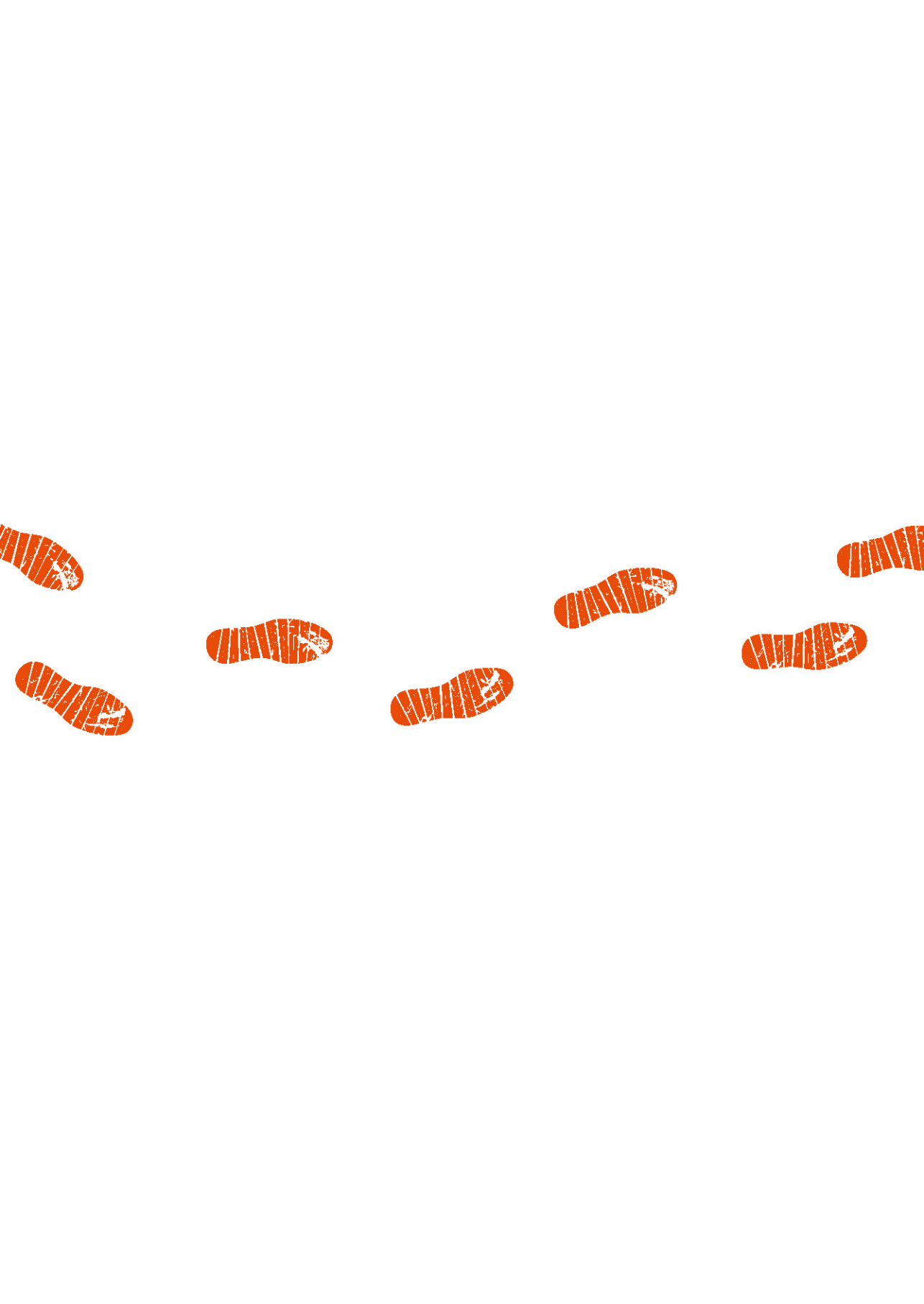
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# 4

## A Dutch paediatric palliative care guideline: a systematic review and recommendations on advance care planning and shared decision-making

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## **ABSTRACT**

### **Background**

In paediatric palliative care, children with life-threatening and life-limiting conditions, their families, and their health care professionals often face difficult decisions about treatment, goals of care, and delivery of care. Advance care planning and shared decision-making are strategies that can improve quality of care by discussing goals and preferences on future care. In this paper, we provide recommendations that aim to optimize advance care planning and shared decision-making in paediatric palliative care in the Netherlands.

### **Methods**

A multidisciplinary guideline panel of 20 experts in paediatric palliative care and nine (bereaved) parents was established to develop recommendations on advance care planning and shared decision-making. We performed systematic literature searches to identify quantitative and qualitative evidence and used the GRADE (CERQual) methodology for appraisal of evidence. Recommendations were formulated based on quantitative and qualitative evidence, clinical expertise, and patient and family experiences.

### **Results**

We identified 4 RCTs that reported on the effect of advance care planning interventions in paediatric palliative care and 33 qualitative studies on barriers and facilitators to advance care planning and shared decision-making. We formulated 28 strong recommendations in close collaboration with a multidisciplinary guideline panel that provide guidance to offer advance care planning and shared decision-making, involve children and their family, and communicate information about care and treatment.

### **Conclusion**

The identified evidence and recommendations support the use of advance care planning and shared decision-making in paediatric palliative care. We emphasize the importance of education and training on communication skills to further improve integration of advance care planning and shared decision-making. Additionally, we call for more research in the identified knowledge gaps to further optimize advance care planning and shared decision-making and improve quality of care.

### **Keywords**

Evidence-based guideline, paediatric palliative care, advance care planning, shared decision-making



## BACKGROUND

Children with life-threatening and life-limiting conditions and their families need palliative care to relieve physical, psychological, social, and spiritual suffering and improve quality of life during the entire disease trajectory, from diagnosis till the end-of-life and during bereavement (1). These children often receive high complex care that can last for months or years. This care is often provided by multiple health care professionals and can be delivered at the hospital, home, or elsewhere (2). During the disease trajectory, these children, their families, and health care professionals face difficult decisions about goals of care and related treatment, place of care, and delivery of care dependent on the situation and prognosis of the child (3, 4).

It is increasingly recognized that children, families, and health care professionals value person-centred approaches to identify goals and preferences for care and treatment to inform decision-making when receiving palliative care (3, 5). Advance care planning and shared decision-making are conversational approaches that can be used to give substance to care and treatment together with child and family. These approaches focus on open and equivalent exchange of knowledge, experiences, values, goals, and preferences between children, families, and health care professionals (6, 7).

Advance care planning enables individuals to define goals and preferences for future medical care and treatment, to discuss these goals and preferences with the child, its family and health care professionals, to record these, and review these if appropriate (7). The outcomes of an advance care planning conversation can guide the child, family, and health care professionals in determining what treatment policy supports the best interest of the child and aligns with the family's values and preferences. In this way, advance care planning is extremely helpful when a decision on the treatment is needed (8).

In paediatric palliative care, many decisions on care and treatment need to be made. In these decisions, there is often not one best option and many uncertainties regarding the child's condition or disease evolution pertain. Each option can have advantages and disadvantages, which may be experienced or valued differently among children, family, or health care professionals. Shared decision-making is a collaborative process that can support stakeholders in making these preference-sensitive decisions (9). In this process, the child (if possible), family and health care professionals are working together to make joint decisions on the best care and treatment (9). The goals and preferences discussed and recorded in advance care planning conversations can guide the shared decision-making process(10).

Advance care planning and shared decision-making are acknowledged as key elements of paediatric palliative care (3). However, a recent qualitative study among parents in the Netherlands has shown that the use of these person-centred approaches in paediatric

palliative care remains to be very challenging (11). Clinical practice guidelines (CPGs) are powerful tools in which knowledge from scientific literature, clinical expertise and patient experiences are combined to provide recommendations which can enhance delivery of high quality care and contribute to the integration of care services (12-14).

As part of the revised Dutch CPG on paediatric palliative care, we provide new recommendations that focus on two key elements of paediatric palliative care: advance care planning and shared decision-making. In this paper, we present an overview of the evidence, clinical expertise, and recommendations on these topics.

## **METHODS**

The full methodology of the Dutch CPG for paediatric palliative care has been published in a separate paper (15).

### **Scope**

This guideline provides guidance on palliative care for all children aged 0 to 18 years with life-threatening or life-limiting conditions and their caregivers, brothers, and sisters (hereafter referred to as families) throughout the entire palliative trajectory (from palliative diagnosis till after end-of-life), with the ultimate goal to improve quality of paediatric palliative care and thereby quality of life of children and their families (16). Here, we provide recommendations for advance care planning and shared decision-making.

### **Multidisciplinary guideline development panel**

The guideline development panel consisted of an expert panel of 20 professionals with expertise in paediatric palliative care and a panel of nine (bereaved) parents (Appendix A). Professionals from multiple disciplines such as paediatricians, paediatric nurses, medical pedagogical care providers, and specialists in intellectual disabilities, were included in the guideline development panel. Within the expert panel, a core group of 11 experts was established to ensure consistency throughout the guideline. The other nine experts were assigned to the working group advance care planning and shared decision-making. The addressed topics and clinical questions were selected based on priorities of health care professionals and parents (15). An overview of the working structure and guideline development process is shown in Appendix B and C.

### **Representation of patients and their families**

To ensure representation of patients and their families, different methods were used (15). Two members of the core group were dedicated to ensure the representation of patients and their families during the entire guideline process. Additionally, a panel of 9 (bereaved) parents of children with life-threatening or life-limiting conditions reviewed the first drafts of all guideline texts and recommendations and reviewed the complete concept guideline.

We ensured parents represented a broad spectrum of experiences by including parents of children with a variety of palliative conditions, ages, and stages of disease (currently receiving palliative care or deceased).

### **Identification of quantitative studies**

The working group formulated one clinical question on the effect of advance care planning interventions (Appendix D). Therefore, we updated the literature search on paediatric palliative interventions that was conducted for the former CPG (2013) until January 24, 2020 (Appendix E). Studies were selected according to inclusion criteria related to study design (randomized controlled trials (RCTs), controlled clinical trials (CCTs), and systematic reviews (SRs) of RCTs and CCTs; study population (children aged 0 to 18 with life-threatening or life-limiting conditions according to the definition of the World Health Organization(16)) and study subject (paediatric palliative care interventions related to advance care planning and shared decision-making). Only studies published in English or Dutch language were included (Appendix F).

Included studies were summarized in evidence tables. We categorized evidence by outcome measures in summary of findings tables. Then, we formulated conclusions of evidence for each outcome measure. The quality of the total body of evidence was graded using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method (17).

### **Identification of qualitative studies**

Additionally, the working group formulated a clinical question to identify barriers and facilitators to advance care planning and shared decision-making (Appendix D). To find studies on this topic, we first searched for existing evidence-based guidelines that performed a systematic literature search on this topic. We found one evidence-based guideline, 'End of life care for infants, children and young people with life-limiting conditions (2016)' of the National Institute for Health and Care Excellence (NICE) (18). We used the original systematic literature search that was conducted in this existing guideline and updated it until 16 September, 2020 (Appendix E). Studies were selected based on inclusion criteria related to study design (qualitative studies, mixed-methods observational studies with qualitative data and SRs of qualitative studies), study population (children aged 0 to 18 years old with life-threatening or life-limiting conditions according to the definition of the World Health Organization(16)), their parents and health care professionals) and study outcomes (barriers and facilitators to advance care planning or shared decision-making). Moreover, only studies published in English or Dutch language were included (Appendix F).

We used evidence tables to extract barriers and facilitators to advance care planning and shared decision-making in themes and subthemes and formulated conclusions of evidence for each theme or subtheme. The quality of the total body of evidence was assessed with the adapted GRADE Confidence in the Evidence from Reviews of Qualitative research

(GRADE CERQual) methodology (19). As we updated the systematic search of the NICE-guideline, we integrated the conclusions of evidence in our updated conclusions of evidence. Additionally, the recommendations in the NICE-guideline were used to refine considerations and recommendations (15).

### **Translating evidence into recommendations**

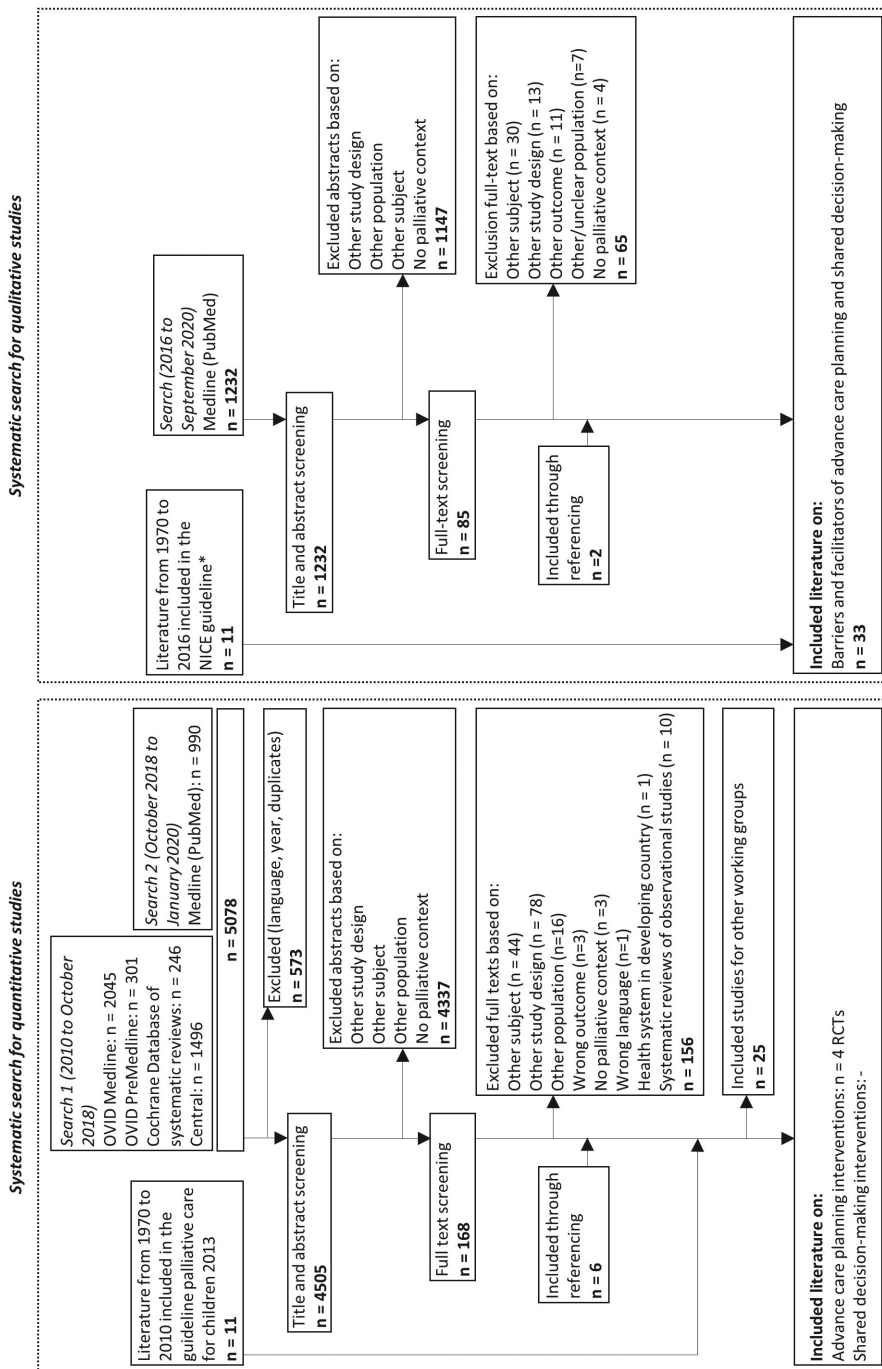
Recommendations were based on evidence from scientific literature, expert opinion, and patient and family values. For each clinical question, the relevant considerations related to the scientific literature, patient preferences, expert opinion, legal and ethical considerations, applicability and feasibility, and potential benefits and harms, were described (15). We followed the criteria for the strength of recommendations according to published methods (17, 20) (Appendix G). Recommendations were categorised as strong to do (green), moderate to do (yellow) or strong not to do (red).

## **RESULTS**

### **Identification of evidence**

The systematic literature search for quantitative studies on paediatric palliative care interventions yielded 5078 citations of which 168 citations were subjected to full-text screening. A total of four RCTs on the effect of advance care planning interventions in children with cancer or human immunodeficiency virus (HIV) infections were identified (21-24). No studies on the effects of shared decision-making were identified.

The updated systematic literature search for qualitative studies on barriers and facilitators to advance care planning and shared decision-making identified 1238 eligible citations. We excluded 1147 citations based on title/abstract and 85 citations were included for full-text screening. We included a total of 33 qualitative studies on barriers and facilitators of advance care planning and shared decision-making, of which 22 studies (6, 25-45) were newly published studies and 11 studies were identified in the original search of the NICE-guideline (18). In Figure 1, a flow chart of the study selection process of both systematic searches is presented.



**Figure 1** Flow chart of the study selection process

\* We only used the conclusions of evidence from the 11 identified studies from the search of the NICE guideline

***Evidence on effect of advance care planning interventions***

We included a total of four RCTs that all described the effect of the Family-Centred Advance Care Planning (FACE) intervention as compared to usual care combined with information provision sessions in family format on development, safety, and school and career planning (21-24). The FACE-intervention aims to facilitate advance care planning conversations between adolescents and their adult surrogates in three weekly sessions. The effects of the FACE-intervention were studied in adolescents with cancer (22, 24) and adolescents with an HIV-infection (21, 46). In Table 1, the conclusions of the evidence are shown. A full overview of all conclusions of evidence corresponding evidence tables, and summary of findings tables can be found in Appendix I, J and K.

The studies reported the effects of different outcome measures, including the completion of a legal statement of treatment preferences, level of congruence in treatment preferences, anxiety, depression, quality of life, and spiritual well-being. The studies showed that adolescents with cancer and HIV-infection in the intervention group were more likely to complete a legal statement of treatment preferences than the control group (very low quality of evidence) (21, 22). Additionally, it was found that the FACE-intervention increased agreement on treatment preferences (very low quality evidence) (23, 24) and treatment restrictions (low quality evidence) (21, 23) between adolescents with cancer or HIV-infection and their adult surrogates. Moreover, the FACE-intervention increased agreement between adolescents with cancer or HIV-infection and their adult surrogates to give family leeway (low quality evidence) (23, 24). However, this effect did not sustain at three month follow-up (low quality evidence) (23).

Furthermore, risk of depression was lower among adolescents with cancer three months after participating in the FACE-intervention (very low quality evidence). This effect was not found among adolescents with HIV-infection and adult surrogates of adolescents with cancer or HIV-infection (very low quality evidence) (21, 22). Adolescents with cancer that participated in the FACE-intervention reported a higher spiritual well-being at three month follow-up as compared to the control group (very low quality evidence) (22). The studies reported no significant effect on anxiety and quality of life in adolescents with cancer or HIV-infection after three months (very low quality evidence) (21, 22).

**Table 1.** Conclusions of evidence on advance care planning interventions in paediatric palliative care

<b>Effect of advance care planning interventions in palliative care for children aged 0 to 18 years with life-threatening and life-limiting condition</b>	
<b>Family-centred advance care planning intervention vs. control or usual care in adolescents with cancer and HIV-infection and their adult surrogates</b>	<b>Quality of evidence</b>
↑ <i>completion of a legal statement of treatment preferences</i> among adolescents with HIV-infection or cancer and their adult surrogates.	⊕⊕⊕⊕ VERY LOW (2 RCT) (21, 22)
↑ <i>congruence in treatment preferences</i> post-session-2 and at 3-month follow-up among adolescents with HIV-infection and their adult surrogates concerning long hospitalization, functional impairment, and mental impairment. Unclear if effect was significant.	⊕⊕⊕⊕ VERY LOW (1 RCT) (23)
↑ <i>congruence in treatment preferences</i> post-session-3 among adolescents with cancer and their adult surrogates concerning long hospitalization, treatment would extend my life, functional impairment, mental impairment, attempting cardiopulmonary resuscitation, and mechanical ventilation. This effect was not significant for the situation attempting cardiopulmonary resuscitation.	⊕⊕⊕⊕ VERY LOW (1 RCT) (24)
↑ <i>agreement to limit treatment</i> post-session-2 among adolescents with HIV-infection and their adult surrogates concerning long hospitalization, and mental impairment. This effect was not significant in the situation functional impairment.	⊕⊕⊕⊕ VERY LOW (1 RCT) (23)
↑ <i>agreement to limit treatment</i> at 3-month follow-up among adolescents with HIV-infection and their adult surrogates concerning functional impairment. This effect was not significant for long hospitalization and mental impairment.	⊕⊕⊕⊕ LOW (2 RCTs) (21, 23)
↑ <i>agreement to give family leeway</i> post-session-2/3 among adolescents with cancer and their adult surrogates. This effect was not significant among adolescents with HIV-infection.	⊕⊕⊕⊕ LOW (2 RCTs) (23, 24)
No significant effect on <i>agreement to give family leeway</i> at 3-month follow-up among adolescents with HIV-infection and their adult surrogates.	⊕⊕⊕⊕ VERY LOW (1 RCT) (23)
No significant effect on <i>anxiety</i> at 3-month follow-up among adolescents with HIV-infection or cancer.	⊕⊕⊕⊕ VERY LOW (2 RCTs) (21, 22)
↓ depression at 3-month follow-up among adolescents with cancer after intervention. No significant effect among adolescents with HIV-infection.	
No significant effect on <i>depression</i> 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.	
↑ <i>spiritual well-being</i> at 3-month follow-up among adolescents with cancer.	⊕⊕⊕⊕ VERY LOW (1 RCT) (22)

### ***Evidence on barriers and facilitators to advance care planning and shared decision-making***

We identified ten themes from the included qualitative literature that cover barriers and facilitators to advance care planning and shared decision-making: 1) information provision, 2) involvement, 3) interpersonal relations and communication, 4) holistic approach to care, 5) timing, 6) preparation, 7) documentation, 8) setting, 9) support, 10) education. Within these themes, we formulated various conclusions of very low to moderate quality evidence. For each conclusion we distinguished whether it was perceived as a facilitator or a barrier. Furthermore, we indicated whether the conclusion was reported by parents, health care professionals and/or children. Lastly, we indicated for each conclusion whether it was reported in the NICE-guideline (18). In Table 2, all conclusions of moderate quality evidence are shown. A full overview of all conclusions of evidence, corresponding evidence tables, and summary of findings tables can be found in Appendix I, J and K.

Regarding the theme information provision, regular provision of complete, unbiased, and understandable information about the child's condition, likely treatment outcomes and treatment options was considered essential by parents and health care professionals (25, 26, 28, 29, 32, 35, 37, 39-41, 43, 45). Health care professionals found it helpful when families themselves indicated their preferred type and amount of information (26, 27). Parents reported that the acknowledgement of uncertainties about the diagnosis and prognosis was important (31, 35, 43). Uncertainties that led to guesses and disagreements among health care professionals were considered a barrier as perceived by parents (36, 38, 43). Health care professionals found information provision very difficult, especially due to these uncertainties in diagnosis and prognosis (28, 32, 45).

Acknowledging parents as experts of their own child was seen as an important facilitator for parental involvement in advance care planning and shared decision-making (6, 29-31, 35, 36, 38, 39, 41, 43, 45). In addition, including the child's perspective was considered essential (6, 30, 31). The large individual variation in the desired level of parental involvement (25-31, 37, 40, 41, 43, 45) and child involvement (26-31, 34, 36, 37, 39) in treatment decision-making was perceived as a barrier. Moreover, health care professionals reported variation in preferred level of their own involvement as a barrier as well (26, 45). Furthermore, both parents and health care professionals experienced barriers on a personal level to participate in advance care planning or shared decision-making. For example, parents found it difficult to share their perspectives with health care professionals, as they feared this could impact their child's treatment in a unfavourable way (25, 26, 28, 29, 36-38, 45) and health care professionals found it difficult to address sensitive themes (28, 30, 32, 40-42). Parents reported that good experiences with care could facilitate shared decision-making (6, 35).



For communication and interpersonal relations, parents and health care professionals considered the use of open, honest, and clear lay language as facilitators (26-29, 32, 36, 38, 41). Additionally, parents acknowledged that communication by a trusted health care professional (29, 38), the use of interpreters for non-native speakers (29), reassuring non-verbal and compassionate communication, offering support, and active listening were essential facilitators (28, 32, 43). Both health care professionals and parents reported that long-lasting trusted relationships between parents and health care professionals facilitated advance care planning and shared decision-making (26, 28, 32, 35, 38, 40, 43, 45). However, parents did note that relationships were easily compromised when they did not feel heard (29, 38, 41, 45). Additionally, different perspectives between health care professionals and parents were seen as hindering (27, 31, 42, 45).

Within the theme holistic approach to care, parents and health care professionals considered recognizing the impact of the child's illness on all aspects of the child's and family's life as a facilitating factor (6, 25, 30-32, 35, 36, 39, 41). In addition, parents reported that talking about their hopes, faith, and religion empowered them in their decision-making process (28, 44). Furthermore, parents considered acknowledgement of their beliefs (44), their hopes (26, 36, 37, 43), and provision of culturally sensitive information (39) as facilitators. However, parents also reported a variety in preferences on how health care professionals should support hope (26, 36, 37, 43). Health care professionals worried that parents' hopes, faith, and religion may lead to disregarding of medical evidence (28, 44). Both parents and health care professionals agreed that disagreements due to cultural background hindered advance care planning and shared decision-making (28, 32, 45).

With regards to the timing, preparation, documentation and setting of advance care planning or shared decision-making conversations, both parents and health care professionals distinguished multiple facilitating factors. First of all, recognizing advance care planning as a dynamic and continuous process and as a standard part of care promoted its use (31-33, 35, 36, 41). Parents stressed that they should be given sufficient time to consider (still) possible treatment options (25, 29). Additionally, a personal conversation when handing out supplementary written materials were considered facilitators (31, 36). It was important that advance care planning conversations were conducted in an appropriate and comfortable setting preferably a quiet room with adequate seating, without distractors, possibly away from the hospital or at home (32, 33, 35, 41, 43). Key family members and health care professionals should be present during these conversations (35, 36, 41). Moreover, parents considered connections to other families in similar situations to share experiences as supportive (29, 36, 39, 45). Finally, offering education and training to health care professionals was considered beneficial in enhancing the quality of advance care planning conversations and shared decision-making (26, 30, 36, 40, 41).

**Table 2.** Conclusions of evidence on barriers and facilitators to advance care planning and shared decision-making in paediatric palliative care

<b>Barriers and facilitators in advance care planning and shared decision-making for children aged 0 to 18 years with life threatening and life-limiting conditions, their families, and their health care professionals</b>		
<b>Theme /subtheme</b>	<b>Facilitators<sup>#</sup></b>	<b>Barriers<sup>#</sup></b>
<b>Information provision</b>		
Information provision on treatment and prognosis	<ul style="list-style-type: none"> <li>• Providing frequent complete, unbiased, and understandable information about the child's condition, likely treatment outcomes and treatment options (25, 26, 28, 29, 32, 35, 37, 39-41, 43, 45).<sup>*, a, b</sup></li> <li>• Acknowledging of uncertainties on diagnosis and prognosis as an aspect of the child's unique situation (31, 35, 43).<sup>a</sup></li> <li>• HCPs prefer parents and teenagers to provide type and amount of information (26, 27).<sup>b</sup></li> </ul>	
Prognostic uncertainty		<ul style="list-style-type: none"> <li>• HCPs find it complicated to give consistent and clear information due to prognostic uncertainty (28, 32, 45).<sup>*, b</sup></li> <li>• Guesses by HCPs and disagreements among HCPs due to prognostic uncertainty (36, 38, 43).<sup>*, a</sup></li> </ul>
<b>Involvement</b>		
Involvement of parents	<ul style="list-style-type: none"> <li>• Acknowledging parents as the expert of their child (6, 29-31, 35, 36, 38, 39, 41, 43, 45).<sup>*, a</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Individual variation in the preferred level of parent involvement in ACP and decision making i.e., parents should be final decision-maker<sup>a, b</sup>, parents make decisions in collaboration with HCPs<sup>a, b</sup>, parents do not want to be involved<sup>a, b</sup>, parents feel like there is no choice to be made<sup>a</sup> (25-31, 37, 40, 41, 43, 45).<sup>*, a, b</sup></li> </ul>

Table 2. Continued

<b>Barriers and facilitators in advance care planning and shared decision-making for children aged 0 to 18 years with life threatening and life-limiting conditions, their families, and their health care professionals</b>		
<b>Theme /subtheme</b>	<b>Facilitators<sup>#</sup></b>	<b>Barriers<sup>#</sup></b>
Involvement of children	<ul style="list-style-type: none"> <li>Considering the child perspective during ACP and shared decision-making (6, 30, 31).<sup>a</sup></li> </ul>	<ul style="list-style-type: none"> <li>Individual variation in the preferred level of child involvement in ACP and decision making i.e., all children should be involved, level of child involvement is dependent on age, the decision that needs to be made, or the situation of the child (26-31, 34, 36, 37, 39).<sup>*, a, b, c</sup></li> <li>Uncertainty of HCPs on their role in communicating with the child (26, 27, 30, 31)(26, 27, 30, 31).<sup>b</sup></li> </ul>
Involvement of HCPs		<ul style="list-style-type: none"> <li>Individual variation in the preferred level of HCP involvement in decision making i.e., HCPs should solely provide information, HCPs should orient parents to the decision most beneficial for the child, HCPs should be the final decision-maker in certain situations (26, 45).<sup>b</sup></li> </ul>
Personal facilitators/ barriers to advance care planning and shared decision-making	<ul style="list-style-type: none"> <li>Good experiences with care facilitate decision-making for parents (6, 35).<sup>*, a</sup></li> </ul>	<ul style="list-style-type: none"> <li>Parents experienced difficulty in advance care planning and decision-making i.e. some parents do not feel ready to make decisions, some parents do not want their child to suffer but want the child to live as long as possible, some parents cannot foresee consequences, and some parents want to keep option open (25, 26, 28, 29, 36-38, 45).<sup>*, a, b</sup></li> <li>HCPs experienced stress addressing sensitive themes (28, 30, 32, 40-42).<sup>b</sup></li> </ul>
<b>Interpersonal relations and communication</b>		
Communication	<ul style="list-style-type: none"> <li>Using open, honest, and clear lay language (26-29, 32, 36, 38, 41).<sup>*, a, b</sup></li> <li>Communication and information provision by a trusted HCP (29, 38).<sup>a</sup></li> <li>Using of interpreters for non-native speakers (29).<sup>a</sup></li> <li>Using open and reassuring nonverbal cues (43).<sup>a</sup></li> <li>HCPs that show compassion, give support, and listen actively (28, 32).<sup>*, a</sup></li> </ul>	

Table 2. Continued

<b>Barriers and facilitators in advance care planning and shared decision-making for children aged 0 to 18 years with life threatening and life-limiting conditions, their families, and their health care professionals</b>		
<b>Theme /subtheme</b>	<b>Facilitators<sup>#</sup></b>	<b>Barriers<sup>#</sup></b>
Family-provider relationship	<ul style="list-style-type: none"> <li>Long-lasting, trusted relationships between parents and HCPs (26, 28, 32, 35, 38, 40, 43, 45).<sup>*, a, b</sup></li> </ul>	<ul style="list-style-type: none"> <li>Relationships between parents and HCPs are fragile and easily compromised when parents do not feel heard (29, 38, 41, 45).<sup>*, b</sup></li> <li>Disagreements between HCPs and parents, difficulty to reach agreement with families (27, 31, 42, 45).<sup>*, a, b</sup></li> </ul>
<b>Holistic approach to care</b>		
Living with illness	<ul style="list-style-type: none"> <li>Acknowledging the impact of the child's illness on all aspects of the child's and families daily live (6, 25, 30-32, 35, 36, 39, 41).<sup>*, a, b</sup></li> </ul>	
Hope	<ul style="list-style-type: none"> <li>Support parents' hope (26, 36, 37, 43).<sup>a</sup></li> </ul>	<ul style="list-style-type: none"> <li>Varied preferences on how HCPs should support hope (26, 36, 37, 43).<sup>a</sup></li> </ul>
Faith and Religion	<ul style="list-style-type: none"> <li>Hope, faith, religion empower parents to make decisions (28, 44).<sup>*, a</sup></li> <li>HCPs acknowledging parent's beliefs (44).<sup>*, a</sup></li> </ul>	<ul style="list-style-type: none"> <li>HCPs worry that hope, faith, and religion may allow parents to disregard medical evidence in decision-making (28, 44).<sup>*, b</sup></li> </ul>
Attention for different cultures	<ul style="list-style-type: none"> <li>Providing culturally sensitive information (39).<sup>*, a</sup></li> </ul>	<ul style="list-style-type: none"> <li>Disagreements due to differences in cultural background (28, 32, 45).<sup>*, a, b</sup></li> </ul>
<b>Timing</b>		
Ongoing process	<ul style="list-style-type: none"> <li>Acknowledging ACP as an ongoing process and continuous part of the child's care (31-33, 35, 36, 41).<sup>*, a, b</sup></li> </ul>	
Sufficient time for decision making	<ul style="list-style-type: none"> <li>Giving parents sufficient time between receiving information and making decisions, to think about several options prior to the actual decision-making (25, 29).<sup>*, a</sup></li> </ul>	
<b>Preparation</b>		
	<ul style="list-style-type: none"> <li>No moderate quality evidence was found</li> </ul>	
<b>Documentation</b>		
	<ul style="list-style-type: none"> <li>Personal conversation when handing out supplementary written materials (31, 36).<sup>*, a, b</sup></li> </ul>	

**Table 2.** Continued

<b>Barriers and facilitators in advance care planning and shared decision-making for children aged 0 to 18 years with life threatening and life-limiting conditions, their families, and their health care professionals</b>		
<b>Theme /subtheme</b>	<b>Facilitators<sup>#</sup></b>	<b>Barriers<sup>#</sup></b>
<b>Setting</b>		
	<ul style="list-style-type: none"> <li>Comfortable and appropriate setting of ACP meetings (32, 33, 35, 41, 43). <sup>*, a, b</sup></li> <li>Key family members and HCPs have the opportunity to be present during ACP conversations (35, 36, 41). <sup>*, a, b</sup></li> </ul>	
<b>Support</b>		
	<ul style="list-style-type: none"> <li>Parents connecting to family-members and other parents in similar situations (29, 36, 39, 45). <sup>*, a</sup></li> </ul>	
<b>Education</b>		
	<ul style="list-style-type: none"> <li>ACP and communication training for HCPs (26, 30, 36, 40, 41). <sup>*, a, b</sup></li> </ul>	

<sup>#</sup> all facilitators/barriers for which moderate quality evidence was found are presented in this table.

<sup>\*</sup> conclusions of evidence were presented in NICE guideline as well.

a. facilitator/barrier reported by parents

b. facilitator/barrier reported by HCPs

c. facilitator/barrier reported by children

abbreviations: ACP = advance care planning; HCP= Health Care Professional; NICE = National Institute of health Care Excellence

## Translating evidence into recommendations

Existing studies described the effectivity of advance care planning interventions and the barriers and facilitators to advance care planning and shared decision-making. Our recommendations are based on the conclusions from the existing evidence and the consensus of the guideline development panel. The guideline development panel formulated a total of 28 recommendations on advance care planning (n=11), shared decision-making (n=10), roles of child, family and health care professionals in advance care planning and shared decision-making (n=3), and communication skills during advance care planning and shared decision-making (n=4). All recommendations are shown in Table 3.

**Table 3.** Recommendations on advance care planning and shared decision-making in paediatric palliative care

<b>Recommendations on advance care planning and shared decision-making palliative care for children aged 0 to 18 years with life- threatening and life-limiting conditions, their families, and health care professionals (n=28)</b>	
<b>Advance care planning</b>	
<b>Do</b>	1 Offer ACP conversations as a standard of care for all children with a palliative diagnosis and their families. In doing so, consider the specific situation and burden bearing capacity of child and family. <sup>a</sup>
	2 Integrate ACP as a continuous and dynamic process in the care of child and family from diagnosis through the end of life by holding regular conversations. <sup>b</sup>
	3 Start ACP conversations early in the disease process to encourage acceptance and allow space to prepare for the future. <sup>b</sup>
	4 Hold timely conversations with the child and family when the need to prepare for specific scenarios increases, as the child's condition deteriorates or when the child approaches end of life. <sup>b</sup>
	5 Provide explanations and written information to child and family to prepare for an ACP conversation and provide opportunities to include others they may wish to have present during the conversations. <sup>b</sup>
	6 Include the content of ACP conversations and any treatment arrangements in the medical record. <sup>b</sup>
	7 Have a health care provider trusted by the child and family lead the ACP conversations. This may be the primary caregiver, or another trusted caregiver, such as a case manager, or a caregiver outside the treatment team trained in ACP conversations. <sup>b</sup>
	8 When preparing and conducting ACP conversations, use a conversation guide to provide structure and to ensure relevant topics are covered.
	9 Structure the ACP process through preparation, interviewing and reporting.
	10 Discover, discuss, and note in the ACP process what the child and family's values, goals and preferences are for future care and treatment medically, psychologically, spiritually, and socially.
	11 With the consent of parents and child, share specific treatment agreements with all health care professionals involved.
<b>Shared decision-making</b>	
<b>Do</b>	12 Think ahead of time what treatment decision(s) must be made in the short and longer term and how you will explain the need for these decisions to child and/or parents.
	13 Consider in advance what (treatment) options are available and how you will explain them in a way that the child and/or parents can understand.
	14 Consider in advance how many conversations you think you will need to come to a decision and within what time frame you would prefer to have these conversations. Explain this to the child and parents.
	15 Start the conversation with an agenda and ask the child and/or his parents what they want to discuss.
	16 During the conversation, strike a good balance between the information you give and the information you want to receive from the child and/or his parents.

Table 3. Continued

<b>Recommendations on advance care planning and shared decision-making palliative care for children aged 0 to 18 years with life- threatening and life-limiting conditions, their families, and health care professionals (n=28)</b>	
Do	17 Explain the advantages and disadvantages of the treatment options clearly and concretely. This includes the option to "wait and see" and the option to forgo further curative or life-sustaining treatments and focus entirely on comfort care.
	18 Give the child and/or his parents the opportunity to ask questions about the various treatment options and to share their views and experiences.
	19 Consult with the child and/or parents as to their preference and, if asked, explain your preference as well.
	20 Come to a decision that all involved are comfortable with and summarise it. Prevent the child and/or his parents from feeling too burdened by the responsibility of this decision.
	21 Involve the child even if he or she is under 12. Do this in a way that is developmentally appropriate. This also applies to the words you choose. <sup>b</sup>
<b>Roles of child, family and health care professionals in advance care planning and shared decision-making</b>	
Do	22 Involve child and family in framing ACP and shared decision-making in terms of form, content, preferred place, time and stakeholders and tailor this process to their needs. <sup>b</sup>
	23 Involve the (perspective of the) child in ACP conversations and shared decision-making in accordance with the child's developmental age. <sup>b</sup>
	24 In the ACP process and in shared decision-making, recognize the child and family as experts in living with illness and in assessing their quality of life. Ensure your actions reflect due consideration for the knowledge and experiences of child and family. <sup>b</sup>
<b>Communication skills during ACP and shared decision-making</b>	
Do	25 Regularly provide child and family with clear and honest information about diagnosis, prognosis, treatment, and uncertainties surrounding the child's situation throughout the disease process. Match this information to their (language) abilities and needs. <sup>b</sup>
	26 Use specific communication skills such as exploratory listening, acknowledging emotions, using concrete, appropriate and clear language, and formulating value-based goals during ACP conversations and shared decision-making. <sup>b</sup>
	27 During ACP conversations and shared decision-making, consider the communication preferences and cultural, religious, and philosophical beliefs of child and family. <sup>b</sup>
	28 Be aware in your preparation and during ACP conversations and shared decision-making that these discussions can be perceived as very difficult by the child and family. Do this by exploring child and family attitudes toward ACP and responding empathetically to their emotions without making the emotions the focus.

a. For this recommendation, very low to low quality evidence was identified.

b. For this recommendation, moderate quality evidence was identified.

Abbreviations: ACP = Advance care planning;

### ***Recommendations on advance care planning***

Multiple RCTs indicated that an advance care planning intervention can enhance agreement on treatment preferences among adolescents with serious illnesses and their adult surrogates. No negative impact on quality-of-life related outcomes was reported (21-24). Although the quality of evidence was very low to low, the guideline development panel acknowledged the benefits of advance care planning for children to be prepared for the future and to guide shared decision-making. This was supported by the identified qualitative evidence. We therefore strongly recommend that advance care planning conversations should be a standard of care for all children with a palliative disease trajectory and their families (recommendation 1). In addition, various barriers and facilitators to advance care planning were embedded in the recommendations formulated by the guideline development panel. We strongly recommend that advance care planning should be a continuous and dynamic process (moderate quality evidence) (31-33, 35, 36, 41) and conversations should be initiated early in the disease process, certainly when the need to prepare for specific scenarios increases (moderate quality evidence) (25, 29) (recommendation 2-4). Furthermore, information materials should be handed out with a personal conversation to prepare child and family for advance care planning conversations (moderate quality evidence) (31, 36) (recommendation 5). All conversations should be documented in the medical record and should be led by a trusted health care professional (moderate quality evidence) (26, 28, 29, 32, 35, 38, 40, 43, 45) (recommendation 6-7). The guideline development panel recognized that strategies to improve practical application of advance care planning are key for the integration into clinical practice. The use of a conversation guide can be a helpful strategy to facilitate integration by raising awareness among health care professionals on the advance care planning process, advance care planning topics and creating a standard way of documenting advance care planning conversations (47-50). As a result, we strongly recommend using a conversation guide to structure the advance care planning process (recommendation 8-10). With consent of child and family, specific treatment agreements can be shared with all involved health care professionals (recommendation 11). Furthermore, the guideline development panel notes that leading advance care planning conversations requires specific communication skills, such as exploring child and family perspectives openly, neutrally, and empathetically, responding to emotions appropriately, and presenting the own professional perspectives based on scientific insights (51).

### ***Recommendations on shared decision-making***

With regards to shared decision-making, the guideline development panel acknowledged that the recommendations should be targeted at the application of shared decision-making in clinical practice and recognized this was dependent on legal and ethical considerations. Additionally, the panel concluded the identified evidence was not conclusive enough to formulate specific recommendations on the practical application of shared decision-making. According to the guideline development panel, the shared decision-making process is



usually structured along four steps: 1) acknowledging that a decision needs to be made, 2) describing treatment options and (dis)advantages for each relevant option, 3) discussing the preferences, needs, and situation of child and family and possible consequences of each treatment option, 4) coming to a joint decision on the treatment policy and discussing preferences in the parents' decisional role. Although shared decision-making can often facilitate decision-making in paediatric palliative care, the guideline development panel noted that shared decision-making might not be appropriate when an emergency occurs which requires an immediate response. The guideline development panel therefore strongly recommends health care professionals to think ahead of time what treatment decision(s) must be made, consider in advance what treatment options are available, how these can best be explained, and that multiple conversations might be needed to come to a decision (recommendation 12-14). Additionally, it is strongly recommended to structure each conversation by using an agenda (recommendation 15). During each conversation health care professionals should strike a balance between the information they provide and receive, explain advantages and disadvantages clearly and concretely, give all participants the opportunity to ask questions, discuss the preferences of child and family, and provide their own preferences only if asked (recommendation 16-19).

Regarding child involvement, evidence did show that individual preferences regarding child involvement exist (moderate quality evidence) (26-31, 34, 36, 37, 39). The guideline development panel considered this and recommended to always involve the child in a way that is developmentally appropriate, urging health care professionals to adapt the used language accordingly (recommendation 21).

### ***Recommendations on roles of child, family and health care professionals in advance care planning and shared decision-making***

The evidence showed that parents and health care professionals reported individual variation in preferred level of parent involvement, varying from parents as the final decision-makers, decision making by parents in collaboration with health care professionals, preference of parents not to be involved in decision making, and sometimes parents found it was not possible to make a decision (moderate quality of evidence) (25-31, 37, 40, 41, 43, 45). Similarly, children, parents and health care professionals reported variation in preferred level of child involvement, which was often dependent on age, the decision at hand, and the child's situation (moderate quality of evidence) (26-31, 34, 36, 37, 39). Only two studies reported the preferences of children themselves (26, 34). The guideline development panel acknowledged level of involvement should be tailored to the needs and preferences of child and family. We strongly recommend involving child and family in advance care planning and shared decision-making conversations (recommendation 22). Additionally, we strongly recommend that (the perspective of) the child should be involved while acknowledging the child's developmental age (recommendation 23). We

found moderate quality evidence that parents should be acknowledged as the expert of the child (6, 29-31, 35, 36, 38, 39, 41, 43, 45). The panel translated this in a strong recommendation (recommendation 24).

### ***Recommendations on communication skills during advance care planning and shared decision-making***

Relating to communication, several facilitators have been identified. The panel has used these facilitators to formulate recommendations. As a result, we strongly recommend clear and honest information about diagnosis, prognosis, treatment and uncertainties (25, 26, 28, 29, 31, 32, 35, 37, 39-41, 43, 45), the use of communication skills such as using concrete and appropriate language, explorative listening and acknowledging emotions (31, 35, 43), acknowledging communication preferences, and cultural, religious, and philosophical beliefs of child and family (moderate quality evidence) (26, 28, 36, 37, 39, 43, 44) (recommendation 25-27). Furthermore, evidence showed that parents experienced difficulties with regards to advance care planning and shared decision-making as they did not always feel ready to make decisions, could not foresee consequences or were conflicted in not wanting their child to suffer but also want their child to live as long as possible (moderate quality evidence) (25, 26, 28, 29, 36-38, 45). Therefore, we strongly recommend health care professionals to acknowledge this when preparing for advance care planning conversations and shared decision-making (recommendation 28).

## **DISCUSSION**

Advance care planning and shared decision-making in children with life-threatening and life-limiting conditions and their families are essential to paediatric palliative care (2, 3). These strategies have proven to enhance collaboration among children, families, and health care professionals, and decrease concerns about the future (52, 53). As a result, advance care planning and shared decision-making are expected to contribute to quality of care for children and their families (52).

In the Netherlands, health care professionals, parents, and other stakeholders have expressed the need for guidance with regards to advance care planning and shared decision-making in paediatric palliative care (6, 15, 54). We responded to this need by developing evidence-based recommendations on these topics as part of the revised Dutch CPG for paediatric palliative care. In this paper, we present the identified evidence and provide recommendations to optimize advance care planning and shared decision-making in paediatric palliative care in the Netherlands.

Our recommendations are developed using an evidence-based approach. We systematically searched for RCTs, CCTs and SRs of RCTs on the effects of advance care planning and shared decision-making interventions and qualitative studies on possible barriers and facilitators related to advance care planning and shared decision-making (15). We included

a total of four RCTs and 33 qualitative studies. The four RCTs showed that an advance care planning intervention can enhance agreement on future treatment preferences among adolescents with life-threatening and life-limiting conditions and their adult surrogates without negatively impacting quality-of-life related outcomes. Mainly, due to the imprecision of effects (small number of participants) and potential risk of bias, the total body of evidence was rated as low to very low quality. Despite the low to very low quality evidence, outcomes of advance care planning interventions are promising. In fact, studies strongly indicate that advance care planning interventions can decrease feelings of stress, helplessness, anxiety, and depression among families of paediatric patients (55, 56).

Furthermore, we found a total of 33 qualitative studies that reported on barriers and facilitators to advance care planning and shared decision-making, of which 22 studies were newly published and 11 studies were identified in the original search of the NICE-guideline (18). Meaning that, since the original search of the NICE-guideline in 2016, the total number of included qualitative studies has tripled. As the evidence on barriers and facilitators related to advance care planning and shared decision-making increased substantially, we are able to identify a large set of barriers and facilitators that were reported in various studies by multiple stakeholders. This allowed us to allocate each identified barrier and facilitator to the reporting stakeholder group, namely children, parents, and health care professionals and compare the results. Through this comparison, which was not performed in the NICE-guideline, we found that the different stakeholders mostly reported similar barriers and facilitators. After appraisal of the evidence, we found the majority of identified barriers and facilitators to advance care planning and shared decision-making were of moderate quality evidence. As the conclusions of evidence in the NICE-guideline were largely appraised as low to very low quality, we can conclude that the evidence base on barriers and facilitators related to advance care planning and shared decision-making is strengthened.

Recommendations were developed in close collaboration with a national multidisciplinary guideline panel consisting of professionals from multiple disciplines and parents. It has been shown that incorporation of clinical expertise and patient and family values is invaluable and improves the quality of recommendations (57). As a result, based on clinical expertise, patient and family values, and evidence from international literature, we were able to compile a comprehensive set of strong recommendations that provide guidance on advance care planning and shared decision-making in paediatric palliative care.

As our recommendations were largely based upon international evidence, we believe a large proportion of these recommendations will be applicable in other countries and can be used to optimize advance care planning and shared decision-making on a global scale. However, we recognize that country-specific factors such as organizational infrastructure

and cultural backgrounds should be carefully considered before applying any recommendations in other countries.

We recognize that provision advance care planning and shared decision-making requires specific skills such as exploring child and family perspective openly, responding to emotions appropriately, and presenting the own professional perspectives (51). We therefore emphasize that the provision of education and training in advance care planning and shared decision-making to develop these skills is an essential precondition for the application of recommendations in clinical practice.

Although we found an increased number of studies, we still identified some gaps in knowledge. First of all, we found limited and low quality evidence on the effect of advance care planning interventions and no evidence on the effect of shared decision-making interventions in paediatric palliative care. Additionally, we found limited evidence on the barriers and facilitators reported by children. Only two qualitative studies included children in their study population. In these studies, children reported barriers and facilitators related to two out of ten identified themes, i.e. information provision and child involvement in advance care planning and shared decision-making. Based on the identified knowledge gaps, we call for more research on advance care planning and shared decision-making in paediatric palliative care. Simultaneously, future research should focus on addressing the child's perspective in an age-appropriate way (58).

In conclusion, we developed recommendations based on strengthened evidence in close collaboration with a multidisciplinary guideline panel of professionals and parents. With these evidence-based recommendations, we aim to optimize advance care planning and shared decision-making in paediatric palliative care. Both identified evidence as well as the formulated recommendations support the use of advance care planning and shared decision-making in paediatric palliative care. As advance care planning and shared decision-making require specific skills, we emphasize the importance of education and training to improve integration of advance care planning and shared decision-making in clinical practice. Also, we call for more research into the identified knowledge gaps to further optimize advance care planning and shared decision-making and improve quality of care.

## **SUPPLEMENTARY MATERIAL**

Additional files will be available online once the manuscript is published.

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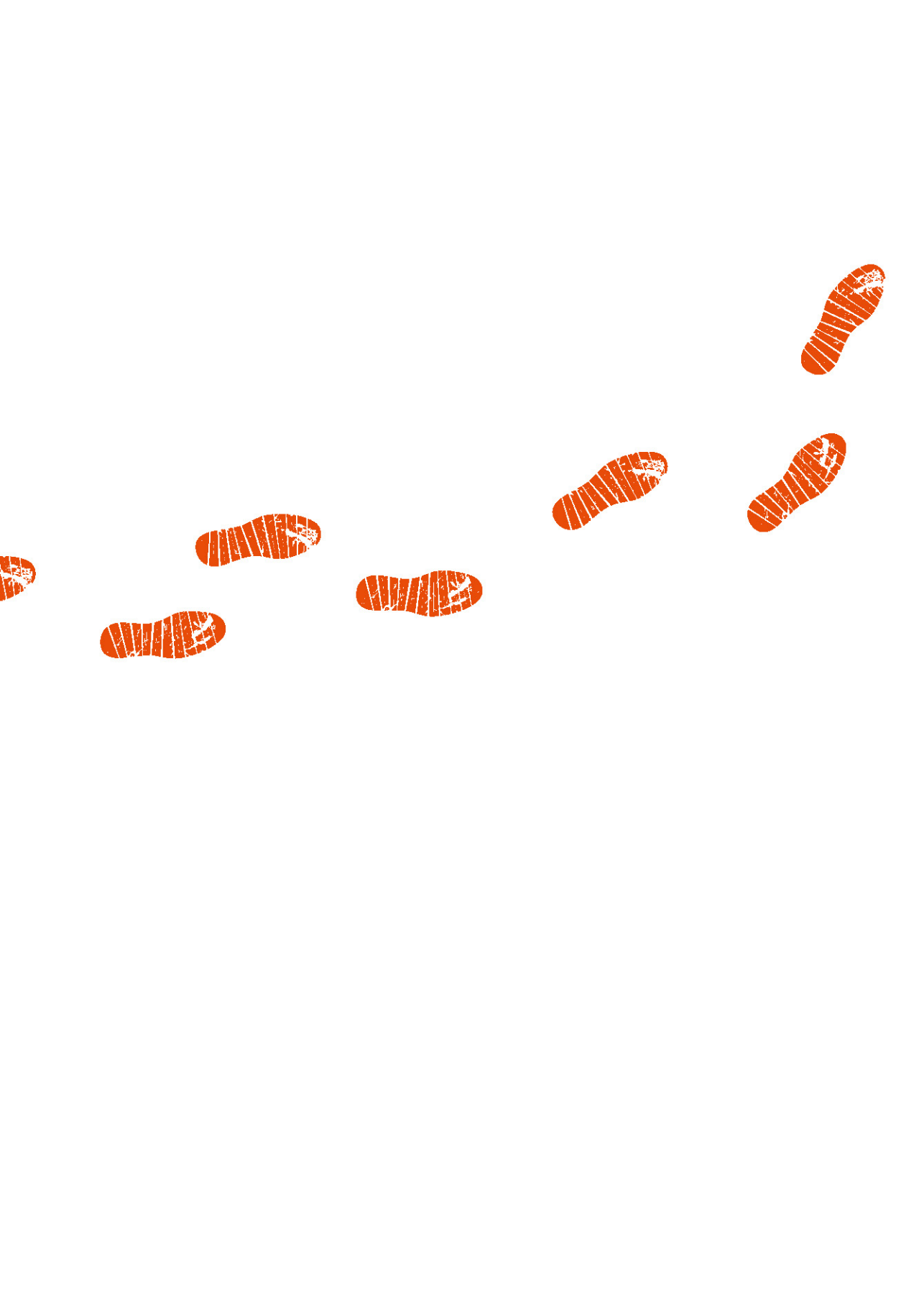
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## A Dutch clinical practice guideline for paediatric palliative care: a systematic review and recommendations on psychosocial care including preloss and bereavement care

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## ABSTRACT

### Background

Children with life-threatening and life-limiting conditions and their families are confronted with many uncertainties, incremental losses, and difficult decisions. Attentiveness to psychosocial care, including psychological, social, and spiritual concerns, is essential during the child's life until end-of-life and during bereavement and determines quality of life and wellbeing of child and family. However, use and integration of psychosocial care is found to be challenging. In this paper, we provide recommendations that aim to optimize psychosocial care including preloss and bereavement care in paediatric palliative care.

### Methods

A multidisciplinary guideline development panel of 25 experts in paediatric palliative care and nine (bereaved) parents was established to develop recommendations on psychosocial care including preloss and bereavement care. We performed a systematic literature search to identify evidence focussing on interventions described in systematic reviews (SRs) of randomized controlled trials (RCTs) and RCTs. We used the GRADE methodology for appraisal of evidence. We used additional literature from guidelines and SRs of observational, qualitative, or mixed-method studies to deal with lack of evidence. Recommendations were formulated based on evidence, additional literature, clinical expertise, and patient and family values.

### Results

We identified a total two SRs of RCTs and six RCTs that reported on the effect of psychological interventions, spiritual support interventions, and a preloss and bereavement care intervention. The evidence showed that only some of the interventions improve certain psychosocial outcomes in children or parents. We were unable to draw conclusions on which intervention is most effective, due to the high variability in interventions and measured outcomes. In total, we formulated 48 recommendations on psychosocial care, including preloss and bereavement care.

### Discussion

With the provided recommendations, we aim to optimize psychosocial care for children with life-threatening and life-limiting conditions and their families. Psychosocial care should be tailored to the child and family. We urge for more research on effectiveness of psychosocial care including preloss and bereavement care interventions among children and parents, but also in siblings. Furthermore, we recommend the use of a standard set of outcome indicators and well-designed multisite RCTs to increase quality of paediatric palliative psychosocial care worldwide.

### **Keywords**

Evidence-based guideline, paediatric palliative care, psychosocial care, preloss and bereavement

## BACKGROUND

Children with life-threatening and life-limiting conditions often receive high complex care which lasts for months or years (1). During the child's disease trajectory, children and their families are confronted with many uncertainties, incremental losses, and difficult decisions (1, 2). These children and their families can experience high levels of suffering and are at risk for poor quality of life (3-5). Paediatric palliative care focuses on relieving physical, psychological, social, and spiritual suffering and ensuring the best quality of life for these children and their families from diagnosis until end-of-life and during bereavement (2, 6, 7).

Multiple studies highlighted a need for improvement of paediatric palliative care such as symptom management to ease distressing symptoms and enhance quality of life in both children and their families (3, 4, 8, 9). Moreover, it is increasingly recognized that not only symptom alleviation, but also attentiveness to psychological, social, and spiritual concerns is essential in paediatric palliative care (10-13), as this determines quality of life and experienced distress among children and their family members (10-13). Furthermore, children and their families experience incremental losses from the moment of diagnosis, throughout the palliative care trajectory, and even new losses after the child's death. Attentiveness to loss, grief, and bereavement is crucial to support children and their families in coping with these losses (14-16).

Psychosocial care which includes the attentiveness to psychological, social, and spiritual concerns, and preloss and bereavement care, is an essential component of paediatric palliative care and provides a meaningful opportunity to enhance the wellbeing of the child and the whole family (10, 16, 17). However, the use and integration of psychosocial care including preloss and bereavement care have been found to be challenging (16, 17). A recent qualitative study among parents in the Netherlands reported that paediatric palliative care still focuses too much on symptom management (18). The study highlights the importance to see the child as a person and focus on the child and family as a whole including psychological, social, and spiritual aspects. Additionally, parents experienced a lack of preloss and bereavement care during the child's palliative trajectory and after the death of their child (18).

Psychosocial care including preloss and bereavement care should be ensured for all children with life-threatening and life-limiting conditions and their families. Clinical practice guidelines (CPGs) are found to be powerful tools in which knowledge from scientific literature, clinical expertise and patient experiences are combined to provide recommendations for clinical practice (19-21). Care delivered in line with these recommendations can decrease variability in provided care, enhance quality of care, and contribute to integration of care services (19-21).

To achieve more optimal psychosocial paediatric palliative care, we provide new evidence-based recommendations focusing on interventions for psychosocial care in which we distinguish psychological interventions, practical and social support, cultural, spiritual, and religious support, and preloss and bereavement care. These recommendations have been developed as part of the revised Dutch CPG on paediatric palliative care (22). In this paper, we present an overview of the evidence, clinical expertise, and recommendations on psychosocial care.

## METHODS

The full methodology of the Dutch CPG for paediatric palliative care is outlined in another publication (22).

### Scope

This guideline aims to improve quality of palliative care for all children aged 0 to 18 years with life-threatening and life-limiting conditions and their caregivers and siblings (hereafter referred to as families), with the ultimate goal to improve quality of life of children and their families. The guideline covers the entire palliative trajectory (from palliative diagnosis till after the child's death continuing in bereavement). (22).

In this paper, we provide recommendations for interventions on psychosocial care including psychological interventions, practical and social support, cultural, spiritual, and religious support, and preloss and bereavement care.

### Multidisciplinary guideline development panel

The guideline development panel included 25 paediatric palliative care experts and a group of nine (bereaved) parents (Appendix A). These experts, of which some had specialized certified training in paediatric palliative care, represented various disciplines such as paediatricians, psychotherapists, psychologists, spiritual counsellors, child life specialists, and paediatric nurses. To maintain consistency throughout the guideline, a core group of 11 experts was formed within the panel. The remaining 14 experts were assigned to two working groups (WGs), one dedicated to psychosocial care, and the other to preloss and bereavement care. The psychosocial care WG tackled three topics for which sub-WGs were established, namely psychological interventions, practical and social support, and cultural, spiritual, and religious support. All topics and clinical questions addressed by the (sub)WGs were prioritized based on input from experts and parents (22). Appendices B and C provide an overview of the working structure and guideline development process.

### Representation of patients and their families

To ensure representation of patients and their families, various methods were utilized (22). Two core group members were assigned to maintain representation of patients and

their families throughout the guideline development process. Additionally, a group of nine (bereaved) parents of children with life-threatening or life-limiting conditions reviewed the initial drafts of all guideline texts and recommendations as well as the draft of the complete guideline. To capture a wide range of experiences, we included parents of children with diverse palliative conditions, ages, and stages of disease (currently receiving palliative care or deceased).

### **Formulation of clinical questions**

The psychosocial care WG formulated four clinical questions on the effect of psychological interventions, practical and social support, and cultural, spiritual, and religious support for children with life-threatening and life-limiting conditions and their family. The WG that focused on preloss and bereavement care formulated four clinical questions on the effect of preloss and bereavement care interventions for children with life-threatening and life-limiting conditions and their family, components of preloss and bereavement care interventions, experiences and needs of parents and health care providers, and communicative strategies (Appendix D).

### **Identification of evidence**

For the eight clinical questions, we updated the systematic literature search conducted for the former CPG (2013) which focused on quantitative studies on paediatric palliative care interventions (last updated January 24, 2020) (Appendix E) (22). Studies were selected based on specific inclusion criteria related to study population (children aged 0 to 18 with life-threatening or life-limiting conditions as defined by the World Health Organization(6)); study design (randomized controlled trials (RCTs), controlled clinical trials (CCTs), and systematic reviews (SRs) of RCTs and CCTs; and study subject (paediatric palliative care psychosocial care interventions including psychological interventions, practical and social support, cultural, spiritual, and religious support, and preloss and bereavement care). Only studies published in English or Dutch were included (Appendix F) (22).

Included studies were summarized in evidence tables and categorized by outcome measures in summary of findings tables (22). We formulated conclusions of evidence for each outcome measure and assessed the quality of the total body of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method (23).

### **Identification of additional literature**

When evidence was insufficient or of low quality, we derived SRs of observational, qualitative, or mixed-method studies from the systematic literature search on paediatric palliative care and through referencing (22). These SRs were considered relevant for the WG that focused on preloss and bereavement care. We synthesized the findings from these SRs in evidence tables and translated these into conclusions of evidence. Given the



variety of study designs included in the SRs, determining both individual study quality and quality of the total body of evidence were not feasible (22).

The conclusions derived from the SRs served as the basis for our recommendations (22). Additionally, we conducted a search for existing evidence-based guidelines that had performed systematic literature searches on this topic. We found one evidence-based guideline, 'End of life care for infants, children and young people with life-limiting conditions (2016)' of the National Institute for Health and Care Excellence (NICE) (24). We used the conclusions of evidence, considerations, and recommendations of the NICE-guideline to inform and support our own recommendations (22).

### **Translating evidence into recommendations**

Multiple factors were considered in translating the evidence into recommendations,: (1) the quality of the evidence (higher quality of evidence was likely to support stronger recommendations), (2) additional literature including evidence-based guidelines and SRs of observational, qualitative, or mixed-method studies, (3) values and needs of patients and their family (4) clinical expertise, (5) acceptability (legal and ethical aspects), (6) feasibility (available time, knowledge and manpower) and (7) benefits versus harms of the interventions (22). The WG members outlined the relevant considerations for each clinical question, and decisions were made through group consensus (22).






The strength of each recommendation was graded using established evidence-based methods (23, 25) (Appendix G). Recommendations were classified as strong to do (green), moderate to do (yellow), or strong not to do (red) (22).


## **RESULTS**

### **Identification of evidence**

The systematic search for quantitative studies on paediatric palliative care interventions resulted in 5078 citations of which 168 citations were subjected to full-text screening (22). Ultimately, eight studies (two SRs of RCTs and six RCTs) on interventions related to psychosocial care including preloss and bereavement care were included (26-33) (Appendix H). Additionally, ten SRs of observational, qualitative, or mixed-method studies on components of preloss and bereavement care interventions, experiences and needs of parents and health care providers, and communicative strategies were included (34-43) (Appendix H).

Appendices J and K present the evidence tables and summary of findings tables. Table 1 provides the conclusions of evidence. Figure 1 offers an overview of the identified evidence and recommendations for each WG (sub) WG.

WGs	Sub-WGs and clinical questions	Identified evidence	Recommendations
WG Psychosocial care	<i>Psychological interventions</i> <ul style="list-style-type: none"> <li>Effect of psychological interventions for children</li> <li>Effect of psychological interventions for family</li> </ul>	<ul style="list-style-type: none"> <li>2 RCTs, 1 SR of RCTs</li> <li>NICE-guideline (no studies)</li> <li>1 RCT, 2 SRs of RCTs</li> <li>NICE-guideline (no studies)</li> </ul>	 Recommendations on psychological interventions N = 8
	<i>Practical and social support</i> <ul style="list-style-type: none"> <li>Social and practical support for children and their families</li> </ul>	<ul style="list-style-type: none"> <li>No studies</li> <li>NICE-guideline (22 qualitative studies)</li> </ul>	 Recommendations on practical and social support N = 8
	<i>Cultural, spiritual, and religious support</i> <ul style="list-style-type: none"> <li>Cultural, spiritual, and religious support for children and their families</li> </ul>	<ul style="list-style-type: none"> <li>2 RCTs</li> <li>NICE-guideline (14 qualitative studies)</li> </ul>	 Recommendations on cultural, spiritual, and religious support N = 11
WG Preloss and bereavement care	<ul style="list-style-type: none"> <li>Effect of preloss and bereavement care interventions for children and their family</li> </ul>	<ul style="list-style-type: none"> <li>1 RCT</li> </ul>	 Recommendations on preloss and bereavement care for parents N = 13
	<ul style="list-style-type: none"> <li>Preloss and bereavement care intervention components for children and their family</li> <li>Experiences of parents and health care providers regarding intervention components</li> <li>Communicative strategies to support parents and family</li> </ul>	<ul style="list-style-type: none"> <li>10 SRs of observational, mixed-method, or qualitative studies</li> </ul>	 Recommendations on preloss and bereavement care for children N = 8

 Strong recommendations to do

**Figure 1.** Identified evidence and recommendations per working group and clinical question

### *Evidence on effect of psychological interventions*

Three studies, two RCTs and one SR of RCTs, reported on psychological interventions that were targeted at improving a variety of psychosocial outcomes in children and adolescents with life-threatening or life-limiting conditions (26, 27, 29). Two RCTs reported on the effects of the Promoting Resilience In Stress Management (PRISM) intervention which aimed to strengthen four resources of resilience including stress-management, goal-setting, cognitive reframing, and meaning-making in four 30-50 minute sessions amongst children and adolescents with cancer (26, 27). The studies showed that hope-finding was significantly increased in children and adolescents with cancer who received the PRISM intervention as compared to the children and adolescents who received usual psychosocial care provided by a social worker (very low quality evidence) (26). However, we found no significant effect of benefit-finding (very low quality evidence) (26). Additionally, no significant difference in percentage of positive health-related quality of life (HR-QoL) trajectories was found between children and adolescents with cancer who participated in the PRISM intervention and those who received usual care (very low quality evidence) (27). When looking more closely at cancer-specific subdomains of HR-QoL, the percentage of positive trajectories in HR-QoL was only significantly increased in the intervention group in two out of eight cancer-specific subdomains, namely worry and nausea (very low quality evidence) (27). One SR of RCTs reported on the effects of an educational problem-solving and social skills intervention for children with cystic fibrosis (29). This intervention showed no significant

difference in psychosocial outcomes including perceived loneliness and social support at three, six, and nine month follow-up in children that received the interventions as compared to usual care (moderate quality evidence) (29).

Three studies, one RCT and two SRs of RCTs, reported on psychological interventions that were targeted at improving several psychosocial outcomes in parents of children with life-threatening or life-limiting conditions (28-30). One RCT investigated the effects of an adapted version of the PRISM intervention directed at parents (PRISM-P) comprising of four 30 to 60 minute sessions. The PRISM-P intervention increased resilience and benefit-finding at six month follow-up among parents who received one on one sessions as compared to usual psychosocial care provided by a social worker (very low quality evidence) (28). No significant effect was found on other outcomes including hope-finding, perceived social support, HR-QoL, perceived stress and psychological distress (very low quality evidence) (28). When the PRISM-P intervention was delivered in group sessions of two to five parents, no significant effect was found in any of the assessed outcomes (very low quality evidence) (28). Additionally, one SR of RCTs reported on the effect of a community-based support programme for mothers of children with cystic fibrosis in comparison to a control intervention consisting of contact with a telephone number. No significant difference in anxiety at 12 month follow-up was found among mothers who received the intervention and those who were in the control group (very low quality evidence) (29). Finally, one SR of RCTs reported on the effect of different psychological interventions for parents of children with cancer including cognitive behavioural therapy, family therapy, problem-solving therapy and multi-systemic therapy in comparison to different control interventions including treatment as usual, active control, or wait-list control (30). The psychological interventions showed significant improvement in parenting behaviour post-treatment, this effect did not sustain at follow-up (low quality evidence) (30). Additionally, psychological interventions did improve parent mental health at follow-up, this effect was not seen directly after treatment (very low quality evidence) (30).

### ***Evidence on effect of cultural, spiritual, and religious support***

Two RCTs described interventions directed at providing spiritual support (31, 32). Iranian mothers of children with cancer received a spiritual training package comprising of seven 90-minute group sessions and reported less stress, anxiety, and depression post-treatment in comparison to the wait-list control group (very low quality evidence) (31). All outcomes remained decreased at three month follow-up, but the effect was only found to remain significant for anxiety (very low quality evidence) (31). Additionally, an educational spiritual intervention consisting of six 45-minute educational sessions on cancer disease, diagnosis, treatment, side effects, diet, spirituality, and meaning-making, decreased burn-out scores among parents of children with cancer (very low quality evidence) (32).

### ***Evidence on preloss and bereavement care interventions***

One RCT reported on a preloss and bereavement care intervention comprising of three components including a support package with information, peer supporter's contact via telephone, and contact with a health care provider two to six weeks after death of the child (33). The preloss and bereavement care intervention had no significant effect on grief reactions among mothers whose children died at age three or younger.

**Table 1.** Conclusions of evidence on paediatric palliative psychosocial care interventions including preloss and bereavement care interventions

<b>Effect of psychosocial care interventions including preloss and bereavement care interventions in palliative care for children aged 0 to 18 years with life-threatening and life-limiting conditions, and their family</b>	
<b>Psychosocial care</b>	<b>Quality of evidence</b>
Psychological interventions	
Promoting resilience in stress management (PRISM) vs. usual care in children and adolescents with cancer	⊕⊕⊕⊕ VERY LOW (1 RCT) (26)
↑ <i>hope-finding</i> at 6-month follow-up	
No significant effect on <i>benefit-finding</i> at 6-month follow-up	
No significant effect on <i>the percentage of positive health-related quality of life trajectories</i> at 6-month follow-up	⊕⊕⊕⊕ VERY LOW (1 RCT) (27)
↑ <i>percentage of positive cancer specific quality of life trajectories regarding the subdomains nausea and worry</i> at 6-month follow-up	
No significant effect on <i>the percentage of cancer specific quality of life trajectories regarding the subdomains, treatment anxiety, procedural anxiety, cognitive, physical appearance, communication, and pain</i> at 6-month follow-up	
Educational problem-solving and social skills interventions vs. usual care in children Cystic Fibrosis	⊕⊕⊕⊕ MODERATE (1 RCT) (29)
No significant effect on <i>loneliness</i> at 3-, 6- and 9-month follow-up	
No significant effect on <i>perceived social support of peers and classmates</i> at 3-, 6- and 9-month follow-up	
Promoting resilience in stress management, parent-directed (PRISM-P) one on one sessions vs. usual care in parents of children with cancer	⊕⊕⊕⊕ VERY LOW (1 RCT) (28)
↑ <i>resilience</i> at 6-month follow-up	
↑ <i>benefit-finding</i> at 6-month follow-up	
No significant effect on <i>hope, perceived social support, health-related quality of life, perceived stress, and psychological distress</i> at 6-month follow-up	⊕⊕⊕⊕ VERY LOW (1 RCT) (28)
Promoting resilience in stress management, parent-directed (PRISM-P) group sessions vs. usual care in parents of children with cancer	
No significant effect on <i>resilience, benefit-finding, hope, perceived social support, health-related quality of life, perceived stress, and psychological distress</i> at 6-month follow-up	

Table 1. Continued

<b>Effect of psychosocial care interventions including preloss and bereavement care interventions in palliative care for children aged 0 to 18 years with life-threatening and life-limiting conditions, and their family</b>	
Community-based support programme vs. control (contact with a telephone number) in mothers of children with cystic fibrosis	⊕⊕⊕⊕ VERY LOW (1 RCT) (29)
No significant effect on <i>anxiety</i> at 12 month follow-up	
Psychological interventions (cognitive behavioural therapy, family therapy, problem-solving therapy or multi-systemic therapy) vs. treatment as usual, active control or wait-list control in parents of children with cancer	⊕⊕⊕⊕ LOW (5 RCTs) (30)
↑ <i>parenting behaviour</i> post-treatment	
No significant effect on <i>parent behaviour</i> at follow-up (2 to 12 months)	
No significant effect on <i>parent mental health</i> post-treatment	⊕⊕⊕⊕ VERY LOW (9 RCTs) (30)
↑ <i>parent mental health</i> at follow-up (2 to 12 months) intervention	⊕⊕⊕⊕ VERY LOW (6 RCTs) (30)
<b>Practical and social support</b>	
Unknown effect of practical and social support	No studies
<b>Cultural, spiritual, and religious support</b>	
Spiritual training package for parents vs. wait-list control in mothers of children with cancer	⊕⊕⊕⊕ VERY LOW (1 RCT) (31)
↓ <i>stress</i> post-treatment after intervention	
↓ <i>stress</i> at 3-month follow-up, however no significant difference as compared to the control group	
↓ <i>anxiety</i> post-treatment and at 3 month follow-up	
↓ <i>depression</i> post-treatment	
↓ <i>depression</i> 3-month follow-up, however no significant difference as compared to the control group	
Educational spiritual intervention vs. control in parents of children with cancer	⊕⊕⊕⊕ VERY LOW (1 RCT) (32)
↓ <i>burnout scores</i> post-treatment and at 1 month follow-up	
<b>Preloss and bereavement care</b>	<b>Quality of evidence</b>
Bereavement intervention comprising of a support package, peer supporter's contact and health care personnel's contact vs. usual care in mothers of children who died at age three or younger	⊕⊕⊕⊕ VERY LOW (1 RCT) (33)
No significant effect on <i>grief reactions including despair, panic behaviour, personal growth, blame and anger, detachment, and disorganisation</i> at 6-month follow-up	

### ***Additional literature for preloss and bereavement care***

We included ten SRs of observational, qualitative, or mixed-method studies that reported on preloss and bereavement care intervention components for parents during the child's end-of-life and after the child's death (34-43). We identified eight preloss and bereavement care intervention components including 1) acknowledging the child's life and identity 2) acknowledging and enabling parenthood, 3) establishing keepsakes, 4) establishing follow-up contact with health care providers, 5) providing peer support, 6) providing education and information, 7) providing remembrance activities, and 8) offering therapies. For each component, we described the reported corresponding actions that could be taken. For example, studies described the following actions to acknowledge the child's life and identity: providing the child with a certificate of life, providing the child with a blessing ceremony, acknowledging the child's identity by learning individual needs and routines, and acknowledging birthdays, holidays, and anniversaries. Furthermore, we identified experiences and needs related to these components that were expressed by parents and health care providers. Generally, parents and health care providers experienced the identified preloss and bereavement care intervention components as desirable or helpful during the end-of-life and after the child's death. For example, with regard to the component 'acknowledging and enabling parenthood', parents reported they desired to maintain a relationship with their child during the end-of-life and wished to be actively involved in the child's care during this time. Moreover, most parents expressed that washing, holding, or dressing the child during the end-of-life and after the child's death is helpful and valuable, but also emotionally difficult. They expressed that support and reassurance from health care providers to spend time with their child during the end-of-life and after the child's death is needed. Table 2 summarizes the preloss and bereavement care intervention components, specific actions, and corresponding experiences and needs reported by parents and health care providers.

Furthermore, the studies reported on a number of communicative strategies that provided support to parents during the child's end-of-life and after the child's death. We identified following strategies including provision of 1) communication, 2) emotional support, 3) hope, 4) knowledge, 5) consistency and continuity of care, and 6) sense of control. For each strategy we summarized positively and negatively labeled aspects that were reported in the SRs. For example, with regards to provision of communication, honest and straightforward communication was positively labeled, while the communication of inadequate and incomplete information about the child was labeled as negative. In table 3, we provide an overview of these strategies and the reported positive and negative aspects.

**Table 2.** Conclusions of evidence on preloss and bereavement care intervention components.

<b>Preloss and bereavement care intervention components, specific actions, and experiences and needs of parents and health care providers<sup>#</sup></b>		
<b>Main category</b>	<b>Specific actions per component</b>	<b>Experiences/needs regarding the intervention component as expressed or experienced by parents and health care providers (HCPs)</b>
Acknowledging the child's life and identity	• Providing the child with a certificate of life (34)	• Not reported
	• Providing the child with a blessing ceremony (34)	• Not reported
	• Acknowledging child's identity (35)	• Learn the infant's individual needs and routines (35)
	• Acknowledging birthdays/holidays/anniversaries (36, 37)	• Not reported
Acknowledging and enabling parenthood	• Maintaining relationship between parent and child (38)	• During the end of the child's life, parents desired to maintain their relationship with their child (38)
	• Washing, holding, or dressing the child both during the end of life and after death (34, 35, 39, 40)	<ul style="list-style-type: none"> <li>• 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 (40)</li> <li>• 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 (40)</li> </ul>

Table 2. Continued

Preloss and bereavement care intervention components, specific actions, and experiences and needs of parents and health care providers <sup>#</sup>		
Main category	Specific actions per component	Experiences/needs regarding the intervention component as expressed or experienced by parents and health care providers (HCPs)
Acknowledging and enabling parenthood	<ul style="list-style-type: none"> <li>Giving parents privacy and input surrounding the death of the child (34, 35, 39)</li> </ul>	<ul style="list-style-type: none"> <li>Parents wanted to be actively involved in the child's care and talk openly with the dying child (41)</li> <li>Acknowledge the wishes of the parents, even when these wishes conflict with the recommendations of the healthcare team (35)</li> <li>Parents preferred to be given control over the how and where the child died (39, 41). Some parents preferred to stay home (41)</li> <li>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(41). 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 (35)</li> </ul>
Establishing keepsakes	<ul style="list-style-type: none"> <li>Safeguarding a lock of hair (34, 40)</li> </ul>	<ul style="list-style-type: none"> <li>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 (38, 40, 42)</li> </ul>
	<ul style="list-style-type: none"> <li>Hand, foot, or face print (34, 40)</li> </ul>	
	<ul style="list-style-type: none"> <li>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) (34-36, 40)</li> </ul>	



**Table 2.** Continued

<b>Preloss and bereavement care intervention components, specific actions, and experiences and needs of parents and health care providers<sup>#</sup></b>		
<b>Main category</b>	<b>Specific actions per component</b>	<b>Experiences/needs regarding the intervention component as expressed or experienced by parents and health care providers (HCPs)</b>
Establishing keepsakes	<ul style="list-style-type: none"> <li>• Pictures (34, 36, 40)</li> </ul>	<ul style="list-style-type: none"> <li>• 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 (40)</li> </ul>
Establishing follow-up contact with HCPs	<ul style="list-style-type: none"> <li>• Follow-up contact (calls, cards, visits, flowers, condolence letters) (34, 36, 37, 39, 43)</li> </ul>	<ul style="list-style-type: none"> <li>• 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 (38)</li> <li>• Parents experienced a strong bond with the hospital staff and felt abandoned if the bond was broken (36, 37, 42)</li> <li>• Follow-up contact was experienced as supportive and appreciated (37-39, 43). Follow-up contact could provide parents with closure, improved coping and facilitated personal growth (35, 36). Some parents felt unable to return to the hospital or that the follow-up meeting left them with unanswered questions (39)</li> </ul>

**Table 2.** Continued

<b>Preloss and bereavement care intervention components, specific actions, and experiences and needs of parents and health care providers<sup>#</sup></b>		
<b>Main category</b>	<b>Specific actions per component</b>	<b>Experiences/needs regarding the intervention component as expressed or experienced by parents and health care providers (HCPs)</b>
Providing peer support	<ul style="list-style-type: none"> <li>Facilitating contact with peers/ support groups (34, 36, 37, 39, 43)</li> </ul>	<ul style="list-style-type: none"> <li>Parents value peer support and expressed a desire to have contact with other families that lost a child (36, 42). Peer support reduced a sense of isolation, resulted in development of healing friendships, improved coping and allowed for personal growth (36)</li> <li>Peer support did not result in a significant change in psychosocial functioning and grief reactions (36)</li> </ul>
	<ul style="list-style-type: none"> <li>Mindfulness based intervention, cognitive behavioural therapy based and group retreat (43)</li> </ul>	<ul style="list-style-type: none"> <li>Mindfulness: showed no significant effect (43)</li> <li>Cognitive behavioural therapy group: significant reduction in overall grief symptoms in the intervention group (43).</li> <li>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 (43)</li> </ul>
Providing education and information	<ul style="list-style-type: none"> <li>Information(sessions), videos folders and booklets (34, 36, 37, 43)</li> <li>Financial advice (34, 36)</li> <li>Educational support meetings for peers and relatives (34)</li> <li>Seminars or workshops on coping and grief (34)</li> <li>Being involved in developing training sessions and research (37)</li> </ul>	<ul style="list-style-type: none"> <li>Parents appreciated being involved in the development and administrating of bereavement education programs and interventions (37)</li> <li>Parents expressed a need for more preparation for death and bereavement (42)</li> </ul>
Providing remembrance activities	<ul style="list-style-type: none"> <li>Memorial ceremonies or services (34, 36, 37)</li> <li>HCPs attending the funeral (34, 37)</li> </ul>	<ul style="list-style-type: none"> <li>Having HCPs attend the funeral may enhance parents' feelings of support from the hospital (35)</li> </ul>
Offering therapies	<ul style="list-style-type: none"> <li>Therapeutic intentional touch (43)</li> <li>Expressive art therapy (43)</li> <li>Referral for individual counselling (36)</li> </ul>	<ul style="list-style-type: none"> <li>Parents expressed a need for bereavement mental health support in addition to follow-up (37)</li> </ul>

<sup>#</sup> This table provides the conclusions of evidence described in the additional literature comprising of ten SRs of observational, mixed-method, or qualitative studies

**Table 3.** Conclusions of evidence on communicative strategies during the child's end-of-life and after death.

Communicative strategies for parents and family during the child's end-of-life and after death <sup>#</sup>		
Strategy	Positively labeled	Negative labeled
Provision of communication/ information	<ul style="list-style-type: none"> <li>• Honest and straightforward communication (38, 42)</li> <li>• Provision of complete information (38)</li> <li>• Provision of information in understandable language (35, 39)</li> <li>• Timely provision of information (35, 39)</li> <li>• Facilitating privacy (38)</li> </ul>	<ul style="list-style-type: none"> <li>• Parents receiving inadequate and incomplete information about the child (including autopsy results) (38)</li> <li>• Parents receiving conflicting information (39, 41) due to involvement of a number of HCP (39)</li> <li>• Parents receiving emotional information in a public area (38)</li> </ul>
Provision of emotional support	<ul style="list-style-type: none"> <li>• Support, expression of emotions, kindness and compassion by HCPs who care for the child (35, 39, 42)</li> <li>• Showing dignity and respect (42)</li> <li>• Comforting the parents with a hug, smile or beverage (35)</li> <li>• Delivering difficult news in a sensitive and caring manner (42)</li> </ul>	<ul style="list-style-type: none"> <li>• Lack of sensitivity and empathy (38)</li> <li>• Lack of physical bereavement care (38)</li> <li>• Lack of emotional support and compassion: parents reported that nurses had difficulties supporting them emotionally when care shifted from curing to palliative care (38)</li> </ul>
Provision of hope	<ul style="list-style-type: none"> <li>• Maintenance of hope while accepting their child's prognosis (41, 42)</li> <li>• Not give up hope until it is clear that there is no other course (35)</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>
Provision of knowledge/ expertise	<ul style="list-style-type: none"> <li>• HCPs have experience and show confidence in caring for the child (35)</li> </ul>	<ul style="list-style-type: none"> <li>• 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 (35)</li> </ul>
Provision of consistency and continuity of care (personnel)	<ul style="list-style-type: none"> <li>• Access to medical staff day/night (39, 41)</li> <li>• Coordination and continuity of care (41)</li> <li>• Establishing the relationship between HCP and child facilitated death conversations (41)</li> </ul>	<ul style="list-style-type: none"> <li>• Inconsistency in HCPs near end of life (41)</li> <li>• Sense of being abandoned by HCPs (41)</li> </ul>

**Table 3.** Continued

<b>Communicative strategies for parents and family during the child's end-of-life and after death <sup>#</sup></b>		
<b>Strategy</b>	<b>Positively labeled</b>	<b>Negative labeled</b>
Provision of sense of control	<ul style="list-style-type: none"> <li>Personal control and authority over the child's death and life, helped parents with keeping fear and uncertainty within limits of tolerability (41). Provision of informational, emotional and instrumental support enhanced sense of control (41). 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 (41)</li> </ul>	<ul style="list-style-type: none"> <li>Feeling unprepared for child's death (41)</li> <li>Loss of control (39, 41)</li> </ul>

<sup>#</sup> This table provides the conclusions of evidence described in the additional literature comprising of ten SRs of observational, mixed-method, or qualitative studies

### Translating evidence into recommendations

The guideline development panel formulated 27 recommendations on psychosocial care including psychological interventions (n=8), practical and social support (n=8), and cultural, religious, and spiritual support (n=11). Furthermore, a total of 21 recommendations were formulated on preloss and bereavement care. Recommendations were based upon evidence, additional literature, clinical expertise, and patient and family values. Table 4 provides an overview of all formulated recommendations. We indicated for each recommendation whether it was supported by evidence or additional literature.

#### *Recommendations on psychological interventions*

The evidence showed that some psychological interventions can improve certain psychosocial outcomes in both children with life-threatening and life-limiting conditions and their parents (26-30). In the identified evidence, we found a large variability in intervention characteristics and measured outcomes (26-30). Additionally, the quality of evidence was often rated as very low. Therefore, the guideline development panel was unable to recommend specific psychological interventions. Nevertheless, the panel recognized that psychological support could facilitate children with life-threatening and life-limiting conditions and their families in processing their experiences, concerns, and thoughts. To facilitate appropriate psychological support, the panel stated that the primary health care provider should be responsible for timely initiation of psychosocial care in consultation with the family (recommendation 1, 9, 28). Moreover, the panel emphasized that psychological support should be tailored to the individual needs and preferences of child and family.

The panel recognized that in order to tailor psychological support appropriately, attentiveness to the child's age, developmental stage, and changes in the child's condition is crucial. Furthermore, the panel highlighted the importance of providing clear information on emotional and psychological consequences of the child's disease trajectory and monitoring the wellbeing of siblings and other family members actively (recommendation 2-7, 11, 12). The panel realized that the considerations used are not only essential in provision of psychological support but are the basis for provision of practical and social support, cultural, spiritual, and religious support, and preloss and bereavement care as well. Therefore, these considerations were used as a starting point for formulating all recommendations.

### ***Recommendations on practical and social support***

We found no evidence on the effects of practical and social support for children with life-threatening and life-limiting conditions and their family. Therefore, the guideline development panel formulated recommendations based on the NICE-guideline, clinical expertise, and patient and family values. With regards to practical and social support, low to moderate quality evidence from the NICE guideline showed that support for accessing care, and support from family members and local communities is helpful, as reported by parents. The panel acknowledged this and recommended that tailored practical and social support should be offered to the child and family. Additionally, the panel strongly recommended that when having conversations with child and family, health care providers should establish carefully what child and family already know, allow space, and time for emotions, and prepare parents on difficult questions children might ask (recommendation 11, 13). Furthermore, very low to moderate quality evidence from the NICE-guideline showed that parents and other family members greatly benefited from respite care but had difficulties to access it. Both parents and health care providers indicated that awareness and understanding of the benefits of respite care is important. The panel recognized that child and family do not always know what forms of practical support exist. They recommended that the child and family should be informed about existing and available practical support, such as respite care, financial support, and support at work (recommendation 14). Also, moderate quality evidence from the NICE-guideline showed that parents appreciated support that was provided before and after their child's death. Moreover, they appreciated continuity in care and staff during the end-of-life and after their child's death. Therefore, the panel recommended to discuss arrangements that can be made prior to and after the child's death (recommendation 16). Moreover, they highlighted the importance of providing continuity in health care providers as much as possible to create trust and peace of mind (recommendation 10). Finally, the panel emphasized that not only child and family but also health care providers might need practical and social support (recommendation 15).

### ***Recommendations on cultural, spiritual, and religious support***

We found very low quality evidence that (educational) spiritual trainings can improve psychosocial outcomes (31, 32). The effectivity of these interventions was studied in populations with cultural, religious, and spiritual backgrounds that were different from the Dutch population (31, 32). Therefore, the guideline development panel was unable to state whether these same interventions would be effective for child and family in the Netherlands and therefore could not recommend these specific spiritual interventions. Additionally, very low to moderate quality evidence in the NICE guideline showed that parents reported a wide variety in their attitudes and needs regarding cultural, spiritual, and religious support, and experienced benefits and difficulties with regard to one's beliefs. Moreover, parents reported the use of different aphorisms, rituals, and practices. As a result, the panel could not give recommendations on specific needs and preferences related to cultural, spiritual, and religious support. Instead, the panel emphasized that health care providers should consider and explore child and families' cultural, spiritual, and religious beliefs, needs, values and wishes and that child and family should have access to cultural, spiritual, and religious support (recommendations 19, 20, 21). The panel emphasizes this is especially essential during decision-making, communication of bad news and meaning-making (recommendation 17, 18, 22-26). Spiritual counsellors can support child and family, regardless of their background, when existential questions may arise. Therefore, the panel recommended to engage a spiritual counsellor if necessary (recommendation 27).

### ***Recommendations on preloss and bereavement care***

We found very low quality evidence from one RCT, that a preloss and bereavement care intervention, comprising of a support package and health care provider or peer contact, had no significant effect on grief reactions among mothers (33). From the additional literature comprising of ten SRs, we identified multiple preloss and bereavement care intervention components and communicative strategies that were experienced as helpful or desirable by both parents and health care providers (Table 2 and 3) (34-43). Based on these results, the guideline development panel emphasized the importance of offering preloss and bereavement care to children with life-threatening and life-limiting conditions and their family. Furthermore, the panel highlighted the importance of understanding the extent of losses that parents encounter. As parental coping with loss and grief entails both containing feelings of grief and experiencing them, losses may be more intertwined with daily experiences than health care providers may be aware of. Therefore, the panel recommended health care providers to be alert to the losses that parents experience, which vary per person (recommendation 29, 30). Moreover, the panel recognized that health care providers can have a great impact on how parents experience the child's end-of life and can support parents by engaging in conversation with time and attention and seeing the child as a person and family as a whole. It is recommended for health care providers to inform parents on grief reactions, attune their care to the parents' coping,

to be sensitive to signals from parents, to discuss child and family wishes at arranged times, and to be attentive to the impact of culture, spirituality and religion on loss and grief (recommendation 31, 32). Furthermore, health care providers should offer time and space to talk about feelings of loss and grief. However, they should be careful not to disrupt the parents' coping by, for instance, postponing the exploration of grief when parents are in need of containing their grief. Therefore, the panel recommended to appoint a few health care providers that explore the topic of loss and grief with parents so that others may offer them some respite on the topic (recommendation 33). Based on the identified preloss and bereavement care components and communicative strategies that parents and health care providers perceived as desirable, the panel recommended to make parents feel safe and secure by seeing and acknowledging the child, to actively offer information about possible support, and to provide multiple preloss and bereavement care conversations over time (recommendation 34-38). Health care providers play an important role in the continuity of care and support after the child's death. During follow-up conversations, they can support parents to build a narrative around their child's (end-of-) life, by acknowledging the child's identity, discussing the disease trajectory, exploring future needs regarding bereavement care, and facilitating the parents to provide feedback (recommendation 39, 40).

Finally, the panel emphasized the importance of supporting the sick child and sibling during experiences of loss, grief, and bereavement. It is recommended to explore with parents whether or not and how to talk to their children about approaching end-of-life, to explain to children what will happen in a developmentally appropriate way, to give the child the opportunity to express emotions and feelings, to involve siblings at the time of death by giving them a meaningful task, and to help children and siblings regulate emotions by assigning words to expressions or emotions (recommendation 41-46). Furthermore, the panel highlighted that children often grieve intermittently and conceptualization of death may change as children mature and recommend health care providers to consider this when providing support, which may also include prolonging support over a longer period of time as children grieve new losses as they reach new developmental stages (recommendation 47, 48).

**Table 4.** Recommendations on paediatric palliative psychosocial care interventions including preloss and bereavement care interventions

<b>Recommendations on psychosocial care interventions, including preloss and bereavement care interventions for children aged 0 to 18 years with life-threatening and life-limiting conditions, their families, and health care providers (n=48)</b>		
<b>Psychosocial care</b>		
Psychological interventions		
Do	1	The primary health care provider is responsible for initiating psychosocial care, but other health care provider can also identify and draw attention to the need for psychosocial care. The interpretation of psychosocial care takes place in consultation with the child, family, and multidisciplinary team.
	2	Provide clear information to child and family (including siblings) about the emotional consequences that may be appropriate for the child's condition.
	3	Be alert that child and family (including siblings) may have problems in the areas of: <ul style="list-style-type: none"> <li>• Social emotional development.</li> <li>• Cognitive development.</li> <li>• Mental health.</li> </ul>
	4	Be aware that it is important for children to have the space and opportunities in activities and conversations to be able to express themselves appropriate to their developmental stage about the experience of their illness and impending death. Note that there may be developmental differences in emotional responses, experiences and understanding of death.
	5	If emotional burden persists, refer child and family to expert psychosocial care services to help with the processing of profound experiences and stress, and assist with coping and building resilience. Consider a child life specialist, medical social worker, or a psychologist. To provide support for religious and spiritual suffering and answer questions on meaning, a spiritual counsellor may be consulted. <sup>a, b</sup>
	6	Actively monitor the wellbeing of siblings and provide appropriate support including practical and social support, educational, psychological, or cultural, spiritual, and religious support.
	7	Keep in mind that other family members (e.g. grandparents) and loved ones (e.g. friends, boyfriends, or girlfriends) who are important to the child and family may need support including practical and social support, educational, psychological, or cultural, spiritual, and religious support. Be aware that emotions of other family members and loved ones may also have a significant effect on child and family.
	8	Respond promptly to rapid changes in the child's condition, as children may need rapid access to psychosocial support including practical and social support, educational, psychological, or cultural, spiritual, and religious support.
Practical and social support		
Do	9	The primary health care provider is responsible for initiating psychosocial care, but other health care providers can also identify and draw attention to the need for psychosocial care. The interpretation of psychosocial care is made in consultation with the child, family, and multidisciplinary team.
	10	Strive for as much continuity in care providers as possible. Keep in mind that this is important for confidence in the care and provides peace of mind for children and their parents or health care providers.



**Table 4.** Continued

<b>Recommendations on psychosocial care interventions, including preloss and bereavement care interventions for children aged 0 to 18 years with life-threatening and life-limiting conditions, their families, and health care providers (n=48)</b>	
Do	11 When having conversations with child and parents, such as when changes in the course of illness occur, it is important to: <ul style="list-style-type: none"> <li>• Allow time and space for emotions.</li> <li>• Provide honest and open information appropriate for the child and family. Also provide space for those who do not want to know.</li> <li>• Establish what the parents and child already know.</li> </ul>
	12 With changes in the course of illness, give parents the opportunity and space to reflect with health care providers on how they will communicate with the child and siblings. Help parents by creating this space.
	13 Inform parents about potentially confrontational questions that child or siblings may ask. Explain that parents do not have to have ready answers and can use the questions to find out more about what is on the child's or sibling's mind. Explain that parents do not have to hide their emotions from their child(ren). Children are usually perceptive to the feelings of their loved ones so hiding emotions can be confusing for a child. Explain to parents that they can explain to their children that they can grief and remain available to them.
	14 Be alert that children and parents have different needs regarding practical and social support and that these needs may change during the course of the illness. This may include the following: <ul style="list-style-type: none"> <li>• Social support including attention to parenting, relationship with spouse or partner or sibling support. If necessary, involve a (medical) social worker, a child life specialist, psychologist, or spiritual counsellor. Also refer to peer to peer contact groups if necessary.</li> <li>• Material support including housing, home modifications, aids for medication administration or mobility and transportation.</li> <li>• Practical support such as access to respite care, attention to the work situation of parents or attention to the wishes of the child, family and loved ones. If necessary, engage wish foundations such as Make a Wish, Make a Memory, Living Memories Foundation.</li> <li>• Educational support including attention to educational facilities at home and in the hospital.</li> <li>• Financial support including attention to financial and organizational issues.</li> </ul>
	15 Be alert that health care providers may also need practical, social, and spiritual support.
	16 Discuss necessary practical arrangements with parents or health care providers after their child's death and provide them with written information. Emphasize that things may feel different after death and that arrangements can always be adjusted. These may include arrangements regarding: <ul style="list-style-type: none"> <li>• care of the body.</li> <li>• funeral preparations.</li> <li>• postmortem examination.</li> <li>• relevant legal considerations, including: <ul style="list-style-type: none"> <li>– the involvement of a 'child death overview panel'.</li> <li>– mandatory notification of the coroner after death.</li> <li>– determination of the death.</li> </ul> </li> </ul>

Table 4. Continued

<b>Recommendations on psychosocial care interventions, including preloss and bereavement care interventions for children aged 0 to 18 years with life-threatening and life-limiting conditions, their families, and health care providers (n=48)</b>	
Cultural, spiritual, and religious support	
Do	17 In discussions with children and their parents, investigate whether there are aspects of their religious or philosophical beliefs that should be considered in care, especially in decision-making about treatment options. <sup>a</sup>
	18 Ask about the uniqueness and specialness of the child and the specific meaning-making of parents, especially with regard to their child's quality of life and his or her place in the family.
	19 Explore whether children and their parents would like to talk to someone about their beliefs and values (e.g., cultural, spiritual, and religious). Refer to a spiritual counsellor for this purpose, if necessary.
	20 Consider and enquire about what rituals are performed and what needs the children and parents may have, especially in the terminal phase.
	21 Be open to spiritual experiences that may play a role in children and families without being linked to religion or a philosophical framework. Ask what is meaningful, and important to them at this time.
	22 Be alert to the influence of culture and, if parents wish, include their family or other people in their network in communication around decision making, as they may otherwise exert an unseen influence on the decision-making process.
	23 Be open to the fact that parents have the right to "consciously not want to know". Also provide space when parents want to know more.
	24 Be aware that certain terminology can create misunderstandings. For example, "We are going to discontinue treatment" suggests that treatment is available but is being withheld from this child.
	25 Be aware that in many cultures the child's spiritual well-being takes precedence over the importance of hearing the truth and that for religious reasons it may be difficult for parents to agree to discontinue treatment.
	26 Keep in mind that if parents hold out hope for a good outcome until the end it does not mean that they have not heard or understood the bad news.
	27 Engage a spiritual counsellor when uncertain about the appropriate approach to people of a different culture or religion or for information about performing rituals.
<b>Preloss and bereavement care</b>	
Preloss and bereavement care for parents	
Do	28 The primary care provider is responsible for initiating preloss and bereavement care conversations. In consultation with child, family and multidisciplinary team including primary care providers, it is ensured that the desired preloss and bereavement care conversations take place.
	29 Loss is what parents experience as loss; this can vary from person to person. Be alert to loss experiences from the time the child is suspected of a serious condition until well after the child's death.

**Table 4.** Continued

<b>Recommendations on psychosocial care interventions, including preloss and bereavement care interventions for children aged 0 to 18 years with life-threatening and life-limiting conditions, their families, and health care providers (n=48)</b>	
Do	30 Be alert to parents' experiences of loss, even some interventions may feel like a step backwards to parents and thus a loss. Provide support if parents need it.
	31 During the end of life of their child and in crisis situations, parents usually try to remain strong to support their child and to cope with the situation. During this period, parents may deeply suppress their own emotions. Assist and support parents to cope at this time.
	32 Explain to parents what normal grief reactions to expect from themselves and other people. Grief reactions are normal reactions in an abnormal situation. <sup>c</sup>
	33 Offer parents emotional peace of mind during the palliative phase. Designate one or two health care providers who will talk with parents about their feelings of loss and grief if the parents have the capacity to do so. Be sensitive to what the parents need, for example, is their coping more loss-oriented or recovery-oriented. Other health care providers can keep the atmosphere lighter and less serious unless parents initiate a deeper conversation.
	34 Be quick to recognise signals from parents, such as questions or comments, that parents want to talk about loss or deeper concerns.
	35 Whenever possible, discuss parents' wishes, the child's prognosis, and loss at arranged times. This ensures that parents know when to prepare emotionally for such a conversation and when parents should not expect it. <sup>c</sup>
	36 Make parents feel safe and secure in their child's palliative journey by: seeing and acknowledging the child, approaching parents as equal partners, not making decisions apart from parents, and keeping parents fully informed. <sup>c</sup>
	37 Actively offer initiatives or information to parents about possible support in terms of choices that can be made, making memories, loss and grief, and support options for parent and family. <sup>c</sup>
	38 Discuss how parents want to say goodbye to their child. Consider cultural differences. Discuss whether there are religious aspects that are important in dealing with loss and mourning and what health care providers can do/contribute to that regard.
	39 Prepare parents for winding down and stopping support from regular health care providers and transferring care. Ensure that parents continue to feel supported immediately after the death and the ensuing bereavement period, and that parents know how they can access additional support. <sup>c</sup>
	40 Provide space for parents to have multiple preloss and bereavement care conversations with health care providers who were involved in their child's care before, during and after death. Because children receive care and treatment in different settings, this may require multiple conversations with different health care providers. Ensure the presence of familiar health care providers who can reflect on the child's life and identity, answer questions, and go through the illness and death process and the process of decision-making. <sup>c</sup>

Table 4. Continued

Recommendations on psychosocial care interventions, including preloss and bereavement care interventions for children aged 0 to 18 years with life-threatening and life-limiting conditions, their families, and health care providers (n=48)		
Preloss and bereavement care for children		
Do	41	Explore with parents whether or not and how they want to talk to their children about the approaching end-of-life and death. <sup>c</sup>
	42	Explain to children in developmentally appropriate ways what is going on and what will happen.
	43	Give the child the opportunity to express their emotions and feelings to a trusted adult outside the family.
	44	Involve siblings at the time of death by giving them a meaningful task appropriate to their developmental age and level of responsibility.
	45	Help children regulate and normalise emotions by assigning words to behavioural expressions of emotions.
	46	Help siblings find a way to adequately express their emotions.
	47	Children grieve intermittently. At times they experience the loss and at other times the loss does not exist for a while. Support children in this and also accept that children quickly turn their attention to other activities.
	48	Children's conceptualisation of death changes and develops as they mature. As a result, after several months or years, a child may have to process new aspects of their grief and new questions may arise.

- a. For this recommendation, very low to low quality evidence was identified
- b. For this recommendation, moderate quality evidence was identified
- c. For this recommendation, systematic reviews of observational, qualitative, or mixed-method studies were identified

DISCUSSION

It is widely recognized that a child's diagnosis with a life-threatening or life-limiting condition impacts the psychosocial functioning of the child and the entire family (5). This is not only relevant during the child's life, but also after the death of the child (17, 44). Provision of psychosocial care including preloss and bereavement care is essential for child and family, enhances quality of life and is often mentioned as being a crucial part of paediatric palliative care (4, 5, 13, 14). However, studies frequently report a lack of attention to psychosocial care including preloss and bereavement care (5, 18). In this paper, we present the identified evidence and provide recommendations to optimize psychosocial care including psychological interventions, practical and social support, cultural, spiritual, and religious support, and preloss and bereavement care in paediatric palliative care.

We formulated recommendations by using an evidence-based approach. We systematically searched for interventions described in SRs of RCTs and CCTs, RCTs, and CCTs in scientific literature. As a result, we identified eight studies reporting on effectivity of psychological

interventions, spiritual training interventions, and a preloss and bereavement care intervention (26-33). We concluded that the evidence could only partly answer our clinical questions. The quality of the total body of evidence was rated as very low to moderate. As we expected limited evidence on these topics, we identified additional literature including an evidence-based clinical practice guideline (24) and ten SRs of observational, qualitative, or mixed-method studies (34-43).

The recommendations were developed in close collaboration with a national multidisciplinary guideline development panel consisting of professionals from multiple disciplines and parents. Based on the identified evidence, additional literature, clinical expertise, and patient and family values, we were able to compile a comprehensive set of strong recommendations that provide guidance on psychosocial care including preloss and bereavement care. As our recommendations were largely based upon international evidence, we believe a large proportion of these recommendations will be applicable in other countries and can be used to optimize psychosocial care including preloss and bereavement care. However, we recognize that country and culture specific factors should be carefully considered before applying any recommendations.

The identified studies described the effects of a variety of interventions related to psychosocial care, of which only some interventions were found to significantly improve certain psychosocial outcomes in children with life-threatening and life-limiting conditions or their parents. As a result, we identified multiple gaps of knowledge. First, the majority of the studies reported on effects of psychological, spiritual, and preloss and bereavement care interventions among parents. Only three studies focused on the effectivity of psychological interventions among children. The majority of conclusions of evidence were rated as very low quality evidence. Additionally, we found no evidence on practical and social support among both children with life-threatening and life-limiting conditions and their family. Finally, we have found no evidence on the effectivity of any psychosocial care interventions among siblings. Both social and practical support including respite care and psychosocial care interventions for siblings have been well documented knowledge gaps but are yet to be addressed (10, 14, 16, 44, 45). Therefore, we urge for well-designed multisite parallel RCTs to address these knowledge gaps.

Moreover, we found a large variability in reported psychosocial outcomes and outcome measurements, which made it difficult to compare the effectivity of interventions. As a result, we could not draw a definitive conclusion on which intervention can best be used. This was in line with the findings of a recent SR that reported significant heterogeneity in used outcomes in paediatric palliative care (46). In this SR, 136 outcomes in 46 outcome domains were used to measure the effect of specialized paediatric palliative care interventions (46). In order to improve comparability between interventions, we strongly suggest developing a standard set of outcome indicators for paediatric palliative care with

harmonized outcome definitions and measurement tools (47). Adopting this standard set of outcomes for paediatric palliative care across organizations and countries, could facilitate the identification of best practices and further improve quality of paediatric palliative care worldwide.

When translating evidence into recommendations, it became very clear that psychosocial care including psychological interventions, practical and social support, cultural, spiritual, and religious support, and preloss and bereavement care is considered beneficial for all children with life-threatening and life-limiting conditions and their families. Psychosocial care including preloss and bereavement care should not only be offered to every child and family but should also be tailored to the child and family as a whole. We recognize that provision of tailored psychosocial care, requires adequate staffing, time, funding, and education on the importance of psychological, social, and spiritual needs assessment and support (14, 48-50). We emphasize that addressing these issues is a precondition for application of recommendations in clinical practice (50).

Furthermore, it is increasingly recognized that caring for children who are suffering, and their families can lead to distress and burnout among health care providers (7, 14). Health care providers who provide paediatric palliative care should receive support to prevent distress, compassion fatigue, and burnout. However, there remains a lack of studies on the effectivity of interventions aiming to prevent distress and burnout among health care providers (7, 14). We strongly urge for more research on this topic to formulate evidence-based recommendations.

In conclusion, with the provided recommendations, we aim to optimize psychosocial care including preloss and bereavement care for children with life-threatening and life-limiting conditions and their families. We identified that psychosocial care requires a personal approach tailored to the child and family. We urge for more research on effectiveness of psychosocial care, including psychological interventions, practical and social support, cultural, spiritual, and religious support, and preloss and bereavement care interventions among children with life-threatening and life-limiting conditions and parents, but also in siblings. Furthermore, we recommend the use of a standard set of outcome indicators and well-designed multisite RCTs to increase quality of psychosocial care including preloss and bereavement care worldwide.

## **SUPPLEMENTARY MATERIAL**

Additional files will be available online once the manuscript is published.

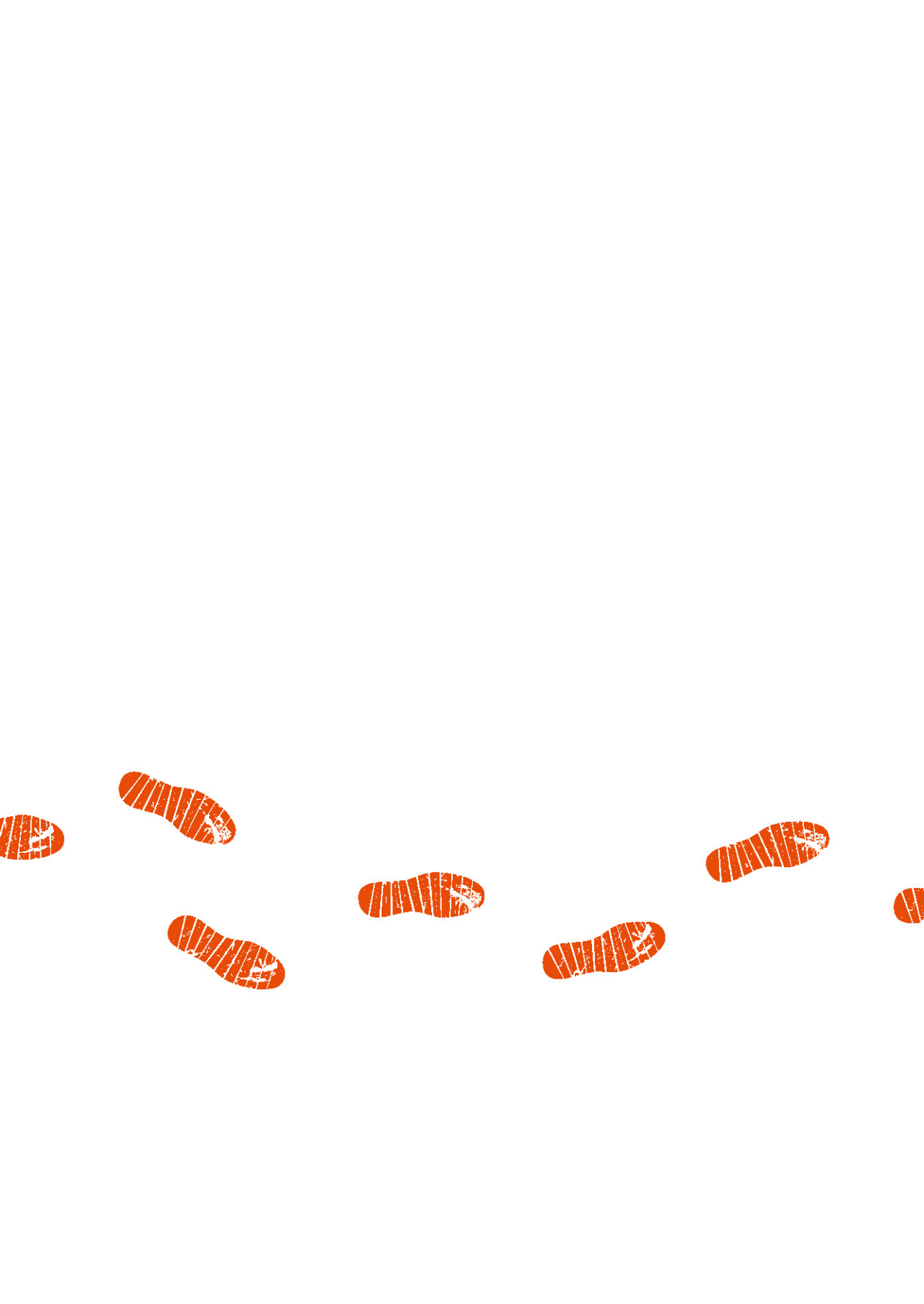
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# 6

## Summary and general Discussion



## SUMMARY

Too often children with life-threatening and life-limiting conditions and their families fail to receive adequate and consistent paediatric palliative care that meets their physical, psychological, social, and spiritual needs (1-3). With the development of the revised Dutch clinical practice guideline for paediatric palliative care, we aim to optimise paediatric palliative care and improve quality of life for all children aged 0 to 18 years with life-threatening and life-limiting conditions and their families.

In this thesis, the methodology and the results of the revised Dutch clinical practice guideline for paediatric palliative care are described. Each chapter of this thesis focuses on a different aspect of the guideline.

### **The methodology of the revised Dutch clinical practice guideline for paediatric palliative care**

In *Chapter 2*, we described the methodology for the revision of the Dutch clinical practice guideline for paediatric palliative care and provided an overview of the identified evidence. Together with a multidisciplinary guideline development panel consisting of 72 paediatric palliative care experts and nine parents of children with life-threatening or life-limiting conditions, we developed recommendations focusing on multiple topics related to paediatric palliative care. The recommendations were based upon evidence from international scientific literature, additional literature, patient and family values, and clinical expertise. We described the approaches that were used to deal with expected and unexpected challenges, which we encountered during the development of this guideline. First, to prevent unmanageable amounts of work in providing recommendations on the multiple selected topics, we re-used evidence by updating two existing systematic literature searches and focusing on high-quality evidence. We searched for quantitative evidence including systematic reviews (SRs) of randomised controlled trials (RCTs) and clinical controlled trials (CCTs), RCTs, and CCTs, and qualitative evidence. Second, to deal with a lack of evidence, we searched for additional literature sources including guidelines, textbooks, and SRs of observational, qualitative, or mixed-method studies, which we used to refine recommendations. Third, to improve dissemination of the revised guideline in the Netherlands, we collaborated with many stakeholders in paediatric palliative care and ensured the guideline was approved by all relevant professional and patient associations. Finally, to deal with a high workload, we learned it was beneficial to appoint one full-time researcher who coordinated the entire guideline development process.

### **Recommendations for symptom treatment in paediatric palliative care**

*Chapter 3* covered the evidence and recommendations on interventions to treat symptoms in paediatric palliative care including anxiety & depression, delirium, dyspnoea, haematological symptoms, coughing, skin complaints, nausea & vomiting, neurological

symptoms, pain, death rattle, fatigue, paediatric palliative sedation, and forgoing hydration & nutrition. In this chapter, we identified three SRs of RCTs, and 15 RCTs that reported on the effects of specific (non) pharmacological interventions to treat symptoms in paediatric palliative care. Only a few of these interventions showed significant symptom relief. With the identified evidence, we could only partly answer eight out of 27 formulated clinical questions on interventions to treat symptoms. For the majority of clinical questions, the overall quality of evidence was rated as low to very low. We included 29 guidelines and 2 textbooks, to deal with the lack of evidence. The guideline development panel emphasised that the primary focus of every treatment-related decision should be the quality of life and the values and needs of the child and their family. This principle was considered the foundation for all recommendations on symptom treatment. Other key considerations were treatment effects, anticipated burden of treatment on the child, potential adverse effects, and the child's prognosis and life expectancy. Regarding paediatric palliative sedation and forgoing hydration and nutrition, the entire process including communication, preparation, execution, and evaluation was covered in the recommendations. In total, 221 recommendations on symptom treatment were formulated.

### **Recommendations for provision of advance care planning & shared decision-making in paediatric palliative care**

In *chapter 4* the evidence on advance care planning and shared decision-making in paediatric palliative care was presented along with the formulated recommendations. We identified very low to low quality evidence from four RCTs indicating that an advance care planning intervention can enhance agreement on future treatment preferences among adolescents with life-threatening and life-limiting conditions and their adult surrogates without negatively impacting quality of life related outcomes. Additionally, 33 qualitative studies on barriers and facilitators to advance care planning and shared decision-making were found, of which 22 studies were newly published since the original systematic literature search, tripling the total number of included qualitative studies. Most identified barriers and facilitators were of moderate quality evidence. Based on the identified evidence, clinical expertise and patient and family values, 28 strong recommendations were formulated which provided guidance to offer advance care planning and shared decision-making, involve children and their family, and communicate information about care and treatment.

### **Recommendations for provision of paediatric palliative psychosocial care including preloss and bereavement care**

*Chapter 5* outlined the evidence and described the provided recommendations on paediatric palliative psychosocial care including preloss and bereavement care. We identified two SRs of RCTs and six RCTs that reported on the effect of psychological interventions, spiritual support interventions, and a preloss and bereavement care intervention. The

evidence showed that only some of the interventions improve certain psychosocial outcomes in children with life-threatening or life-limiting conditions or their parents. We were unable to draw conclusions on which intervention is most effective, due to the high variability in interventions and measured outcomes. To deal with lack of evidence, we included ten SRs of observational, qualitative, or mixed-method studies on components of preloss and bereavement care interventions, experiences and needs of parents and health care providers, and communicative strategies. The guideline development panel highlighted the importance of tailoring psychosocial care to the needs and preferences of the child and family, providing clear information on emotional and psychological consequences of a child's palliative disease trajectory, and monitoring the wellbeing of siblings and other family members. These considerations formed the basis for formulating the recommendations. In total, 27 recommendations on psychosocial care including psychological interventions, practical and social support, and cultural, religious, and spiritual support were established. Furthermore, a total of 21 recommendations were formulated on preloss and bereavement care.

## GENERAL DISCUSSION

In this general discussion, we reflect upon the methods used for the development of the revised Dutch clinical practice guideline for paediatric palliative care, the scope of the guideline, research in paediatric palliative care, and implementation of the guideline.

### Methods used for guideline development

#### *Strengths and limitations*

In 2013, the first clinical practice guideline for paediatric palliative care was published in the Netherlands. This guideline had several shortcomings. First, only one systematic search was performed to identify SRs on paediatric palliative care, and none of the identified studies met the inclusion criteria. Therefore, it was not possible to critically appraise evidence (4). As a result, recommendations were largely based upon existing international paediatric palliative care guidelines and sources that were most frequently used in daily practice, i.e. two textbooks on paediatric palliative care, and Dutch guidelines for adult paediatric palliative care (4). Another shortcoming was the lack of structured involvement of patient and parent representatives throughout the guideline process (4).

In the revision of the Dutch clinical practice guideline for paediatric palliative care (this thesis), we tackled these shortcomings. First, we searched for evidence and included original studies on paediatric palliative care. We systematically searched for high-quality quantitative evidence, including SRs of RCTs and CCTs, RCTs and CCTs for clinical questions on effectiveness of paediatric palliative care interventions. In addition, we systematically searched for qualitative evidence for the clinical question on barriers and facilitators to advance care planning and shared decision-making. We used the Grades of Recommendations Assessment, Development, and Evaluation (GRADE) methodology and GRADE Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual) methodology to critically appraise quality of quantitative and qualitative evidence and rate strength of recommendations (5, 6).

The GRADE (CERQual) methodology is a highly structured, transparent system that identifies multiple preset factors which determine quality of evidence (5, 7). As a result, the GRADE (CERQual) methodology enables more consistent judgements that support better-informed clinical decisions (5, 7). However, it should be noted that although the GRADE (CERQual) methodology increases objectivity in critically appraising quality of evidence, variation in quality appraisal is plausible as observers can differ in how strictly evidence is graded. Therefore, we were consistent and transparent in the critical appraisal of the evidence in the summary of findings tables, describing reasons for downgrading and upgrading the evidence.

For this guideline, we used multiple types of evidence including quantitative and qualitative studies. We also developed a strategy for when evidence was lacking or when the level of evidence was too low. When evidence was lacking or the level of evidence was too low, we searched for additional literature including existing guidelines paediatric palliative care, guidelines on general paediatrics and adult palliative care, textbooks on paediatric palliative care and SRs of observational, qualitative, or mixed-method studies. The textbooks and SRs were only considered relevant for specific topics. If additional literature was not available, we formulated consensus-based recommendations informed by clinical expertise and patient and family values.

All recommendations were approved by the entire multidisciplinary guideline development panel which consisted of experts in paediatric palliative care and a group of parents of children with life-threatening and life-limiting conditions. Both experts and parents were involved during the entire guideline development process. Recommendations were only accepted if consensus was reached. By using high quality evidence and developing evidence- and consensus-based recommendations, we were able to develop a large set of recommendations. Transparency in development of recommendations is considered an important criterium for trustworthy guidelines (8). Therefore, we indicated for each recommendation when it was based on evidence or consensus.

Besides the above mentioned strengths of the current guideline, we also see some limitations. First, the development of this guideline was a process that took multiple years. By using an evidence-based approach, we aimed to be as complete as possible in summarising the available evidence. The best way to summarise the evidence is performing a systematic review. However, since this is very time consuming and costly, we performed a selected number of literature searches for specific clinical questions. Developing a guideline is finding a balance between the efforts and the desired results (9, 10). By describing the methods in a transparent way, future guideline developers can become aware where they can improve the process and the critical appraisal of the literature (9, 10).

Second, this guideline included evidence until January, 2020. As a result, the guideline can become outdated. Automated tools for identifying and appraising evidence can be an opportunity for improving efficiency of future guideline updates, allowing an update of a recommendation as soon as new relevant evidence becomes available (8, 11). Currently, multiple automated tools, using machine learning and artificial intelligence, have been developed and are proven successful in reducing workload and maintaining guidelines (12-14). The development of automated tools for identifying and appraising evidence could allow us to include more topics without having to deal with unmanageable amounts of work.

Third, the expert opinion of health care providers and values of parents of children with life-threatening and life-limiting conditions in the development of the consensus-based



recommendations were not systematically collected. To mitigate personal biases, efforts to collect expertise of health care providers and patient and family values systematically and independently can be beneficial (15). Surveys can be used as a tool to systematically and independently identify expert opinions and patient values, limit personal bias and improve transparency of consensus-based recommendations (15).

#### *Implications for future guideline updates*

- Develop automated tools to more efficiently conduct systematic literature searches, study screening, study selection and study appraisal, and thus faster guideline development.
- Develop surveys to systematically and independently involve experts and patients, limit personal bias, and improve transparency of consensus-based recommendations.

### **Scope of the guideline**

#### *Strengths and limitations*

The first Dutch clinical practice guideline for paediatric palliative care published in 2013, provided recommendations on symptom relief, decision-making and organisation of care. In the revised guideline, we aimed to expand and update the guideline with more attention to all four dimensions of palliative care, including the relief of physical, psychological, social, and spiritual suffering. A strength of the revised guideline is that we included multiple missing topics, such as advance care planning, psychosocial care, and preloss and bereavement care, which were considered essential in provision of palliative care for all children with life-threatening and life-limiting conditions and their families (16-20). All included topics were selected based on priorities of health care providers and parents of children with life-threatening and life-limiting conditions.

However, still not all topics relevant in paediatric palliative care are covered in this guideline. For example, our selection of symptoms does not cover the full range of symptoms that may occur during the child's palliative disease trajectory, such as constipation or dysuria (21-24). Another limitation is that the recommendations in the revised clinical practice guideline do not limit to a specific diagnosis and stage of disease. As a result, it is plausible that some topics that are particularly important to a certain diagnosis or stage of disease are not yet covered in the guideline. Moreover, the current guideline provides recommendations that are directed at improving palliative care for children and their families. For some populations such as siblings of children with life-threatening and life-limiting conditions and health care providers caring for children in the palliative trajectory, concerns were not specifically addressed in this guideline. As these populations might need specific support, inclusion of recommendations specifically targeted at these population groups should be considered in the future.

### ***Implications for future guideline updates***

- Consider including new topics, e.g. constipation or dysuria.
- Consider including recommendations for specific diagnosis or stage of diseases.
- Consider including recommendations for specific groups such as siblings of children with life-threatening and life-limiting conditions and health care providers caring for children in the palliative trajectory.

## **Research in paediatric palliative care**

### ***Strengths and limitations***

For the revised guideline we performed systematic literature searches to identify high-quality quantitative evidence on effectivity of paediatric palliative care interventions and qualitative evidence on barriers and facilitators to advance care planning and shared decision-making. As we included evidence from 1970 to 2020, it is plausible that we missed some recently published evidence. However, based on the number of studies we found in a large time frame; we expect that we missed only a small number of studies that most likely will not have a direct influence on our identified knowledge gaps.

In recent years, 49 studies out of 62 included studies on effectivity of paediatric palliative care interventions (SRs of RCTs/CCTs, RCTs and CCTs) and of qualitative evidence on barriers and facilitators to advance care planning and shared decision-making in paediatric palliative care were published between 2010 and 2020. This new evidence of high-quality studies (is important to provide an evidence based for our guideline. However, despite the increase of evidence in paediatric palliative care, we identified multiple knowledge gaps within paediatric palliative care research. For 24 out of 38 formulated clinical questions, we were unable to find any evidence, mainly including questions on the effectiveness of interventions for symptom treatment. For other clinical questions, even if we found studies, the quality of the total body of evidence was frequently rated as low to very low.

We identified two key issues that contributed to the low quality of the identified studies. First, we found most studies had significant methodological limitations leading to risk of bias. Second, most studies included a small number of study participants causing imprecision of effects. These issues are considered a common phenomenon in paediatric palliative care research. Due to the small numbers of children who need paediatric palliative care, diversity of diseases, vulnerability of the population and ethical issues, conducting studies in this vulnerable patient population is considered very challenging (25). As a result, most of the recommendations lack a strong evidence basis. This is a limitation of this guideline for paediatric palliative care. A strength is that we showed the existence or lack of evidence in a transparent way.

We noticed another limitation of the current available scientific literature and saw a large variability in paediatric palliative care interventions and measured outcomes. In line with

this, a recent systematic review identified a total of 136 outcomes in 46 outcome domains, which were used to measure the effect of paediatric palliative care interventions (26). As a result, it was difficult to compare effectiveness of interventions between studies.

***Implications for future guideline updates***

- Extrapolate evidence from general paediatrics might be a strategy to fill some knowledge gaps, especially knowledge gaps related to treatment of symptoms. However, caution is needed when extrapolating evidence from paediatrics to paediatric palliative care, as paediatric palliative care requires expertise that is often lacking in general paediatrics (27).

***Implications for future research***

- Improve quality of studies on paediatric palliative care interventions by reducing methodological limitations and imprecision of effects in studies. A way to achieve this is by international multidisciplinary and multi-institutional collaboration to reach higher numbers of participants and perform high-quality clinical trials.
- Develop a standard set of outcomes for paediatric palliative care with harmonised outcome definitions and measurement tools.
- Design studies that include the knowledge gaps mentioned in Table 1.

**Table 1.** Identified knowledge gaps

<b>Identified knowledge gaps</b>
<b>Symptom treatment</b>
The effectivity of non-pharmacological and pharmacological interventions for children with life-threatening and life-limiting conditions to treat anxiety & depression, delirium, dyspnoea, coughing, skin complaints, nausea & vomiting, neurological symptoms, pain, death rattle, and fatigue.
The effectivity of paediatric palliative sedation on depth of sedation, quality of life and lifespan in children with life-threatening and life-limiting conditions or with a (very) severe multiple (intellectual) disability at the end-of-life.
The effectivity of forgoing hydration and nutrition on quality of life, lifespan, and parental quality of life on depth of sedation, quality of life and lifespan in children with life-threatening and life-limiting conditions at the end of life.
<b>Advance care planning and shared decision-making</b>
The effectivity of advance care planning interventions for children with life-threatening and life-limiting conditions.
The effectivity of shared decision-making interventions for children with life-threatening and life-limiting conditions.
Barriers and facilitators of advance care planning and shared decision-making as reported by children with life-threatening and life-limiting conditions.
<b>Psychosocial care including preloss and bereavement care</b>
The effectivity of psychological interventions, social and practical support, and cultural, spiritual, religious support for children with life-threatening and life-limiting conditions.
The effectivity of preloss and bereavement care interventions for parents of children with life-threatening and life-limiting conditions.

## Implementation of the guideline

### *Strengths and limitations*

A strength of our guideline process is that we developed a guideline together with many Dutch health care providers and parents. This will support future implementation of the guideline. Furthermore, at the end of the guideline process, we ensured that the revised guideline was approved by all relevant professional and patient associations in the Netherlands. This meant that these associations consider the clinical practice guideline as a standard for providing paediatric palliative care, which facilitates the dissemination of the guideline among their audience.

However, a limitation is that we were not able to develop this guideline with a wider international community. Nevertheless, as we used international evidence, we expected that a large proportion of provided recommendations, except recommendations that are specific for the Dutch context (organisation of care), will be applicable to other contexts and can be of great added value. Therefore, we believe the revised guideline can facilitate the optimisation of paediatric palliative care and positively influence the further integration

of paediatric palliative care not only in the Netherlands but also on a global level. Furthermore, the provision of a detailed methodology in this thesis can support other countries in developing recommendations specific to their country.

### ***Implications for guideline implementation***

- Disseminate the guideline for paediatric palliative care in national and international context.
- Focus on the integration and use of recommendations in clinical practice by
  - Providing education and training to health care providers on how to use the recommendations in clinical practice.
  - Organising adequate staffing, time, and funding, for paediatric palliative care services. Factors such as access to financial resources and the organisational infrastructure impact the quality of palliative care and differ among countries (3, 28).
  - Development of tools that support the use of guidelines, such as individual care plans. Individual care plans are highly suitable tools that can be used to improve implementation of guidelines by translating general recommendations into a personal plan for an individual patient (29, 30). In the Netherlands, an individual care plan for paediatric palliative care is being implemented in clinical practice (29). This individual care plan uses the recommendations of the revised guideline to develop a personalised plan for the individual child and the family (29). The individual care plan has a potential to enrich individual paediatric palliative care based on recommendations provided in the revised guideline and improve continuity of care (29). Thus, the use of individual care plans represents a valuable opportunity for optimising implementation of the revised clinical practice guideline for paediatric palliative care.

6

### **Conclusion**

The aim of this thesis was to further improve the quality of paediatric palliative care and thereby the quality of life of children aged 0 to 18 years with life-threatening and life-limiting conditions and their families during the entire disease trajectory by developing the revised clinical practice guideline for paediatric palliative care. The revised clinical practice guideline for paediatric palliative care was developed according to a standardised methodology that ensures trustworthiness of guidelines. By using this methodology, we provided a large set of recommendations based on evidence and consensus for essential components of paediatric palliative care including symptom treatment, advance care planning, shared decision-making, and psychosocial care including preloss and bereavement care.

The insights gained during the development of the revised guideline and the findings of this thesis open opportunities to further optimise the guideline and paediatric palliative

care research. We elaborated on several opportunities with regards to improving efficacy and quality in guideline development, broadening the scope of the guideline for paediatric palliative care in the future, addressing identified knowledge gaps, and improving dissemination and implementation of the guideline.

The summarised implications for guideline development, paediatric palliative care research and guideline implementation will facilitate the further optimisation of paediatric palliative care, not only in the Netherlands, but also globally.

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# 7

Nederlandse Samenvatting

**Richting optimalisering van kinderpalliatieve zorg**

Een richtlijn voor de klinische praktijk



Te vaak krijgen kinderen met levensbedreigende en levensduur verkortende aandoeningen en hun gezinnen onvoldoende kinderpalliatieve zorg. Het doel van kinderpalliatieve zorg is het verbeteren van kwaliteit van leven van deze kinderen en hun gezinnen. Kinderpalliatieve zorg richt zich niet alleen op het verlichten van lichamelijke klachten, maar ook op het bieden van psychologische, sociale en spirituele steun. Met de ontwikkeling van de herziene Nederlandse richtlijn palliatieve zorg voor kinderen, willen we de kinderpalliatieve zorg optimaliseren en daarmee de kwaliteit van leven verbeteren voor alle kinderen van 0 tot 18 jaar met levensbedreigende en levensduur verkortende aandoeningen en hun gezinnen.

In dit proefschrift worden de methodologie en aanbevelingen van de herziene richtlijn voor kinderpalliatieve zorg beschreven. Elk hoofdstuk van dit proefschrift richt zich op een ander aspect van de richtlijn.

### **De methodologie van de herziene Nederlandse richtlijn palliatieve zorg voor kinderen**

In *hoofdstuk 2*, beschrijven we de methodologie die is gebruikt om de richtlijn palliatieve zorg voor kinderen te herzien. Daarnaast geven we een overzicht van beschikbaar wetenschappelijk bewijs over kinderpalliatieve zorg. Samen met een multidisciplinaire richtlijnwerkgroep bestaande uit 72 deskundigen op het gebied van kinderpalliatieve zorg en een groep van negen ervaringsdeskundige ouders van kinderen met een levensbedreigende of levensduur verkortende aandoening, ontwikkelden we aanbevelingen gericht op meerdere onderwerpen die betrekking hadden op kinderpalliatieve zorg. De aanbevelingen waren gebaseerd op wetenschappelijk bewijs, aanvullende literatuur zoals richtlijnen en tekstboeken, ervaringen van kinderen met een levensbedreigende of levensduur verkortende aandoening en hun gezinnen, en klinische expertise. We beschreven verschillende manieren waarop we zijn omgegaan met verwachte en onverwachte uitdagingen die we tegenkwamen tijdens de ontwikkeling van deze richtlijn. Ten eerste, om onhanteerbare hoeveelheden werk te voorkomen, hergebruikten we wetenschappelijk bewijs door twee bestaande systematische literatuurzoekopdrachten te updaten en ons te richten op wetenschappelijk bewijs van hoge kwaliteit. We zochten naar systematische reviews, gerandomiseerde klinische studies, klinische studies met een controle groep, en kwalitatieve studies. Ten tweede, maakten we, wanneer er sprake was van onvoldoende wetenschappelijk bewijs, gebruik van aanvullende literatuurbronnen zoals richtlijnen, tekstboeken en systematische reviews van observationele, kwalitatieve of gemengde methode studies. Deze aanvullende literatuur werd gebruikt om onze overwegingen en aanbevelingen aan te scherpen. Ten derde, werkten we samen met vele belanghebbenden in de kinderpalliatieve zorg om de verspreiding van de herziene richtlijn in Nederland te faciliteren. Ook zorgden we ervoor dat de richtlijn werd goedgekeurd door alle relevante beroeps- en patiëntenverenigingen. Tot slot, om de hoge werkdruk aan te kunnen, stelden we één fulltime onderzoeker aan die het hele richtlijnontwikkelingsproces begeleidde. Dit bleek goed te werken.

## **Aanbevelingen voor symptoombehandeling in de kinderpalliatieve zorg**

In *hoofdstuk 3*, geven we een overzicht van het geïdentificeerde wetenschappelijk bewijs en de aanbevelingen over behandeling van symptomen in de kinderpalliatieve zorg, waaronder angst & depressie, delier, dyspneu, hematologische verschijnselen, hoesten, huidklachten, misselijkheid & braken, neurologische symptomen zoals epilepsie, pijn, reutelen, vermoeidheid, palliatieve sedatie bij kinderen en vocht & voeding onthouding. In dit hoofdstuk identificeerden we drie systematische reviews en 15 gerandomiseerde klinische studies. Deze studies beschreven de effecten van verschillende specifieke (niet) medicamenteuze interventies om symptomen in de kinderpalliatieve zorg te behandelen. Slechts enkele van deze interventies toonden significante verlichting aan in de specifieke symptomen. Uiteindelijk, konden we slechts acht van de 27 geformuleerde klinische vragen over interventies om symptomen te behandelen gedeeltelijk beantwoorden met het gevonden wetenschappelijk bewijs. Als er wetenschappelijk bewijs werd gevonden, werd voor de meeste klinische vragen de algehele kwaliteit van het bewijs beoordeeld als laag tot zeer laag. We gebruikten 29 richtlijnen en twee tekstboeken om met het gebrek aan wetenschappelijk bewijs om te gaan. De richtlijnwerkgroep benadrukte dat bij elke beslissing over de behandeling, de kwaliteit van leven, de waarden en de behoeften van kind en gezin voorop moeten staan. Dit principe werd beschouwd als de basis voor alle aanbevelingen over symptoombehandeling. Andere belangrijke overwegingen waren: het verwachte effect van de behandeling op symptoomverlichting, de verwachte belasting van de behandeling op het kind, mogelijke bijwerkingen van de behandeling en de prognose en levensverwachting van het kind. Met betrekking tot palliatieve sedatie bij kinderen en vocht- en voeding onthouding, werd het gehele proces inclusief communicatie, voorbereiding, uitvoering en evaluatie behandeld in de aanbevelingen. In totaal werden 221 aanbevelingen over symptoombehandeling geformuleerd.

## **Aanbevelingen voor advance care planning en gezamenlijke besluitvorming in de kinderpalliatieve zorg**

*Hoofdstuk 4* presenteert het wetenschappelijk bewijs en de geformuleerde aanbevelingen over advance care planning, ook wel bekend als proactieve zorgplanning, en gezamenlijke besluitvorming in de kinderpalliatieve zorg. Vier gerandomiseerde klinische studies toonden aan dat advance care planning interventies overeenstemming over toekomstige behandelvoorkeuren kunnen verbeteren tussen jongeren met een levensbedreigende of levensduur verkortende aandoening en hun wettelijk vertegenwoordiger zonder dat het de uitkomsten met betrekking tot kwaliteit van leven negatief beïnvloed. Dit wetenschappelijk bewijs was van zeer lage tot lage kwaliteit. Daarnaast vonden we 33 kwalitatieve studies over belemmerende en bevorderende factoren voor advance care planning en gezamenlijke besluitvorming. Van deze 33 kwalitatieve studies, waren er 22 nieuwe studies gepubliceerd sinds het oorspronkelijke systematische literatuuronderzoek was uitgevoerd in 2016. Dit

betekent dat het totaal aantal geïncludeerde kwalitatieve studies verdrievoudigd is in een relatief korte periode. Voor de meeste conclusies uit het wetenschappelijk bewijs over belemmerende en bevorderende factoren, werd de kwaliteit van het bewijs beoordeeld als matig. Op basis van het wetenschappelijk bewijs, de klinische expertise en de ervaringen en perspectieven van kind en gezin werden 28 sterke aanbevelingen geformuleerd die richting geven over het aanbieden advance care planning en gezamenlijke besluitvorming aan kind en gezin, het betrekken van kind en gezin tijdens advance care planning en gezamenlijke besluitvorming en het communiceren van informatie over zorg en behandeling.

### **Aanbevelingen voor het bieden van pediatrische palliatieve psychosociale zorg inclusief zorg bij verlies en rouw**

*Hoofdstuk 5* geeft een overzicht van wetenschappelijk bewijs en beschrijft de aanbevelingen over psychosociale zorg, inclusief zorg bij verlies en rouw. We identificeerden twee systematische reviews en zes gerandomiseerde klinische studies die rapporteerden over het effect van psychologische interventies, interventies met betrekking tot spirituele ondersteuning en een interventie over rouwzorg. Uit het wetenschappelijk bewijs kwam naar voren dat voor slechts enkele van de interventies bepaalde psychosociale uitkomsten kunnen verbeteren bij kinderen met een levensbedreigende of levensbeperkende aandoening of hun ouders. Vanwege de grote variatie in interventies en gemeten uitkomstmaten, konden we geen conclusies trekken over welke interventie het meest effectief is. Vanwege het gebrek aan bewijs, zochten we naar aanvullende literatuur. We vonden tien systematische reviews van observationele, kwalitatieve of gemengde methode studies over onderdelen van interventies met betrekking tot zorg bij verlies en rouw, ervaringen en behoeften van ouders en zorgverleners, en communicatieve strategieën. De richtlijnwerkgroep benadrukte het belang van psychosociale zorg afgestemd op de behoeften en voorkeuren van kind en gezin, het geven van duidelijke informatie over de emotionele en psychologische gevolgen van het palliatieve traject van een kind en het monitoren van het welzijn van broers en zussen en andere familieleden. Deze overwegingen vormden de basis voor het formuleren van de aanbevelingen. In totaal werden 27 aanbevelingen opgesteld over psychosociale zorg, waaronder psychologische interventies, praktische en sociale ondersteuning en culturele, religieuze en spirituele ondersteuning. Daarnaast werden in totaal 21 aanbevelingen geformuleerd over zorg bij verlies en rouw.

### **Conclusie**

Het doel van dit proefschrift was het verder verbeteren van de kwaliteit van de kinderpalliatieve zorg en daarmee de kwaliteit van leven van kinderen tussen 0 en 18 jaar met levensbedreigende en levensduur verkortende aandoeningen en hun gezinnen gedurende het gehele ziekteproces, door het ontwikkelen van de herziene Nederlandse richtlijn palliatieve zorg voor kinderen. De herziene richtlijn is ontwikkeld volgens een standaard

methodologie die de betrouwbaarheid van richtlijnen waarborgt. Door gebruik te maken van deze methodologie hebben we een reeks aanbevelingen kunnen formuleren over verschillende essentiële onderwerpen in de kinderpalliatieve zorg, waaronder behandeling van (moeilijk te behandelen) symptomen, advance care planning, gezamenlijke besluitvorming, psychosociale zorg, en zorg bij verlies en rouw. De aanbevelingen zijn gebaseerd op wetenschappelijk bewijs, klinische expertise en ervaringen en perspectieven van kind en gezin.

De inzichten die zijn opgedaan tijdens de ontwikkeling van de herziene richtlijn en de bevindingen in dit proefschrift bieden mogelijkheden om de richtlijn en het onderzoek naar kinderpalliatieve zorg verder te optimaliseren. We hebben verschillende mogelijkheden uitgewerkt met betrekking tot het verbeteren van de effectiviteit en kwaliteit van richtlijnontwikkeling, het verbreden van de inhoud van de herziene richtlijn in de toekomst, het aanpakken van kennishiaten om onderzoek over kinderpalliatieve zorg te verbeteren en de implementatie van de richtlijn.

Deze mogelijkheden voor het verbeteren van richtlijnontwikkeling, het verbreden van de inhoud van de richtlijn, het verbeteren onderzoek naar kinderpalliatieve zorg en het verbeteren van de implementatie van de richtlijn, kunnen de verdere optimalisatie van kinderpalliatieve zorg bevorderen, niet alleen in Nederland, maar ook wereldwijd.





# Appendices

Curriculum vitae

PhD portfolio

Dankwoord



## CURRICULUM VITAE

Kim Cecile van Teunenbroek was born on July 1<sup>st</sup> 1994, in Amersfoort, the Netherlands.



She studied Health Sciences at Maastricht University in Maastricht from 2012 to 2015. During her bachelor, she participated in the Honours programme at the Faculty of Health, Medicine, and Life sciences, for which she travelled to India to do research and map the health care system there. Also, she followed the minor Global Health at Karolinska Institutet in Stockholm, Sweden.

After she finished her bachelors, she followed the Master Global Health at Maastricht University. During this master, she did an internship in Kathmandu, Nepal at the Special Education and Rehabilitation Center for children with a disability. There, she interviewed parents of children with a disability, teachers, health care professionals, and policy makers to identify

opportunities and challenges for improving the care for children with disabilities in rural areas. In 2017, Kim started her second master Health Education and Promotion at Maastricht University. She did her internship in youth care where she studied diet and exercise consultation for parents of children who were overweight.

After she finished both masters, she started working for an online platform which developed personal health checks. In 2019, she started as a PhD candidate at the Princess Máxima Center for paediatric oncology in Utrecht, at the department of Quality of Life. During her PhD she developed the revised Dutch guideline for paediatric palliative care which was published in November, 2022. She organised several events such as the yearly Princess Máxima Center Research Retreat in 2023. Also, she started a project in which she pilot-tested the LATER Individual Care Plan at the long-term follow-up outpatient clinic for survivors of childhood cancer in the Prinses Máxima Center. Currently, she is coordinating the implementation of the LATER Individual Care Plan at the LATER outpatient clinic.

## PHD PORTFOLIO

**Name:** Kim C. van Teunenbroek

**Period:** October 2019 to July 2024

**Promotoren:** Prof. Dr. Leontien C. M. Kremer and Prof. Dr. Mr. A. A. Eduard Verhagen

**Copromotoren:** Dr. Erna M. C. Michiels and Dr. Renée L. Mulder

**Institution:** Princess Máxima Center for pediatric oncology

Courses	Year
Evidence-Based Guideline Development	2019
Supervision of Master students	2020
The Art of Presenting Science	2021
InDesign	2021
Introductory course Clinical and Translational Oncology	2021
Academic Writing in English	2021
Scientific Artwork: Data Visualisation and Infographics with Adobe Illustrator	2022
Bij- en nascholing 'Professional in de kinderoncologie'	2022
Introduction to Epidemiology	2022
Mindfulness	2022
Peer to peer sessions	2022
Introduction to Statistics	2023
Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)	2023
Conferences & presentations	Year
Princess Máxima Center Research meeting (oral presentation)	2020
Guidelines International Network (GIN) conference (poster presentation)	2021
Pediatric Palliative Care Oncology Symposium	2021
Quality of Life Symposium	2021
Nederlands-Vlaamse Wetenschapsdagen (oral presentation)	2022
Symposium Samenwerking maakt sterker! Next step in kinderpalliatieve zorg	2022
International Symposium on Late Complications After Childhood Cancer (ISLCCC) (poster presentation)	2022
Congress of the International Society of Paediatric Oncology (SIOP) (poster presentation)	2022
Princess Máxima Center Research Retreat (oral presentation)	2022
Stichting Kinderoncologie Nederland (SKION) day (poster presentation)	2022
Symposium Wegwijs in de Kinderpalliatieve zorg (oral presentation)	2023
European Association for Palliative Care (EAPC) World Congress (two oral presentations and a poster presentation)	2023

Ideafactory Kenniscentrum Kinderpalliatieve zorg (poster presentation)	2023
Princess Máxima Center Research meeting (oral presentation)	2024
International symposium on late complications after childhood cancer (ISLCCC)	2024
Yearly Princess Máxima Center Research Retreat	2021 – 2023
Yearly Clinical Translational Oncology PhD Retreat	2020 – 2023
<b>Seminars &amp; meetings</b>	<b>Year</b>
Weekly Princess Máxima Center research meetings	2019 – 2024
Monthly research group meetings	2019 – 2024
Monthly Dutch Childhood Cancer Survivor study meetings	2023 – 2024
<b>Supervising</b>	
Dayna van Heel, Master student Medicine (honours programme), Utrecht University	2020 – 2022
Eva van Schie, Bachelor student Health Sciences, Policy & Health Care Management, Erasmus University	2023 – 2024
Pien Verkouteren, Master student Medicine, Utrecht University	2024

## DANKWOORD

Ik weet nog goed dat toen ik begon aan mijn PhD traject, ik aan Erna vroeg: 'wat is nou eigenlijk precies de bedoeling?' Waarop zij antwoordde 'we gaan een richtlijn over palliatieve zorg voor kinderen maken, en jij gaat dat project coördineren en zorgen dat alles op rolletjes loopt.' Ik heb haar toen met grote ogen aangekeken, geen idee wat me nou allemaal te wachten stond. Nu vijf jaar later, is het dan zover, de richtlijn is af, de publicaties zijn geschreven, en de implementatie van de aanbevelingen is in volle gang. Ik ben ontzettend trots op het resultaat. In de afgelopen jaren ben ik bijgestaan door heel veel mensen. Aan jullie allemaal, dit is voor jullie:

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Een kerngroep hebben voor de richtlijn is fijn, maar zonder **de richtlijnwerkgroep** bestaande uit ontzettend veel **experts** op het gebied van kinderpalliatieve zorg en **ervaringsdeskundige ouders**, was deze richtlijn palliatieve zorg voor kinderen er nooit gekomen. Aan jullie allemaal, ontzettend veel dank voor al jullie hulp in het beoordelen van de literatuur, het schrijven van de overwegingen, en het formuleren van de aanbevelingen. Verder hebben jullie als **coauteurs** of **collaborators** bijgedragen aan alle manuscripten in dit proefschrift. Daardoor is de inhoud van de richtlijn palliatieve zorg voor kinderen nu ook beschikbaar voor het internationale publiek.

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