Despite advancing treatment, up to one fourth of first-world deaths in children still occurs due to serious illness, such as cancer, neurological conditions, and genetic and congenital conditions. There are indications that this group of children can suffer from burdensome symptoms at the end of life. A broad evaluation of the quality of end-of-life care for children with serious illness is therefore advised, and quality indicators tailored specifically to the child at the end of life have been requested nationally as well as internationally for this purpose. This dissertation developed such pediatric-specific indicators for potentially appropriate and potentially inappropriate end-of-life care, and measured them within Belgian population-level administrative healthcare data.

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APPROPRIATENESS OF END-OF-LIFE CARE IN CHILDREN WITH SERIOUS ILLNESS

THE DEVELOPMENT AND MEASUREMENT OF PEDIATRIC-SPECIFIC POPULATION-LEVEL QUALITY INDICATORS FOR BIG DATA

Veerle Piette

Thesis submitted in fulfillment of the requirements for the Joint Doctoral degree of:

Medical Sciences
Faculty of Medicine and Pharmacy
Vrije Universiteit Brussel (VUB)

&

Health Sciences
Faculty of Medicine and Pharmacy
Ghent University (UGent)

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‘And’
is a powerful word

J. Friel

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> "Remember the little seed in the plastic cup? The roots go down and the plant goes up and nobody really knows how or why, but we are all like that. […] Everything you need to know is in there somewhere. […] And it is still true, no matter how old you are, when you go out into the world, it is best to hold hands and stick together."
>
> *From Robert Fulghum, 'All I Ever Really Needed to Know I Learned in Kindergarten'*

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CONTENTS

CHAPTERS ARE BASED ON THE FOLLOWING PUBLICATIONS

CHAPTER 1

Piette V, Beernaert K, Cohen J, Pauwels N, Scherrens AL, van der Werff ten Bosch J, Deliens L. Healthcare interventions improving and reducing quality of life in children at the end of life: a systematic review. Pediatr Res. 2020 Jul;89:1065–1077. [Published]

CHAPTER 2

Piette V, Deliens L, van der Werff ten Bosch J, Beernaert K, Cohen J. Face-Validated Quality Indicators for Appropriateness of End-of-Life Care in Children with Serious Illness:A Study Using the RAND/University of California at Los Angeles Appropriateness Method.J Pediatr. 2022 Feb;241:141-146. [Published]

CHAPTER 3

Piette V, Smets T, Deliens L, van Berlaer G, Beernaert K, Cohen J. Population-level analysis of appropriateness of end-of-life care for children with neurological conditions. J Pediatr. 2022 Nov. [Accepted]

CHAPTER 4

Piette V, Smets T, Deliens L, De Gendt C, van der Werff ten Bosch J, Cohen J, Beernaert K. The quality of end-of-life care for children dying from cancer assessed using big data. [To be submitted]

CHAPTER 5

Piette V, Smets T, Deliens L, de Bulpaep S, Cohen J, Beernaert K. Quality of end-of-lifecare for children with genetic and congenital conditions: A nationwide cohort study usingquality indicators and big data. [To be submitted]

GENERAL INTRODUCTION

1. INTRODUCTION

Measurement of quality of end-of-life care in children with serious illness is considered a growing yet overlooked priority within children's healthcare (1,2). Population-level quality evaluations have been performed for adult's end-of-life care, based on routinely collected administrative healthcare data (3–6). No pediatric-specific quality indicators for administrative healthcare data are currently available. A 2017 report by a Belgian public health palliative care evaluation board emphasized the unique position of children's end-of-life care and the need for tailored indicators (7). Current measurements for quality of children's end-of-life care within administrative data have been carried out with adult or non-validated quality indicators for end-of-life care (8,9). However, such measurements may not adequately reflect children's practices of end-of-life care (10). Clinical and socio-demographic disparities in children's end-of-life care quality require further attention (11-13).

Children's end-of-life care and its quality evaluation have increasingly gained attention in recent decades (14). The increased evidence of high suffering of children at the end of life (15,16) and rising prevalence and increased life-prolonging treatment possibilities for children with serious illness (13) has raised concerns about the quality of end-of-life care for children (16). Concerns about overly intense healthcare use and lack of continuity of care drive a demand for pediatric-specific quality indicators for children's end-of-life care (17). The 2003 US Institute of Medicine publication *When Children Die* emphasizes the need for systemic inspection of and changes within children's end-of-life care provision (18). Such evaluation of the quality of care can provide guidance for future steps to care improvement in practice, research and policy: A system-level evaluation can reveal patterns of care provision that cannot be observed through individual or institutional clinical practice due to the relative rarity of a child's death and the spread of casualties over different care providers and wards (19,20).

The purpose of this dissertation was to develop population-level pediatric-specific quality indicators for appropriateness of end-of-life care for children dying with cancer, neurological conditions, and genetic and congenital conditions; to measure these indicators within administrative databases; and to look into possible disparities within appropriateness and inappropriateness of end-of-life care. The development and measurement of the indicators was limited to variables measurable within administrative, routinely collected databases. Such databases are composed by mutualities and private institutions in Belgium, and contain mainly reimbursed healthcare use including medication, treatments, and visits by care providers.

This chapter will further discuss the prevalence, symptoms and trajectories of children at the end of life, and then discuss the background and rationale for the development of pediatric-specific indicators for quality of end-of-life care, as well as the current quality measurement for children's end-of-life. This chapter will also describe the research objectives, delineations of concepts, study design and methodologies that are used in the further chapters of this dissertation.

2. PREVALENCE, SYMPTOMS, AND TRAJECTORIES OF CHILDREN AT THE END OF LIFE

A significant proportion of children still dies of complex chronic conditions (15,21,22). While the majority of children's deaths in first-world countries occurs due to traumatic events such as accidents (23), and medical advancements such as experimental trials have increased survival probabilities for some serious illness, generally up to one third of children still dies of complex chronic conditions (15,21,23–25). Malignant neoplasms are reported to represent 9% of overall deaths in US children and adolescents, whereas congenital anomalies represent 4,8% of overall children deaths (26). European population-level studies report that of deaths caused by complex chronic conditions, 26,6% is due to cancer, 20,1% due to neuromuscular conditions, leaving 53,3% of deaths due to other complex chronic conditions such as genetic and congenital conditions (21).

Symptom burden is reported by parents to be considerably high for all children with complex chronic conditions at the end of life, and symptom control poses considerable challenges for pediatric teams. Almost half of children with cancer are reported by parents to suffer from burdensome symptoms at the end of life, such as pain, fatigue, dyspnea, and loss of appetite (27,28). One third of children with non-cancer and non-cardiologic complex chronic conditions suffer from high symptom burden in the last days of life according to parents (15). Symptom treatment is said to often remain insufficient (28). Sixty-one percent of physicians indicated in a 2005 survey that they sometimes feel end-of-life treatments they offer for children are overly burdensome (29) Nevertheless, peer-reviewed studies and opinion pieces show that targeted interventions can benefit children as well as their families. For instance, symptom management and controlled pain benefit quality of life of the child at the end of life and provide lower long-term grief levels in bereaved parents of a child with cancer (30). Therefore, looking into the treatments and medications which are given to children at the end of life, can provide some indication of the quality of end-of-life care provided.

The end-of-life phase trajectory may differ between children in terms of disease progression (31–33), demographics (34), symptoms (32) and other factors (32). Current classifications for disease progression do not correlate entirely (35), yet following four categories are utilized often within studies (35-37), defined by expert opinion through public health instances: 1. Having a life-threatening condition for which curative treatment failed (e.g. cancer), 2. Having a life-shortening condition for which life-lengthening treatments can be employed (e.g. cystic fibrosis), 3. Having a progressive condition for which no curative treatment currently exists (e.g. batten disease), and 4. Having a non-progressive, complex condition for which complications can lead to a premature death (e.g. severe cerebral palsy) (32).

3. BACKGROUND AND RATIONALE FOR PEDIATRIC-SPECIFIC QUALITY INDICATOR DEVELOPMENT

Pediatric-specific quality indicators have been lacking and requested frequently by the national and international pediatric field (10). Pediatric end-of-life care practices differ significantly from adult end-of-life practice (2,7,10). Pediatric care professionals have advocated for the development of end-of-life care quality indicators that are specific to children, asserting that "practices validated in adult palliative care rarely translate to pediatrics" (10).

Adult and children's care and end-of-life care likely differ and these differences would likely translate to different quality indicators for end-of-life care quality measurement (7,1). The number of children that dies due to serious illness is small compared to the dying adult population, and the causes of death differ in terms of pathology, prevalence, and survival chances (7). Children typically have conditions with a genetic origin and surface specifically during childhood (7), are less prevalent (7), and certain conditions such as acute lymphoblastic leukemia show survival differences for the pediatric and adult population, attributable to factors of clinical trial participation, medical care access, patient and physician attitudes, and physician location and specialty (38). The duration of end-of-life care can vary broadly as opposed to adult care, varying from years to days (7). Developmental needs and changes in those needs may occur during and impact the illness trajectory (7). Children are reported to be more sensitive to disparities such as poverty and racial prejudice (1). End-of-life care for seriously ill children is seen as separate from end-of-life care for children that die unexpectedly, such as accidental death (39), which differs with regard to timing and treatments - end-of-life care for children dying due to trauma is oriented mainly towards near-death end-of-life decisions and treatments such as the continuation of resuscitation (40,41). Children's care is embedded in a distinct nuclear family system and societal context (7,1), with the death of a child impacting parents and siblings in a way that is increasingly uncharacteristic for a modern life span (7,42).

4. CURRENT QUALITY MEASUREMENTS FOR PEDIATRIC END-OF-LIFE CARE

Evidence on healthcare use in children at the end of life is currently present mainly for resource-intensive care and comfort care, and is often disease-specific, limited to cancer (17,43). Measurement of indicators for children, adolescents and young adults with cancer at the end of life using population-level data (8,11,12,17,44-46) indicates that children with cancer generally receive many intensive treatments at the end of life and low comfort measures. Population-level US databases indicate that one to two thirds of children and adolescents with cancer receive high-intensity interventions at the end of life, such as chemotherapy and intubation (8,44). Taiwanese children at the end of life similarly received chemotherapy and intensive care visits in the majority of cases (47). Referral to hospice, on the contrary, in children with cancer is low (44).

While no studies formally evaluated quality of end-of-life care in children with neurological and genetic and congenital conditions to our knowledge, some studies provide numbers for healthcare use in this population at the end of life. Studies report that this population typically receives increasing medications such as opioids, medical interventions such as gastric- or gastro-jejunal tube insertion (32). Reminiscent of a quality indicator measurement, a study "encouragingly" finds that deaths do not occur mainly in the context of intensive or emergency care, but rather in a hospice or home setting (32).

Disparities within children's quality of end-of-life care have been identified previously, such as for age, nationality. Equity within children's end-of-life care has been cited as an overarching concern for children's health care due to increasing evidence for disparities (1). In England, for instance, a population-level study found the prevalence of life-limiting conditions in children and young people is significantly higher for non-white populations (13) and experienced more instability within the end-of-life disease trajectory (48). Administrative data may be well-positioned to analyze such disparities, as normally hard-to-reach subgroups are included in the cohort.

5. THE STRUCTURE OF CHILDREN'S PALLIATIVE AND END-OF-LIFE CARE IN BELGIUM

Knowledge of the structuring of children's pediatric and palliative care may be necessary for interpretation of further findings. In Belgium, pediatric end-of-life care provision is centered around the settings and institutions of pediatric liaison teams, university and local hospitals, pluri-disciplinary teams and established care networks, primary care, and respite care facilities (7,49).

Pediatric end-of-life care provision is formally assigned to and coordinated by five pediatric liaison teams. The teams are acknowledged by royal decree since 2010 (49), with two teams situated in the Flanders region and three situated in the Walloon region (49). They are tasked with terminal care provision for children between 0 and 18 with a potentially fatal condition besides curative and palliative care provision (7). The teams are connected to the five largest Belgian pediatric centers, which stimulate home care provision and provide support for the care team supporting the patient. They monitor continuity of care between hospital, the family and care providers or residential facilities (7). The liaison teams only partly receive fixed funding, and part of the funding is provided philanthropically via e.g. children's cancer donation funds (7). University and local hospitals provide an attending physician to the child (7). While pediatric liaison teams are primarily connected to the university hospitals, they also provide support to local hospitals (7). Pluridisciplinary teams and care networks refer to the disease-specific reference centra, as recognized by the Belgian Royal decrees. For example, nine

neuromuscular reference centra are recognized by the Belgian government, which work to provide multidisciplinary help to children and adults with neuromuscular diseases. Most of these reference centra are connected to a university hospital, similar in structure to the pediatric liaison teams. Primary care involvement constitutes of support provided by the family physician and governmentally unacknowledged and private initiatives to provide end-of-life care for children, such as by care services provided by pediatric nurses or private respite institutions (7). Primary care involvement is reported to be minimal compared to involvement of other care domains, such as pediatric liaison teams (7). Respite care facilities can temporarily (1 up to 32 days) take in patients below 19 which could or will prematurely die due to a serious illness, in order to provide specialized medical care for the child and provide relief for parents from the large care burden that they experience in caring for a child at the end of life (7,49). Additionally, working groups such as the Belgian Pediatric Palliative Care Group connect care providers from various centers (7).

6. OBJECTIVE AND AIMS

The main objective of this dissertation is to assess the quality of end-of-life care for children with serious illness in terms of appropriateness, using pediatric-specific quality indicators, for children dying with cancer, neurological conditions and genetic and congenital conditions.

This objective can be divided into 2 aims:
Aim 1: To develop pediatric-specific quality indicators for potentially appropriate and potentially inappropriate end-of-life care for population-level databases with routinely collected data. We aim to identify healthcare interventions such as treatments, medications, and care providers, that, when provided at the group or population level, indicate potentially appropriate or inappropriate end-of-life care for children with serious illness. We aim to develop indicator sets for each of the three illness groups: cancer, neurological conditions, and genetic and congenital conditions.
Aim 2: To measure the pediatric-specific indicators in population-level administrative databases with routinely collected data. We aim to measure each indicator set in seven Belgian national databases. This way, we aim to evaluate appropriateness of end-of-life care for children with serious illness. We also aim to examine what clinical and socio-demographic factors may account for differences in potentially appropriate or inappropriate end-of-life care for children dying from cancer, neurological conditions, and genetic and congenital conditions.

7. DELINEATIONS OF CONCEPTS FOR INDICATOR DEVELOPMENT

Certain delineations were made prior to indicator development: in terms of disease, age, illness

trajectory, and variable availability.

Indicator sets were developed for the disease groups of cancer, neurological conditions and genetic and congenital conditions, as defined by the framework of complex chronic conditions (51). Disease groups were chosen for prevalence, national care provision structure, and research gaps. Illness groups were also chosen as they cover the majority of complex chronic conditions (52) that can lead to death in a child. The illness groups also mirror the structure of pediatric hospital wards in Belgium, which typically includes a separate oncology and neurology ward. There is a paucity of research into end-of-life care especially for children with neurological, genetic and congenital conditions at the end of life (50). The framework of complex chronic conditions was chosen over other frameworks, such as life-limiting or life-threatening conditions (53), for category availability and comparability purposes: The complex chronic conditions framework provides a disease categorization that aligns well with our disease selection, and many other studies refer to these same categories, facilitating comparison and interpretation (11,12,15,24,34,54-55).

Indicator sets were developed for the age category of 1 to 17, excluding the group of children between 0 and 1 (mainly neonatal deaths). Indicators were not developed for the age group of 0-1 years old due to large differences in terms of pathology and duration of end-of-life care. Most deaths for this age group are associated with prematurity, pregnancy, or childbirth (18) and would require different quality measures from those for children suffering from cancer, neurological conditions, and genetic and congenital conditions.

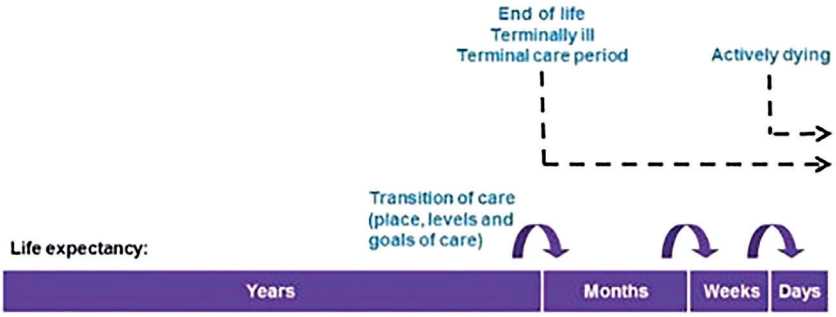
The indicators were limited to terminal care or end-of-life care. End-of-life care constitutes part of palliative care, yet the two terms are not interchangeable despite common misconceptions (50). End-of-life care refers to the last months, weeks and days of life of the child. Our definition of end-of-life care was based on a conceptual framework of end-of-life care definition developed based on systematic review (See below for a figure visualizing the framework) (56).

We developed indicator sets to be measured with available Belgian administrative databases, limiting indicator development to variables measurable with national administrative healthcare data. As databases are previously and routinely collected, the development of indicators was limited to variables already present within the databases. Available variables were predominantly reimbursements for medications, treatments, and care providers, certain healthcare-related financial and administrative measures.

The developed quality indicators were specified to measure appropriateness of end-of-life care. Appropriateness means the “expected health benefit for quality of life of the child exceeds the expected negative consequences for quality of life of the child by a sufficiently wide margin that the procedure is worth doing, exclusive of cost” (57). Inappropriate care was defined as the inverse. An indicator had to express a percentage that can increase or decrease on a population level, the concept measured with an indicator had to be applicable to the majority

of the full population of children of the illness group, and the measured treatment, medication or administrative act had to occur or had to be estimated to occur in 5%-95% of the children in the illness group. For instance, medications to palliate nausea from intravenous chemotherapy are not relevant as a measurement within the group of children with genetic and congenital conditions, as chemotherapy is not often provided from a population-level perspective.

Figure 1: The definition of the end-of-life period as utilized within this dissertation, as defined according to the systematic review by Hui et al. (56)



8. METHODS USED WITHIN THIS DISSERTATION

8.1 Development of pediatric-specific quality indicators

8.1.1. Modified RAND/UCLA Appropriateness method

As shown in **Chapter 1**, indicators were developed using a modified RAND/UCLA Appropriateness method (58,59). The RAND/UCLA Appropriateness method is a consensus or Delphi method, which are traditionally used to develop quality indicators (58,59). The followed method included following steps:

1. Literature review: A scoping review and systematic review were done to identify potential indicators
2. Interviews with experts: Pediatric care professionals with expertise in pediatric end-of-life care were done to identify potential indicators
3. Expert panels: The potential indicators from step 1 and step 2 were scored by pediatric care professionals to select the final indicators.

The three steps were performed separately for each illness group.

8.1.2 Literature review

A scoping review (**Chapter 2**) and systematic review (**Chapter 1**) were performed, respectively to identify previously published pediatric- and adult-specific indicators, and to identify what health care interventions are associated with improved and/or decreased quality of life in children at the end of life, according to peer-reviewed literature. Indicators for scoping review selection had to adhere to our definition for an indicator to be selected. Results from the systematic review were translated to potential indicators.

8.1.3 Expert interviews

We performed interviews (**Chapter 2**) with pediatricians, nurses, psychologists, physiotherapists, pharmacologists, care coordinators, general practitioners and social workers, from hospitals, care teams, and general practice. For the disease group of cancer, 19 unique experts participated, whereas 21 unique experts participated for neurological conditions and 17 unique experts were present in the panel for genetic and congenital conditions. Pilot interviews to test interview materials prior were performed with 3 international pediatric care professionals. Interviews were performed to gather potential indicators, as pediatric-specific indicators were expected to be scarce in literature, and to provide input for potential indicators from professionals aside from literature. Potential indicators were extracted from the interviews.

8.1.4 Expert panels

Indicator sets were constructed in an internal research group meeting, based on the potential indicator list and by combining similar formulations and concepts. Hereafter, expert panels were done with the same group of experts that were interviewed, to score the indicator sets. The panels included three rounds: 1. an individual scoring round, 2. a collective group discussion, and 3. another individual scoring round. Indicators were retained if there was a consensus among experts that the indicator was suitable to measure appropriateness of end-of-life care.

8.2 Measuring pediatric-specific quality indicators

8.2.1 Using Administrative databases

To measure the previously developed indicators, we obtained access to linked databases with population-level administrative data. Data are collected from the Belgian Intermutualistic Agency, Statistics Belgium, and the Belgian Cancer Registry.

The Belgian Intermutualistic Agency provided 3 databases:

- A sociodemographic database containing information such as age,
- A healthcare database containing reimbursements, e.g. for treatments within a hospital, and
- A pharmaceutical database with reimbursed medication from public pharmacists.

Statistics Belgium provided 3 databases:

- A death certificate database containing underlying and intermediate causes of death for all deaths in Belgium from Belgian death certificates,
- A population registry database with sociodemographic information such as education level, and
- A census database with data from the last census in Belgium, such as housing comfort characteristics.

The Belgian Cancer Registry provided 1 database, which contains the first and second (if applicable) cancer diagnosis, as well as date of diagnosis for children with cancer.

These databases were linked, i.e. connected to each other for each child with the use of a unique identifier per database per child.
For all databases, data is provided on a population level. For example, health care data is collected through reimbursements, and health care insurance is mandatory in Belgium.
Databases were linked with ethics and privacy guidelines in mind – for example, all unique identifiers were pseudonymized to avoid identification. National approval for access to databases was obtained via the 'Informatieveiligheidscomité'.

8.2.2 Decedent cohort studies: Evaluating appropriateness of end-of-life care for children with cancer, neurological conditions, and genetic and congenital conditions

Using the datasets described above, we conducted a decedent cohort study for each illness group (**Chapter 3-5**), using the constructed indicator sets for each illness group. For each disease group, we selected all children aged between 1 and 17 who died in Belgium between 2010 and 2017. We measured the quality indicators previously developed for each disease group, which occurred within the themes of treatment, medication and monitoring, place of care and dying, care providers and services, and administrative measures. Differences in appropriateness and inappropriateness were looked at for the clinical and socio-demographic factors of age, sex, disease category, nationality, having siblings, year of death, and region.

9. OUTLINE OF THIS DISSERTATION

The introduction of this dissertation, describes the context, the objectives and methodology of

this research study. **Part one** describes the development of the pediatric-specific indicators and contains two chapters: the systematic literature review (Chapter 1) and the validation of the indicators through the RAND/UCLA method (Chapter 2). **Part two** describes the measurement of the pediatric-specific quality indicators: For children who died with neurological conditions (Chapter 3), children who died with cancer (Chapter 4), and children who died with genetic and congenital conditions (Chapter 5) in Belgium. The discussion goes into the interpretation of our main findings. It summarizes the main results and concerns the implication of these findings for research, practice and policy, and ends with some concluding comments.

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PART 1
Developing pediatric-specific indicators of potentially appropriate and potentially inappropriate end-of-life care

CHAPTER 1

Healthcare interventions improving and reducing quality of life in children at the end of life: a systematic review

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ABSTRACT

Background Children with serious illness suffer from symptoms at the end of life that often fail to be relieved. An overview is required of healthcare interventions improving and decreasing quality of life (QOL) for children with serious illness at the end of life.

Methods A systematic review was performed in five databases, January 2000 to July 2018 without language limit. Reviewers selected quantitative studies with a healthcare intervention, for example, medication or treatment, and QOL outcomes or QOL-related measures, for example, symptoms, for children aged 1–17 years with serious illness. One author assessed outcomes with the QualSyst and GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) Framework; two authors checked a 25% sample. QOL improvement or reduction was categorized.

Results Thirty-six studies met the eligibility criteria studying 20 unique interventions. Designs included 1 randomized controlled trial, 1 cross-sectional study, and 34 cohort studies. Patient-reported symptom monitoring increased QOL significantly in cancer patients in a randomized controlled trial. Dexmedetomidine, methadone, ventilation, pleurodesis, and palliative care were significantly associated with improved QOL, and chemotherapy, stem cell transplant, and hospitalization with reduced QOL, in cohortstudies.

Conclusions Use of patient-controlled symptom feedback, multidisciplinary palliative care teams with full-time practical support, inhalation therapy, and off-label sedative medication may improve QOL. Curative therapy may reduce QOL.

INTRODUCTION

Despite medical advancements in therapy and treatment, a substantial proportion ofchildren with serious illness such as cancer or neuromuscular conditions will still die of theirdisease. Yearly, between 24.4 and 75.3% of deaths for children between 1 and 17 are caused by serious illness in European and non-European countries, according to a 2017 population-level study (1,2). Partly as a result of medical–technical developments and expanding possibilities of treatment, care for children often remains focused on cure and life prolongation even in the last months of life (3-6). There is a growing recognition that care should focus on maintaining the quality of life (QOL) at the end of life (7).

In order to provide adequate health care at the end of life for children with serious illness, an overview is required, of which healthcare interventions have negative and/or positive effects on children's QOL at the end of life. Such an overview is currently not available. Gathering evidence on the effects of healthcare interventions is indicated as one of pediatric oncology's key priorities (8). A complete overview of all known possible effects of healthcare interventions on QOL and related measures is necessary to support healthcare providers in safe and effective decision making (9), and for the construction of quality measures, suchas quality indicators and evidence-based guidelines (10).

Our main objective was to systematically review peer-reviewed quantitative literature for evidence about (associations indicating) the effects of healthcare interventions on QOL or QOL-related measures at the end of life for children with a serious illness. Specific research questions were: 1. in which designs, populations, and settings were healthcare interventions studied with regard to QOL and QOL-related measures in children at the EOL?; 2. what healthcare interventions were studied?; 3. what healthcare interventions (are associated with) significantly increase(d) or reduce(d) QOL below α 0.05?; and (4) what was the overall study quality and certainty of evidence?

METHODS

Registration

The protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD 42018105109) and published (11). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed, see Supplementary Information 1.

Search strategy

We identified studies by searching in five electronic databases: in MEDLINE, EMBASE, CENTRAL, CINAHL, and Web of Science. A search was performed on July 7, 2018. The language was not limited; the time was limited to publications from 2000 or later. We excluded studies before 2000 as care prior to this date is likely to differ from that of later generations (12), and a scoping review indicated research is scarce before 2000. The MEDLINE search strategy was developed alongside information specialists, based on the Peer Review of Electronic Strategies (PRESS) guidelines (13). The electronic MEDLINE search strategy is provided in Supplementary Information 2.

Study eligibility criteria

Study designs

Interventional and observational designs with quantifiable results, such as randomized controlled trials (RCTs) and cohort and cross-sectional studies. Observational designs were included due to the suspected scarcity of research on children at the end of life (9,14) and to capture any associations of interventions with QOL.

Population

Children with serious illness aged from 1 up to and including 17 years at the end of life, meaning children suffering from a serious illness who are within the last year of their lives. Acutely ill children, neonates, and young adults were excluded; the end-of-life periods of these populations differ for diagnosis, prognosis, and care context. The mean, median, and/or range of age had to be situated between 1 and 17 years. If a paper discussed children in general terms without age reference, the study was also included. The children were considered to be at the end of life when the study described their sample as being at the end of life at the time of admission of the health intervention, using explicit terminology referring to the end of life, such as “terminally ill,” “near death,” or “dying.” Serious illness was defined as having at least one complex chronic condition, according to the definition (in ICD-10-codes) poised in recent literature (15).

Intervention

Healthcare interventions applied to the population as described above. The WHO definition for *health interventions* was used: “any act performed for, with or on behalf of a person or population whose purpose is to assess, improve, maintain, promote or modify health, functioning, or health conditions’ (16).

Outcomes

QOL outcomes relating to the QOL of the child. We included QOL as such as outcome, but also QOL-related measures: outcomes that could be present on a QOL-scale, such as, among others, physical, psychosocial, and spiritual symptoms, and treatment success, burden, intensity, or toxicity. A broad selection of outcomes was necessary for a thorough overview. We only included outcomes at the level of the child, and excluded outcomes for other stakeholders, such as QOL of parents or medical staff.

Study selection

All records were exported to the reference management software Endnote (Version X7.1). Duplicated records were removed. Using Covidence review management software, four authors (V.P., A.I.-S., K.B., and N.S.P.) screened the titles and abstracts. V.P. screened all records, and A.I.-S, K.B., and N.S.P. independently screened one-third of all records. Three authors (V.P., A.I.-S., and N.S.P.) screened full texts. V.P. screened all records, and A.I.-S. and N.S.P. each independently screened half of the records. Any discrepancies were discussed between the two reviewers in question. In case of disagreement, a third reviewer (K.B. or J.v.d.W.t.B.) was consulted. One author (V.P.) hand-searched the reference lists and contacted authors of the selected studies for additional relevant publications.

Data extraction

The following variables were extracted as described in the publication(s): Author(s), title, publication date, article language, journal, data collection, country, aim, healthcare intervention(s), QOL or QOL-related outcome, results for outcome (for main scales, subscales, and sub-analyses), QOL measurement, children's age (mean, median, range, interquartile range; also if the children themselves were not participating), intervention duration, start and end of intervention in days before death, number of participants (children who were directly or indirectly assessed), and children's illness. The following variables were extracted and classified according to the judgment of the authors of this review: study design, who reported the QOL or proxy of QOL outcome, setting, and illness category. Data were extracted from text, tables, and graphs. If data were missing, authors were not contacted for additional information. The authors of selected publications were contacted to verify the extracted data.

Study quality assessment, certainty of evidence, and data analysis

Data extraction, quality assessment, and grading of certainty of the evidence were performed by V.P. A 25% sample was checked by other researchers (A.-I.S. and N.S.P.).

The quality of each individual study was assessed with the quantitative checklist within the QualSyst Tool (17) (scale ranging from 0 to 1.0). The certainty of evidence was assessed with the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) approach (18). We categorized certainty of evidence per healthcare intervention as high (very certain that effect is close to a true effect), moderate (moderately certain), low (limited certainty), or very low (little certainty).

Data synthesis

We summarized results in overview tables. We grouped healthcare interventions and outcomes according to clinical homogeneity and categorized healthcare interventions into two categories, pharmacological or non-pharmacological, and QOL outcomes into five categories as emergent from the data. Original summary measures were kept. Significant results were categorized for QOL improvement or reduction.

RESULTS

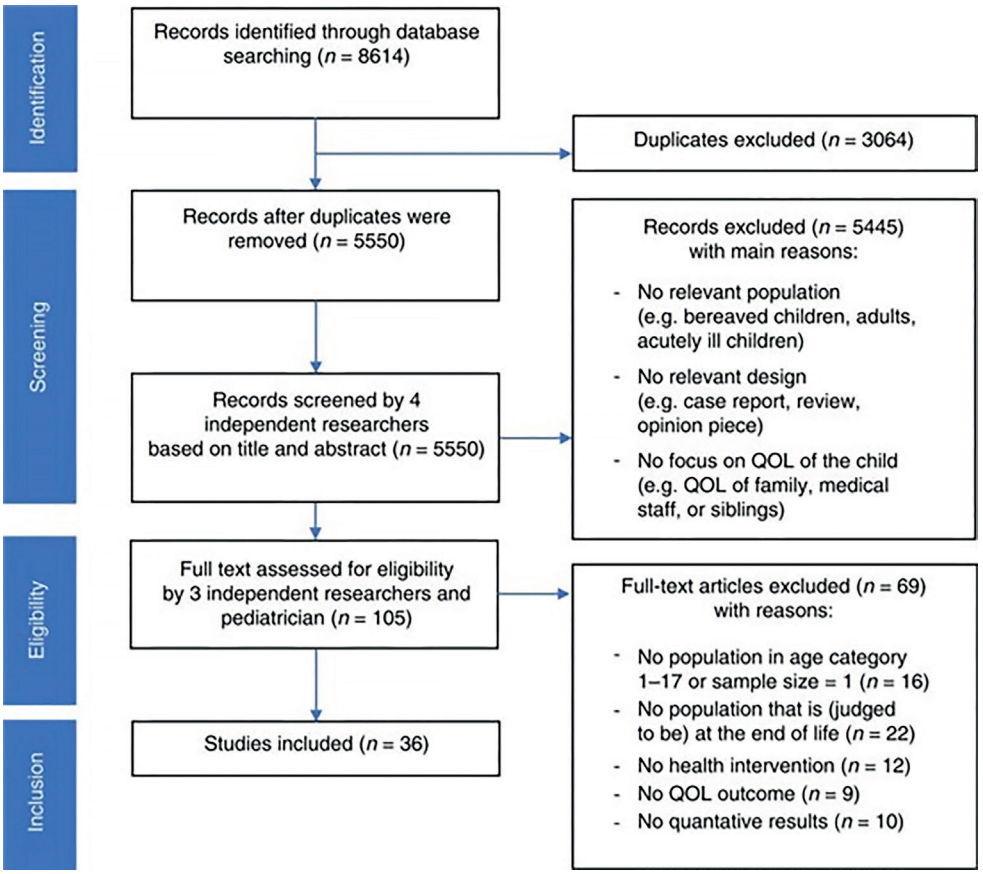
Study selection

As shown in Fig. 1, 8614 studies were identified in MEDLINE, EMBASE, CENTRAL, CINAHL, and Web of Science, and 8578 studies were excluded. Thirty-six studies met the eligibility criteria (19-54).

Study characteristics

Studies mainly had a retrospective cohort (29/36, 81%) or prospective cohort design (5/36, 14%), as illustrated in Table 1. One study had an experimental design (RCT) (1/36, 3%), and another study had a cross-sectional design (1/36, 3%). In two-thirds, children with cancer were studied (23/36, 64%). In one-third (12/36), multiple disorders were studied, for example, a combination of cancer and other disorders. Mean or median age of children ranged from 3.4 years to 17 years. In total, 2493 children were studied. Most healthcare interventions were administered in a hospital setting (16/36, 44%). Outcomes were mostly reported by parents (19/36, 53%).

Fig. 1: Selection and inclusion of studies with reasons for exclusion



Studied healthcare interventions and outcomes

Twenty different healthcare interventions were studied, as shown in Table 1. Seventeen percent (6/36) had QOL as such as an outcome. QOL as such was measured with the PedsQL 4.0 (one study), the Health Utilities Index (one study), the Survey About Caring for Children with Cancer (one study), or an undefined numeric rating scale (three studies). Eighty-three percent of studies (30/36) used QOL-related measures, such as symptoms. Mainly physical symptoms were studied (33/36, 92%).

Significant results

Table 2 shows all significant results. In total, nine interventions revealed statistically significant associations with QOL.

Improved QOL

One pharmacological intervention (dexmedetomidine) and three non-pharmacological interventions (noninvasive mechanical ventilation, pleurodesis, and electronic patient-reported symptom monitoring) were significantly associated with improved QOL (-related measures). Dexmedetomidine was associated with decreased pain, noninvasive ventilation and pleurodesis with decreased cardiopulmonary symptoms, and electronic patient-reported symptom monitoring with improved emotional QOL. Results for dexmedetomidine, pleurodesis, and noninvasive mechanical ventilation resulted from retrospective cohort studies, while the result for patient-reported symptom monitoring was from an RCT.

Two interventions had associations with improved and reduced QOL, but mostly with improved QOL: palliative care was associated with higher quality of life as such, less pain, less dyspnea, more fun, more meaning in life, and better communication, but more constipation and energy loss. Methadone was associated with less pain, less fatigue, and less insomnia, but more dyspnea.

Reduced QOL

One pharmacological intervention (IV chemotherapy) and one non-pharmacological intervention (hospitalization) were significantly associated with reduced QOL and QOL-related measures; both interventions were associated with increased dyspnea. Both results came from the same retrospective cohort study.

Table 1: Characteristics of included studies

Reference	Design	Population of study		Sample size	Setting	Healthcare intervention[a]	Relevant outcome[b]	Report	QualSyst score
		Disease	Age, mean, or median (range), years[c]	Children, no.					
Wolfe et al.(19)	Randomized controlled trial	Cancer	NA (2–20)	98[d]	Various	Patient-reported symptom monitoring	Quality of life Physical symptoms Psychological symptoms Communication	Child Caregivers	0.68
Korzeniewska-Eksterowicz (20)	Retrospective cohort	Cancer	NA (1.88–20)	42/21[e]	Home	Palliative sedation	Physical symptoms	Medical staff	0.41
Schindera et al. (21)	Retrospective cohort	Cancer	10.1 (0–18)	61	Hospital	Chemotherapy Hospitalization	Physical symptoms	NA	0.5
Brook et al. (22)	Retrospective cohort	Cancer	NA (3–16)	12	Home	Home platelet transfusion	Physical symptoms	NA	0.36
Gans et al. (23)	Retrospective cohort	Various	9.6 (1–20)	93	Various	Palliative care	Physical symptoms	Caregivers	0.5
Madden et al. (24)	Retrospective cohort	Cancer	12.5 (NA)	52	Hospital	Methadone	Physical symptoms Psychological symptoms	Child Caregivers	0.45
Groh et al. (25)	Prospective cohort	Various	6 (0–18)	40	Home	Palliative care	Quality of life	Caregiver	0.29
Vollenbroich et al. (27)	Retrospective cohort	Various	3.4 (0–34.3)	38	Home	Palliative care	Quality of life Circumstances of death	Caregiver	0.64
Kuhlen et al. (28)	Retrospective cohort	Cancer	12 (1–27)	49	Home	Palliative care	Physical symptoms	Caregiver	0.45
Hoffer et al. (29)	Prospective cohort	Cancer	15 (3–21)	7	Hospital	Pleurodesis	Physical symptoms	Medical staff	0.42
Groh et al. (26)	Prospective cohort	Various	6 (0–18)	40	Home	Palliative Care	Quality of life Physical symptoms Communication	Caregiver	0.58
Chong et al. (30)	Retrospective cohort	Various	12.2/6.3[f] (0–19)	138[g]	Home	Palliative care	Quality of life Physical symptoms	Child Caregiver	0.86
Friedrichsdorf et al. (31)	Retrospective cohort	Cancer	10.1 (0–17)	60[g]	Home	Palliative care	Quality of life Physical symptoms Psychological symptoms	Caregiver	0.68
Thrane et al. (32)	Retrospective cohort	Various	9.5 (2–16.9)	256	Various	Palliative care	Physical symptoms	NA	0.32
Hooke et al. (33)	Retrospective cohort	Various	5.3 (2–16)	256/48[f]	Hospital	Propofol	Physical symptoms Psychological symptoms	NA	0.55
Hohl et al. (34)	Retrospective cohort	Various	8 (1–18)	18	Hospital	Methotrimeprazine	Physical symptoms	NA	0.41
Rapoport et al. (35)	Retrospective cohort	Genetic	NA (0–15)	7	Various	Forgoing of artificial nutrition and hydratation	Circumstances of death	Caregiver	0.45
Taylor et al. (36)	Retrospective cohort	Cancer	15.5 (0–23)	14	Hospital	Patient-controlled analgesia	Physical symptoms	NA	0.5
Burns et al. (37)	Retrospective cohort	Cancer	8 (0–17)	9	Hospital	Dexmedetomidine	Physical symptoms	NA	0.27
Postovsky et al.	Retrospective	Cancer	17/9[f] (NA)	37	Hospital	Palliative sedation	Physical	NA	0.36

Reference	Design	Population of study		Sample size	Setting	Healthcare intervention[a]	Relevant outcome[b]	Report	QualSyst score
		Disease	Age, mean, or median (range), years[c]	Children, no.					
(38)	cohort						symptoms		
Schiessl et al. (39)	Retrospective cohort	Cancer	8.5 (3–17)	8	Various	Patient-controlled analgesia	Physical symptoms	Child Caregiver Medical staff	0.45
Ullrich et al.(40)	Cross-sectional	Cancer	9.3/10.5[f] (NA)	141[g]	NA	Stem cell transplant	Physical symptoms Psychological symptoms	Caregiver	0.64
Urtubia et al. (41)	Retrospective cohort	Cancer	8 (NA)	99	Hospital	Opioids	Physical symptoms	Child Caregiver	0.68
Dickens et al. (42)	Retrospective cohort	Various	NA (NA)	NA	Various	Palliative care	Physical symptoms Psychological symptoms Circumstances of death	Medical staff	0.27
Rodríguez Zamora et al. (43)	Retrospective cohort	Cancer	9 (NA)	309	Hospital	Palliative care	Physical symptoms	Child Caregiver	0.77
Davies et al.(44)	Prospective cohort	Cancer	8.9 (3–19)	17	Hospital	Methadone	Physical symptoms	Caregiver NA (chart review)	0.54
Bosch-Alcaraz et al. (45)	Retrospective cohort	Various	4 (2–9)	55	Hospital	Noninvasive ventilation	Physical symptoms	NA	0.68
Varma et al.(46)	Retrospective cohort	Cancer	10.3 (0–18)	50	Hospital	Palliative radiation therapy	Physical symptoms	Child Caregiver Medical staff	0.73
Flerlage et al.(47)	Retrospective cohort	Cancer	14 (1.5–21)	9	Hospital	Methylnaltrexone	Physical symptoms	NA	0.41
Anghelescu et al. (48)	Retrospective cohort	Cancer	NA (4–21)	10	Hospital	Epidural and peripheral nerve blocks	Physical symptoms Circumstances of death	NA	0.68
Anghelescu et al. (49)	Retrospective cohort	Cancer	NA (6–15)	3	Hospital	Palliative sedation	Physical symptoms	NA	0.55
Breen (50)	Prospective cohort	Cancer	NA (2–16)	4	Not found	New type of infusion device	Physical symptoms	Medical staff	0.29
Siden and Nalewajek (51)	Retrospective cohort	Various	NA (0–19)	44	Hospice	Opioids	Physical symptoms	Medical staff	0.45
Rima Saad et al. (52)	Retrospective cohort	Various	10.11 (NA)	29	Various	Palliative care	Physical symptoms	Caregiver	0.55
Schmidt et al. (53)	Retrospective cohort	Cancer	6/9.9[f] (NA)	98[d]	Various	Palliative care	Physical symptoms Psychological symptoms	Caregiver	0.59
Wolfe et al. (54)	Retrospective cohort	Cancer	10.8/10.4[f] (NA)	221[d]	NA	Palliative care	Physical symptoms	Caregiver	0.82

NA Not available.; [a]Categorized. Detailed characteristics for healthcare interventions with significant results can be found in Table 4.; [b]Unspecified symptom outcomes were categorized under "Physical symptoms."; [c]When multiple ages were provided for different measurements, the age of the last measurement was chosen.; [d]Groups were summed (e.g., control group and intervention group).; [e]The whole sample size in the study and the sample size for the outcome that was of interest for this review, respectively.; [f]For the intervention group and control group or two compared cohorts, respectively.

Table 2 Significant associations between healthcare interventions and quality of life

Evidence certainty[a]	Healthcare intervention	Quality of life category	Association with quality of life		*P* value[b]
			Quality of life improves	Quality of life reduces	
Pharmacological					
Very low	Dexmedetomidine (37)	Physical symptoms	Pain (37) ↓		<0.001
Very low	IV chemotherapy (21)	Physical symptoms		Dyspnea (21) ↑	<0.001
Very low	Methadone (24)	Physical symptoms	Pain (24) ↓	Dyspnea (24) ↑	<0.001/<0.001[c]/0.03
			Fatigue (24) ↓		0.01
			Insomnia (24) ↓		0.005/<0.001
Very low	Stem cell transplant (40)	Physical symptoms	Constipation (40) ↓	Fatigue (40) ↑	0.05[d]/0.04
				Diarrhea (40) ↑	<0.001
				Number of physical symptoms that cause serious suffering (40) ↑	0.009
Very low	Stem cell transplant (40)	Psychological symptoms		Sadness (40) ↑	0.04
				Afraid (40) ↑	0.03
				Number of psychological symptoms that cause serious suffering (40) ↑	0.007
Non-pharmacological					
Very low	Noninvasive mechanical ventilation (45)	Physical symptoms	Heart rate (45) ↓		<0.001
			Respiratory rate (45) ↓		<0.001
			Partial oxygen saturation (45) ↑		<0.001
Moderate	Electronic feedback intervention program (19)	Quality of life as such	Emotional quality of life in children who survived beyond the intervention (19)↑		0.04
Moderate	Electronic feedback intervention program (19)		Emotional quality of life in children from 8 years onwards who survived beyond the intervention (19) ↑		0.01
Very low	Pleurodesis (29)	Physical symptoms	Respiratory rate (29) ↓		0.03
			Aeriation short term (29) ↑		0.04
Very low	Hospitalization (21)	Physical symptoms		Dyspnea (21) ↑	0.01
Very low	Palliative care (25,26,27)	Quality of life as such	Quality of lifee (25,26,27) ↑		<0.001/<0.001/<0.001
Very low	Palliative care (31,54)	Physical symptoms	Pain (54) ↓	Constipation (31) ↑	0.008/0.01
			Dyspnea (54) ↓	Energy loss (31) ↑	<0.01/<0.07
Very low	Palliative care (31)	Psychological symptoms	Amount of fun (31) ↑		0.03
			Event adding meaning to life (31) ↑		0.02
Very low	Palliative care (26)	Communication	Communication (26) ↑		<0.001

[a]Measured with Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.(18); [b]P values are reported as they appear from left to right in the corresponding row;.[c]For children report and parent report, respectively; [d]P value was reported as 0.046 in the original paper, due to formatting requirements this P value now shows 0.05.; [e] References 25,26 may refer to two similar publication on the same program and the same sample for the same outcome.

One intervention was associated both with improved and reduced QOL, but most associations were with reduced QOL: stem cell transplant was associated with a higher number of physical and psychological symptoms, fatigue, diarrhea, sadness, and fear, but with reduced constipation.

Detailed characteristics of significant results can be found in Table 3.

Characteristics of healthcare interventions with significant results

Table 4 shows the characteristics of healthcare interventions with significant results. Most interventions with significant results were non-pharmacological. Often doses, procedures, duration, and timing of admission were not available. Palliative care programs were mostly physical and psychosocial, and always included a multi-professional team. Most programs had a 24/7 on-call service and helped with coordination of care.

Study quality and evidence certainty

Study quality

QualSyst scores ranged from 0.27 to 0.86, as indicated in Table 1. Qualsyst scores were generally low due to the absence of control groups and the absence of matched comparison groups, inadequate subject/comparison selection or source of information, insufficient description of subject and comparison characteristics, insufficient operationalization, small sample sizes, non-validated measurement tools, unreported estimates of variance, and no controlling for confounding. Detailed QualSyst scores can be found in Supplemental Information 3.

Evidence certainty

Ratings for evidence certainty were very low for all healthcare interventions and related outcomes, except for electronic patient-reported symptom monitoring that had moderate certainty of evidence for emotional QOL, as presented in Table 2 and Supplemental information 4.

Table 3 Detailed characteristics of significant results.

Healthcare intervention	Quality of life outcome	QOL measurement	Scale	Report	Comparison group	Summary statistic	Result	*P* value (95% CI)
Pharmacological healthcare interventions								
Dexmedetomidine (37)	Pain (37)	FLACC	1–10	NA	No	Mean difference	Unspecified decrease before and after daily infusions	<0.001 (NA)
IV chemotherapy (21)	Dyspnea (21)	CTCAE v4.0 Chart review	1–2: Mild 3–5: Severe	NA	No	Odds ratio	15.8-fold Increased odds	<0.001 (3.7–67.5)
Methadone (24)	Pain (24)	PSAS	0-4	Child	No	Mean difference	1.79 Points decrease between baseline and follow-up 1	<0.001 (NA)
							2.44 Points decrease between the baseline and follow-up 2	<0.001 (NA)
Methadone (24)	Pain (24)	PSAS	0–4	Parent	No	Mean difference	2.11 Points decrease between baseline and follow-up 1	<0.001 (NA)
							2.42 Points between baseline and follow-up 2	<0.001 (NA)
Methadone (24)	Fatigue (24)	PSAS	0–4	Parent	No	Mean difference	0.52 Point decrease between baseline and follow-up 2	0.01 (NA)
Methadone (24)	Insomnia (24)	PSAS	0–4	Child	No	Mean difference	1.43 Point decrease between baseline and follow-up 1	<0.001 (NA)
							1.45 Point decrease between baseline and follow-up 2	<0.005 (NA)
Methadone (24)	Insomnia (24)	PSAS	0–4	Parent	No	Mean difference	1.43 Point decrease between baseline and follow-up 1	<0.001 (NA)
							1.24 Point decrease between baseline and follow-up 2	<0.001 (NA)
Methadone (24)	Dyspnea (24)	PSAS	0–4	Parent	No	Mean difference	0.32 Point increase between baseline and follow-up 2.	0.03 (NA)

Healthcare intervention	Quality of life outcome	QOL measurement	Scale	Report	Comparison group	Summary statistic	Result	*P* value (95% CI)
Stem cell transplant (40)	Fatigue (40)	NRS	1–5	Parent	Yes	Percentage difference	22% Increase with SCT compared to non-SCT	0.04 (1;44)
Stem cell transplant (40)	Constipation (40)	NRS	1–5	Parent	Yes	Percentage	16% Decrease with SCT compared to non-SCT	0.046 (−28;−4)
Stem cell transplant (40)	Diarrhea (40)	NRS	1-5	Parent	Yes	Percentage	31% Increase with SCT compared to non-SCT	<0.001 (10;51)
Stem cell transplant (40)	Number of physical symptoms that causes serious suffering (40)	NRS	1–5	Parent	Yes	Percentage	1.3% Increase with SCT compared to non-SCT	0.009 (−0.1; 2.7)
Stem cell transplant (40)	Sadness (40)	NRS	1–5	Parent	Yes	Percentage	23% Increase with SCT compared to non-SCT	0.04 (3;43)
Stem cell transplant (40)	Being afraid (40)	NRS	1–5	Parent	Yes	Percentage	24% Increase with SCT compared to non-SCT	0.03 (2;46)
Stem cell transplant (40)	Number of psychological symptoms that causes serious suffering (40)	NRS	1–5	Parent	Yes	Percentage	0.7% Increase with SCT compared to non-SCT	0.007 (0;1.4)
Non-pharmacological healthcare interventions								
Noninvasive mechanical ventilation (45)	Heart rate (cardiac frequency) (45)	Decrease of heart rate	Pulses per minute	NA	No	Mean difference or Hodges–Lehmann estimate	22.49 Decrease	<0.001 (NA)
Noninvasive mechanical ventilation (45)	Respiratory rate (respiratory frequency) (45)	Respiratory frequency	Respirations per minute	NA	No	See above	9.39 Decrease	<0.001 (NA)
Noninvasive mechanical ventilation (45)	Oxygen saturation (45)	Oxygen saturation	Unclear	NA	No	See above	1.17 Increase	<0.001 (NA)
Noninvasive mechanical ventilation (45)	Partial fraction of oxygen (45)	Unclear	Unclear	NA	No	See above	39.85 Increase	<0.001 (NA)
Electronic feedback intervention program (19)	Emotional quality of life (19)	PedsQL 4.0	0–100	Child or parent	No	Mean difference	6 Point increase in children who survived beyond intervention	0.04 (0.3;11.7)
Electronic feedback intervention program (19)	Emotional quality of life (19)	PedsQL 4.0	0–100	Child or parent	No	Mean difference	8.1 Point increase in children from 8 years onwards who survived beyond intervention	0.01 (1.8;14.4)
Pleurodesis (29)	Respiratory rate (29)	Chart review	Breaths per minute	Physician	No	NA	Unspecified decrease	0.03 (NA)

Healthcare intervention	Quality of life outcome	QOL measurement	Scale	Report	Comparison group	Summary statistic	Result	*P* value (95% CI)
Pleurodesis (29)	Aeriation short term (29)	Chart review		Physician	No	NA	Unspecified increase	0.04 (NA)
Hospitalization (21)	Dyspnea (21)	CTCAE v4.0 Chart review	1–5 Unknown	NA	No	Odds ratio	1.1-fold Increased odds	0.01 (1.0;1.1)
Palliative care (25)	Quality of life (25)	McGill QOL Questionnaire and POS	0–10	Child or parent	No	Mean rank difference	Unspecified increase	<0.001 (NA)
Palliative care (27)	Quality of life (27)	Questionnaire	0–10	Parent	No	Mean rank difference	Unspecified increase	<0.001 (NA)
Palliative care (26)	Quality of life (26)	Questionnaire	1–10	Parent	No	Mean rank difference	Unspecified increase	<0.001 (NA)
Palliative care (54)	Pain (54)	Survey	5-point Likert	Parent	Yes	Percentage difference	19% Decrease of pain for second cohort	0.08 (NA)
Palliative care (54)	Dyspnea (54)	Survey	5-point Likert	Parent	Yes	Percentage difference	21% Decrease of dyspnea for second cohort	<0.001 (NA)
Palliative care (31)	Constipation (31)	SCCC	Symptom presence	Parent	No	Odds ratio	Unspecified increased odds	0.01 (NA)
Palliative care (31)	Energy loss (31)	SCCC	Suffering of symptom presence	Parent	No	Odds ratio	Unspecified increased odds	0.007 (NA)
Palliative care (31)	Amount of fun (31)	SCCC	Great deal/a lot/some Little/none	Parent	Yes	Percentage difference	25% Increase for PC group compared to non-PC group	0.03 (NA)
Palliative care (31)	Event adding meaning to life (31)	SCCC	Great deal/a lot/some Little/none	Parent	Yes	Percentage difference	26% Increase for PC group compared to non-PC group	0.02 (NA)
Palliative care (26)	Communication (26)	NRS	1–10	Parent	No	Mean rank difference	1 Point increase from 7.0 to 8.0	<0.001 (NA)

NA Not available, *FLACC* Face, Legs, Activity, Cry, and Consolability scale, *CTCAE v4.0* National Cancer Institute's Common Terminology Criteria for Adverse Events v4.0, *PSAS* Pediatric Symptom Assessment System, *SCCC* Survey About Caring for Children with Cancer, *POS* Palliative Outcome Scale, *SCT* stem cell therapy, *NRS* Numeric rating scale, *PC* Palliative care.

Table 4 Detailed characteristics of health interventions with significant results

Healthcare intervention	Description	Dose/procedure	Duration, mean, or median (range), days	Period before death, mean, days	Other specifications
Pharmacological healthcare interventions					
Dexmedetomidine (37)	α2-Adrenoreceptor agonist	1 μg/kg bolus over 10 min with continuous infusion at 0.1–3 μg/kg/h	2 (1–111)	NA	Authors reported that bolus doses of 0.1 μg/kg could be administeredup to every 30 min if pain scores were ≥5 (37)
IV chemotherapy (21)	Intravenous cytostatic	NA	NA	30	Disease-oriented, not comfort-oriented, chemotherapy was looked at
Methadone (24)	Opioid	0.1 mg/kg PO q12 hours	17 (NA)[a]; 55 (NA)[b]	NA	The medication was initiated at the standard pediatric analgesic dosing
Stem cell transplant (40)	Surgical cancer-directed therapy	NA	NA	NA	The stem cell transplant was the last cancer-directed therapy the children received
Non-pharmacological healthcare interventions					
Noninvasive mechanical ventilation (45)	Therapy to aid breathing	NA	NA	NA	The ventilation had a palliative character and was used to treat acute or chronic respiratory failure
Electronic feedback intervention (19)	Computer-based data collection system	NA	140 (NA)	NA	The system collected patient's symptoms and HRQoL data and generated printed feedback reports and e-mail alerts
Hospitalization (21)	Inpatient hospital days	NA	NA	30	
Palliative care[d]	Specialized palliative home care (25)	Medical and nursing care A 24/7 on-call service Psychosocial support Coordination of professional assistance	NA	NA	There were two separate teams for adults and children. Services were provided while closely cooperating with the local healthcare professionals, such as general practitioners, pediatricians, nursing, and hospice services
	Specialized palliative home care (26)	Medical and nursing care A 24/7 on-call service Psychosocial support Coordination of professional assistance	11.8 (0.5–58.0)	NA	This program is the same program as mentioned in the line above, reported in a different publication. See above for specifications
	Palliative home care team (27)	Palliative care in cooperation with local healthcare professionals 24/ 7 medical on-call service Coordination of professional assistance	6.5 (1–48 weeks)	NA	Two examples of coordination of professional assistance were included in the paper: transition of care between hospital and home and assistance in appropriate communication
	Home-based palliative care (31)	Scheduled visits by nurses, social work, child life therapist, and chaplain 24/7 medical on-call home service Assessment and treatment of distressing symptoms Coordination of care Psychosocial care	NA	NA	Psychosocial care included counseling and support, assisting with community resources, bereavement support, memory making for siblings, school visits, and motional, spiritual, and bereavement support

Healthcare intervention	Description	Dose/procedure	Duration, mean, or median (range), days	Period before death, mean, days	Other specifications
	Pediatric Advanced Care Team (54)	Clinical consultations to the medical team and the patient and/or family, setting up systemwide improvements to caring for children with advanced cancer, education to pediatric oncology practitioners	NA	NA	Clinical help was provided for inpatient, outpatient, and home settings Examples were provided for systemwide improvements: direct admission policy and the comfort corner
Pleurodesis (29)	Surgical therapy	Pleural fluid was aspirated with a syringe. Then, 500mg doxycycline was mixed with 40ml normal saline	1 (0–19)[c]	NA	Two patients (one as young as 3 years) had repeat pleurodeses with 500 mg doxycycline in each pleural space

NA not available.; [a]Baseline to measurement moment 1.; [b]Baseline to measurement moment 2.; [c]For chest tube placement.; [d]Care was provided by a multidisciplinary team for all programs.

DISCUSSION

To our knowledge, this is the first systematic literature review mapping and synthesizing the effects, and associations indicating effects, of healthcare interventions on QOL in children with serious illness at the end of life, according to the best available evidence. We found 36 eligible studies with a total of 20 different healthcare interventions that were studied in relation to QOL or QOL-related measures. Only one RCT was found, and mainly cohort studies were used to study health interventions and QOL in children at the end of life. Mainly children with cancer were studied. Overall eight medications, ten treatments, and two methods for delivery of care were found to be studied for QOL in terms of healthcare interventions. Six healthcare interventions were significantly associated with improved QOL, and three interventions were significantly associated with reduced QOL in children with serious illness at the end of life. In general, certainty of evidence was very low, mainly due to a lack of measures for bias reduction in cohort studies. The body of evidence shows fragmented research, as different outcomes were studied for various healthcare interventions, and the same outcome was rarely studied for the same intervention, due to which no meta-analysis was possible.

Interpretation of results

Our systematic review revealed various indications could be made for appropriate QOL management in children with serious illness at the end of life.

Electronic symptom monitoring feedback and patient-controlled interventions are hypothesized to be one of the cornerstones of appropriate pediatric end-of-life management. Electronic

symptom monitoring feedback was the only healthcare intervention that reliably improved QOL in children with cancer at the end of life. It seems that a noninvasive form of QOL monitoring can hold a place in the provision of appropriate care for these children. An important element may be the fact the system was patient controlled, an aspect that is also found in the multiple patient-controlled analgesia studies within our selection of papers (36,39). These papers, although not statistically generalizable due to the methods used, showed mainly associations with improved QOL. Therefore, besides the importance of symptom feedback systems being implemented in hospital service for children, one may also carefully hypothesize that patient-controlled interventions are an important aspect of appropriate care in children at the end of life.

Off-label sedative medication and treatments seem to present adequate symptom control in the population at hand. Both QOL-increasing medications that emerged from our selection, methadone and dexmedetomidine, are sedative in nature, and efficient in relieving pain, the main troublesome symptom in children at the end of life (55,56). The main portion of the studies without use of inferential statistics in this review were also sedative in nature (propofol, various opioids, nerve blocks, and forgoing of artificial hydration and feeding). The widespread reporting of sedative medication use could point to its importance for this population in terms of appropriate care provision. It is also to be noted that both significantly effective medications and some non-inferentially studied interventions are off-label for the pediatric population, and off-label prescription may be needed in certain children for appropriate symptom control.

Furthermore, improved breathing could be central to improved QOL for at least a part of the population. Two lung treatments were shown to have associations with improved QOL. Dyspnea is reported to be one of the most disturbing symptoms for children at the end of life (57).

Palliative care interventions seem to be effective for families with children with serious illness at the end of life when they are multidisciplinary, provide 24/7 round-the-clock assistance, medical help for the child, and practical or even emotional help for the parents. Our summary of results for palliative care interventions showed that all significant results in this category resulted from palliative care teams with these characteristics. The clear presence of practical assistance for parents suggests that the QOL of the child also increases when parents receive practical and emotional help. The latter hypothesis is supported by neurodevelopmental research, which has previously shown co-regulation mechanisms between parents and children, especially mothers, are associated with child self-regulation, and this interaction is suggested as a hypothesis to also be of crucial importance in appropriate pediatric end-of-life care (58,59). There was one cohort study out of five that indicated some negative associations of palliative care with QOL, which could be a result of a measurement error, or the palliative

care intervention in question could have been inappropriate, possibly due to intensive psychological counseling, which seemingly characterized this intervention. It could be hypothesized that children at the end of life cannot handle intensive psychological treatment that only provides benefits in the long term.

Curative treatment seemingly negatively impacts the QOL of children at the end of life, although this should be further tested. Both chemotherapy and stem cell transplant significantlyreduced QOL and were explicitly stated to be of curative nature. In adults, negative effects of these interventions are often used as an indicator for inappropriate care, and it is generally believed care at the end of life in children should avoid disease-oriented treatment (3,60,61- 63). The majority of parents still prefer chemotherapy over comfort care at the end of life (64),which probably results from a parent's understandable hope that their child will survive, and highlights the need for measures that indicate when a child has no realistic chance of survivalto assist parents in treatment decision making. Some traditional disease-oriented treatments such as chemotherapy are also used as a comfort measure, for example, to control pain (14),and it is worth investigating which application forms and doses provide symptom relief.

Lastly, there are indications that end-of-life context and place of care can influence QOL: hospitalization significantly improved chances for severe dyspnea in one study we found. However, this result might also reflect the fact that children with severe symptoms are more often hospitalized. Hospitalization is considered stressful for children, but might also provide the only facility for relief in cases where symptoms are severe.

Study quality and evidence certainty

Evidence certainty was moderate for electronic patient-reported symptom reporting (measured via RCT) and very low for all other interventions (cohort studies). RCTs are often not feasible or ethically permissible for children at the end of life, due to the vulnerable population. Most studies, therefore, employed non-interventional, retrospective designs. However, measures that could control bias in these designs were absent in most cohort studies, such as controlling for confounders.

Certainty of evidence was low for studies, yet a stringent quality assessment tool was used (QualSyst), and the standards of this tool are extremely high. Research in pediatric end-of-life care research, due to its ethical and practical confinements, will very rarely score very high on the measures of certainty of evidence compared to other fields. However low the certainty of some evidence, it remains important to generate new hypotheses for further research based on the current state-of-the-art and build theories based on all indications we can gather, rather than to throw away the baby out with the bathwater. In order to gain further knowledge in this field without depleting costly resources and a vulnerable population, hypothesis-driven

research should be thought out in a careful manner that provides a balance between quality of evidence and practicality in studying the population at hand. Significant results were plenty in our selection of studies, and therefore provide ample opportunity for new research questions and construction of main indications for appropriate QOL management in children at the end of life. The overview of evidence in this review allows us to suggest novel hypotheses based on the current state-of-the-art end-of-life care research for children. The calculated risks and sensitivities as a result of a stringent quality analysis should not lead to the conclusion that no evidence is present, yet should seek to falsify the hypotheses that are generated through the current research in order to avoid research waste and to more rapidly progress research into pediatric QOL management.

Research gaps and recommendations emerging from this review

While 20 healthcare interventions have been studied, certain healthcare interventions have not been studied yet for their effects, or the results were not published. Some common healthcare interventions did not surface in our review, such as gastric tubes that the majority of children (67.5%) receive at the end of life (65).

Studies for nonmalignant disorders are lacking: Mainly cancer patients were studied, while half of child deaths resulting from serious illness are due to nonmalignant conditions. Parents with children with nonmalignant conditions report care to be under-resourced and unresponsive, in contrast to parents of children with cancer (66).

Studies for nonphysical outcomes are lacking: Mostly physical symptoms were studied. Pain, for example, was researched often in our review, probably due to systematically available and routinely employed measures with international scoring boards (e.g., FACES, the nonverbal pain scale), resulting in widely and rapidly available data in chart reviews, aside from being the main symptom children suffer at the end of life (67). However, children and their parents also indicate psychological, psychosocial, and existential concerns besides physical ones (57,68).

Future research recommendations are methodologically and content-oriented. Methodologically, more robust, prospective, interventional research should be conducted. When an RCT is not feasible, designs should still use necessary measures to control bias, such as restriction, or matching of the population for confounders. Confidence intervals should be reported. Outcome measures validated for the population at hand should be used, for example, the Pediatric Advanced Care QOL Scale for children with advanced cancer (69). In order to bypass scarce availability of the population, the implementation in hospitals of systematic patient-reported monitoring could be used to create big data QOL sets and gather more evidence in a systematic manner (9,70). As patient-reported symptom monitoring was shown to be beneficial for the child's QOL at the end of life in our review, and patient-reported

outcomes were mentioned in previous research as an indicator of appropriate child health care (71), patient-reported outcomes might be used also for research data collection, providing a database that can be used and spares children of additional questionnaires, causing the population to be less overloaded and bypassing recall and parent–child discrepancy. However, appropriate privacy measures should be taken in this regard, for example, in the case of adolescent–parent conflict. Furthermore, clinically ambiguous interventions that are employed in children at the end of life, for example, antibiotics or clinical trials, should be looked into for their effect on QOL. Ideally, the evaluation of interventions is again done via big databases generated via patient-controlled symptom monitoring systems. Effective interventions for children with nonmalignant disorders could be investigated. The hypothesis that practical support for parents improves QOL of the child, emerging from interpretation of our results, could be further reviewed or be incorporated into intervention research.

Practical recommendations for hospital management are that (self-administered) QOL questionnaires for children are electronically and systematically implemented into pediatric hospital wards by boards and management staff, as has previously already been advocated by previous pediatric oncology research (72). QOL questionnaire administering has shown to provide benefits in singling out high-risk patients in other pediatrics fields (73), shown benefits to improve the mood of children with cancer (19), and could advance pediatric QOL management as a field considerably by providing valuable (anonymized) data. Furthermore, patient-controlled interventions might be implemented routinely into pediatric wards, for example, by providing patient-controlled analgesia or by providing tablets for children to fill out daily questionnaires, although implementation should be carefully monitored.

Practical recommendation for individual case management are that pediatricians in training are presented with the various interventions that are possible and for now are shown to be effective in (some) children with serious illness at the end of life. Knowledge of the possibility of, for example, sedative/off-label medication and inhalation therapy can guide the pediatricianwith a more well-equipped toolbelt for the rare and therefore often difficult symptom management of the dying child, and provide at least some theoretical grounds for practice.

Strengths and weaknesses

Our systematic review is the first to systematically identify the quantitative evidence of the effects of healthcare interventions on QOL and QOL-related measures for children with serious illness at the end of life. Study execution was meticulous: PRISMA guidelines were used for protocol and reporting and a Cochrane systematic review course was followed. The search strategy was validated and peer reviewed by an Information Specialist. Multiple reviewers selected studies using predetermined selection criteria. Our review also has certain limitations.

The search strategy was constructed to be comprehensive, but still might have overlooked studies with relevant results, which was remedied by hand-searching references and contacting the first authors for additional papers. No case studies, qualitative studies or gray literature were included.

CONCLUSION

There are indications that patient-controlled symptom feedback systems, multidisciplinary palliative care teams, sedative medication, and treatments directed at ameliorating breathing could improve QOL for children at the end of life. Curatively oriented treatments are carefully suggested to reduce QOL for children at the end of life.

Future research should include hypothesis-driven studies, more robust designs whenever possible, controlling for confounding, nonmalignant populations, validated outcome measures, and inclusion of QOL outcomes in intervention research, in order to generate more and verify current conclusions about (in)appropriate health care for children at the end of life.

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Supplemental Information 2. Validated MEDLINE Search Strategy (PubMed Interface)

1. Pediatrics

child [mh] OR pediatrics [mh:noexp] OR adolescent [mh] OR minors [mh] OR toddler [tiab] OR toddlers [tiab] OR minors [tiab] OR boy [tiab] OR boys [tiab] OR girl [tiab] OR girls [tiab] OR kid [tiab] OR kids [tiab] OR child [tiab] OR child's [tiab] OR children [tiab] OR children's [tiab] OR childhood [tiab] OR schoolchild [tiab] OR schoolchildren [tiab] OR school age [tiab] OR school aged [tiab] OR school ager [tiab] OR school agers [tiab] OR school ages [tiab] OR adolescence [tiab] OR adolescent [tiab] OR adolescent's [tiab] OR adolescents [tiab] OR adolescents' [tiab] OR underage* [tiab] OR pediatric [tiab] OR pediatrician [tiab] OR pediatricians [tiab] OR pediatrics [tiab] OR paediatric [tiab] OR paediatrician [tiab] OR paediatricians [tiab] OR paediatrics [tiab]

2. End of life

Terminal Care [mh] OR palliative care [mh] OR terminally ill [mh] OR hospice care [mh] OR palliative medicine [mh] OR Hospices [mh] OR right to die [mh] OR respite care [mh] OR hospice and palliative care nursing [mh] OR euthanasia [mh] OR suicide, assisted [mh] OR terminal care [tiab] OR terminal disease [tiab] OR terminal diseases [tiab] OR terminal disorder [tiab] OR terminal disorders [tiab] OR terminal cancer [tiab] OR terminal cancers [tiab] OR terminal nature [tiab] OR terminal ilness [tiab] OR terminal ilnesses [tiab] OR terminal remission [tiab] OR terminal remissions [tiab] OR terminal phase [tiab] OR terminal phases [tiab] OR terminally ill [tiab] OR palliative [tiab] OR palliatively [tiab] OR end of life [tiab] OR end-of-life [tiab] OR eolc [tiab] OR EOL [tiab] OR comfort care [tiab] OR assisted suicide [tiab] OR physician-assisted dying [tiab] OR euthanasia [tiab] OR last month of life [tiab] OR last months of life [tiab] OR last days of life [tiab] OR last day of life [tiab] OR life limiting condition [tiab] OR life limiting conditions [tiab]

3. Proxies for quality of life

Patient Acceptance of Health Care [mh] OR Quality-Adjusted Life Years [mh] OR Symptom Assessment [mh] OR Behavioral Symptoms [mh] OR anxiety [mh] OR dyspnea [mh] OR diarrhea [mh:noexp] OR fatigue [mh] OR constipation [mh] OR vomiting [mh] OR "Outcome Assessment (health care)" [mh] OR nausea [mh] OR depression [mh] OR Quality of life [mh] OR pain [mh] OR appetite [tiab] OR appetite [mh] OR Health status [mh:noexp] OR "health status disparities" [mh] OR Health status indicators [mh] OR Quality adjusted life years [mh] OR Treatment outcome [mh] OR Quality Improvement [mh] OR Patient Satisfaction [mh] OR "Standard of Care" [mh] OR Quality of life [tiab] OR QOL [tiab] OR HRQL [tiab] OR HRQOL [tiab] OR Quality adjusted life year [tiab] OR Quality adjusted life years [tiab] OR HRQL [tiab] OR QALY [tiab] OR QALYs [tiab] OR Life quality [tiab] OR Wellbeing [tiab] OR Well-being [tiab] OR pain [tiab] OR nausea [tiab] OR vomit [tiab] OR vomiting [tiab] OR constipation [tiab] OR diarrhea [tiab] OR dyspnea [tiab] OR fatigue [tiab] OR anxiety [tiab] OR depression [tiab]

4. Design

Clinical Study [ptyp] OR Clinical Trial [ptyp] OR Clinical Trial, Phase I [ptyp] OR Clinical Trial, Phase II [ptyp] OR Clinical Trial, Phase III [ptyp] OR Clinical Trial, Phase IV [ptyp] OR comparative Study [ptyp] OR Controlled Clinical Trial [ptyp] OR Evaluation Studies [ptyp] OR Multicenter Study [ptyp] OR Observational Study [ptyp] OR Pragmatic Clinical Trial [ptyp] OR Randomized Controlled Trial [ptyp] OR Technical Report [ptyp] OR Twin Study [ptyp] OR "non-randomized controlled trials as topic" [mh] OR Health surveys [mh:noexp] OR "adaptive clinical trials as topic" [mh] OR "pragmatic clinical trials as topic"

Supplemental Information 2. Validated MEDLINE Search Strategy (PubMed Interface) (Continued)

[mh] OR "compassionate use trials" [mh] OR "random allocation" [mh] OR "double-blind method" [mh] OR "single-blind method" [mh] OR "comparative effectiveness research" [mh] OR control groups [mesh] OR "Randomized Controlled Trials" [mh] OR Surveys and Questionnaires [mh] OR "historically controlled study" [mh] OR "controlled before-after studies" [mh] OR "follow-up studies" [mh] OR "sampling studies" [mh] OR "longitudinal studies" [mh] OR "preliminary data" [mh] OR "interrupted time series analysis" [mh] OR "empirical research" [mh:noexp] OR "nursing administration research" [mh] OR Early Termination of Clinical Trials [mh] OR "psychopharmacology" [mh] OR "population surveillance" [mh] OR "multicenter studies as topic" [mh] OR "drug evaluation" [mh] OR "outcome assessment (healthcare)" [mh] OR "observational studies as topic" [mh] OR "clinical studies as topic" [mh] OR "national longitudinal study of adolescent health" [mh] OR "case-control studies" [mh] OR "cohort studies" [mh] OR "cross-over studies" [mh] OR "retrospective studies" [mh] OR "feasibility studies" [mh] OR "pilot projects" [mh] OR clinical study [tiab] OR clinical studies [tiab] OR Comparative study [tiab] OR comparative studies [tiab] OR Evaluation Studies[tiab] OR Evaluation study [tiab] OR Multicenter Study[tiab] OR Multicenter Studies [tiab] OR Observational Study [tiab] OR Observational Studies [tiab] OR Twin Study [tiab] OR Twin Studies [tiab] OR trial [tiab] OR trials [tiab] OR random [tiab] OR randomized [tiab] OR randomized [tiab] OR controlled [tiab] OR controled [tiab] OR multicenter [tiab] OR longitudinal [tiab] OR case-control [tiab] OR case-controls [tiab] OR cohort [tiab] OR cohorts [tiab] OR single-blind [tiab] OR double-blind [tiab] OR "cross-sectional studies"[mh] OR cross-sectional [tiab] OR retrospective [tiab] OR followup [tiab] OR non-randomized [tiab] OR pilot study [tiab] OR survey [tiab] OR questionnaire [tiab] OR surveys [tiab] OR questionnaires [tiab] OR case study [tiab] OR laboratory study[tiab]

With time limit: 1/1/2000 - 11/07/2018
No language limit

Based on (validated) existing search strings with irrelevant terms and truncators removed and literature [1–3], reference set, and expert opinion (information specialist and content experts) [4]. Checked with Peer Review of Electronic Search Strategies (PRESS) criteria [5].

This search strategy was validated [4,6] with a set of golden bullets [4]. This selection of golden bullets was made searching the following volumes with the review eligibility criteria by hand: Pediatrics Volume 139 and 140 (2017), Palliative medicine Volume 29 (2015), Journal of Palliative Medicine Volume 18 (2015), Pain and symptom management Volume 47 (2014), Pediatric Blood and Cancer Volume 54 and 55 (2010), Acta Paediatrica Volume 94 (2005).

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Supplemental Information 3. QualSyst Ratings Per Study

Reference	a[a]	b	c	d	e	f	g	h	i	j	k	l	m	n	Total/Amount of points possible(%)
Wolfe et al. (7)	2	2	0	1	2	2	2	0	0	1	2	1	2	2	19/28 (0.68)
Korzeniewska-Eksterowicz et al. (8)	1	2	0	0	NA	NA	NA	2	0	2	0	1	1	0	9/22(0.41)
Schindera et al (9).[b]	2	0	0	2	NA	NA	NA	0	1	1	2	0	1	2	11/22(0.5)
Brook et al. (10)	0	0	1	0	NA	NA	NA	2	0	2	0	0	1	2	8/22(0.36)
Gans et al. (11)	2	1	0	1	NA	NA	NA	1	0	1	2	0	2	1	11/22(0.5)
Madden et al. (12)	2	0	0	1	NA	NA	NA	2	0	1	2	0	2	0	10/22(0.45)
Groh et al. (13)	1	2	0	0	NA	0	NA	0	0	1	1	0	2	0	7/24(0.29)
Vollenbroich et al. (14) [b]	2	0	2	2	NA	NA	NA	0	1	1	2	0	2	2	14/22(0.64)
Kuhlen et al. (15)	2	1	0	1	NA	NA	NA	0	0	2	2	0	2	0	10/22(0.45)
Hoffer et al. (16)	1	2	1	0	NA	0	NA	1	0	1	0	0	2	2	10/24(0.42)
Groh et al. (17)	2	0	2	2	NA	0	NA	1	0	1	2	0	2	2	14/24(0.58)
Chong et al. (18)	2	0	2	2	NA	NA	NA	2	1	2	2	2	2	2	19/22(0.86)
Friedrichsdorf et al. (19)	2	1	1	2	NA	NA	NA	1	1	2	0	1	2	2	15/22(0.68)
Thrane et al. (20) [b]	2	0	0	0	NA	NA	NA	0	0	1	1	0	2	1	7/22(0.32)
Hooke et al. (21)	1	0	1	2	NA	NA	NA	2	0	2	2	0	2	0	12/22(0.55)
Hohl et al. (22)	1	0	2	2	NA	NA	NA	0	0	1	0	0	1	2	9/22(0.41)
Rapoport et al. (23)	1	1	2	1	NA	NA	NA	0	0	1	0	0	2	2	10/22(0.45)
Taylor et al. (24)	2	0	0	2	NA	NA	NA	2	0	2	1	0	2	0	11/22(0.5)
Burns et al. (25) [b]	1	0	1	1	NA	NA	NA	0	0	1	0	0	1	1	6/22(0.27)
Postovsky et al. (26)	1	0	2	0	NA	NA	NA	1	0	1	0	0	2	1	8/22(0.36)

[a] a: Question/objective; b: Study design; c: Method subject/comparison group selection or source of information; d:Subject and comparison group characteristics; e: Interventional and random allocation reported; f: Interventional and blinding of investigators reported; g: Interventional and blinding of subjects reported; h: Well-defined/robust outcome and exposuremeasure(s), Means of assessment reported; i: Sample size; j: Analytic methods; k: Estimate of variance; l:Controlling for confounding; m: Results; n: Conclusion.

[b] Study was judged independently by a second reviewer

Supplemental Information 3. QualSyst Ratings Per Study (Continued).

Reference	a [a]	b	c	d	e	f	g	h	i	j	k	l	m	n	Total/Amount of points possible(%)
Schiessl et al. (27) [b]	2	0	2	2	NA	NA	NA	0	0	1	2	0	1	0	10/22(0.45)
Ullrich et al. (28) [b]	2	1	2	2	NA	NA	NA	0	1	1	2	0	2	1	14/22(0.64)
Urtubia et al. (29)	1	1	2	1	NA	NA	NA	2	2	2	1	0	2	1	15/22(0.68)
Dickens et al. (30) [b]	1	0	0	1	NA	NA	NA	0	1	0	0	0	1	2	6/22(0.27)
Zamora et al. (31)	1	1	2	1	NA	NA	NA	2	2	2	1	1	2	2	17/22(0.77)
Davies et al.(32)	2	0	2	1	NA	0	NA	1	0	2	1	0	2	2	13/24(0.54)
Bosch-Alcaraz et al. (33)	2	0	2	2	NA	NA	NA	0	1	2	2	0	2	2	15/22(0.68)
Varma et al. (34) [b]	1	0	2	2	NA	NA	NA	2	1	1	2	1	2	2	16/22(0.73)
Flerlage et al. (35) [b]	1	0	2	1	NA	NA	NA	2	0	0	2	0	1	0	9/22(0.41)
Anghelescu et al. (36)	1	0	2	2	NA	NA	NA	2	0	2	2	0	2	2	15/22(0.68)
Anghelescu et al. (37)	1	1	2	1	NA	NA	NA	1	0	2	2	0	2	0	12/22(0.55)
Breen (38)	1	1	0	0	NA	0	NA	1	0	1	0	0	1	2	7/24(0.29)
Siden & Nalewajek (39)	1	0	2	1	NA	NA	NA	1	1	2	0	0	1	1	10/22(0.45)
Saad et al. (40)	2	0	0	2	NA	NA	NA	1	1	2	0	0	2	2	12/22(0.55)
Schmidt et al. (41)	2	1	1	1	NA	NA	NA	1	1	2	0	0	2	2	13/22(0.59)
Wolfe et al. (42)	2	1	2	1	NA	NA	NA	2	1	2	2	1	2	2	18/22(0.82)

[a] a: Question/objective; b: Study design; c: Method subject/comparison group selection or source of information; d:Subject and comparison group characteristics; e: Interventional and random allocation reported; f: Interventional and blinding of investigators reported; g: Interventional and blinding of subjects reported; h: Well-defined/robust outcome and exposuremeasure(s), Means of assessment reported; i: Sample size; j: Analytic methods; k: Estimate of variance; l:Controlling for confounding; m: Results; n: Conclusion.

[b] Study was judged independently by a second reviewer.

Supplemental Information 4. GRADE Ratings for Evidence Certainty for Significant Outcomes Per Health Care Intervention.[a] [b]

	Patient-reported symptom monitoring	**Chemo-therapy**	**Hospitalisation**	**Palliative care**	**Pleurodesis**	**Non-invasive mechanical ventilation**	**Dexmedetomidine**	**Stem cell transplant**	**Methadone**
Outcomes[c]	Emotional quality of life	Dyspnea	Dyspnea	QOL Pain Dyspnea Constipation Energy loss Fun Added meaning Communication	Respiratory rate Aeriation	Heart rate Respiratory rate Oxygen saturation	Pain	Constipation Fatigue Diarrhea Number of physical symptoms Number of psychological symptoms Sadness Being afraid	Pain Fatigue Insomnia Dyspnea
Risk of bias	High	High	High	High	High	High	High	High	High
Risk of indirectness	Low	Low	Low	Low	Low	Low	Low	Low	Low
Risk of publication bias	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Inconsistence	High	High	High	High	High	High	High	High	High
Final GRADE rating	Moderate	Very low	Very low	Very low	Very low	Very low	Very low	Very low	Very low

[a] Due to clinical and methodological heterogeneity per health care intervention, assessment of inconsistency and indirectness was not possible.
[b] GRADE ratings were discussed with a second reviewer.
[c] Outcomes were assessed separately for each intervention yet yielded similar GRADE ratings and were therefore listed in the same column.

CHAPTER 2

Face-Validated Quality Indicators for Appropriateness of End-of-Life Care in Children with Serious Illness: A Study Using the RAND/University of California at Los Angeles Appropriateness Method

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ABSTRACT

Objective To develop and face-validate population-level indicators for potential appropriateness of end-of-life care, for children with cancer, neurologic conditions, and genetic/congenital conditions, to be applied to administrative health data containing medication and treatment variables.

Study design Modified RAND/University of California at Los Angeles appropriateness method. We identified potential indicators per illness group through systematic literature review, scoping review, and expert interviews. Three unique expert panels, a cancer (n = 19), neurology (n = 21), and genetic/congenital (n = 17) panel, participated in interviews and rated indicators in individual ratings, group discussions, and second individual ratings. Each indicator was rated on a scale from 1 to 9 for suitability. Consensus was calculated with the interpercentile range adjusted for symmetry formula. Indicators with consensus about unsuitability were removed, those with consensus about suitability were retained, and those with lack of consensus deliberated in the group discussion. Experts included pediatricians, nurses, psychologists, physiotherapists, pharmacologists, care coordinators, general practitioners, social workers from hospitals, care teams, and general practice.

Results Literature review and expert interviews yielded 115 potential indicators for cancer, 111 for neurologic conditions, and 99 for genetic/congenital conditions. We combined similar indicators, resulting in respectively 36, 32, and 33 indicators per group. Expert scoring approved 21 indicators for cancer, 24 for neurologic conditions, and 23 for genetic/congenital conditions.

Conclusions Our indicators can be applied to administrative data to evaluate appropriateness of children's end-of-life care. Differences from adults' indicators stress the specificity of children's end-of-life care. Individual care and remaining aspects, such as family support, can be evaluated with complementary tools.

INTRODUCTION

Children with life-limiting conditions are reported to receive low-quality care at the end of life. Issues include symptom control (1), medical system access and quality (1), care at the time of death (2), continuity of care (3), and pediatric hospice program development (3), as identified by cohort studies surveying bereaved parents. Quality measures to evaluate children's end-of-life care have been requested regularly over the past 2 decades (4-6).

Quality indicators are regularly used to measure quality of care systems (7-11). With quality indicators, measurement can also be done on government-collected administrative health data, which avoids costly and labor-intensive data collections and provides reliable data on a population level (7-9), and is gathered routinely in many countries due to health insurance obligations.[7] Quality indicators are frequently used in adult literature yet lacking in children (4-7).

Appropriateness of care can be evaluated using medication, treatment and other variables from such health care administrative databases. Appropriate care then indicates that the overall “expected health benefit” of given health care interventions within a health care system exceeds the expected negative outcomes of the given health care interventions (7, 11-14). Potentially appropriate or inappropriate care is used as a preferred term given the difficulty to draw definitive conclusions about appropriateness.

In children, most deaths from serious illness result from cancer, neurological conditions, and genetic and congenital conditions (15-20). While there may be similarities across the three illness groups, they differ substantially in terms of care trajectories, treatments and medication being prescribed (15-19), and therefore also in what can be considered appropriate or inappropriate care at the end of life. This implied that, from the outset, three different quality indicator sets, validated by different experts, were aimed for. Therefore, the objective of the study was to develop and face-validate population-level indicators for potential appropriateness of end-of-life care, for children with cancer, neurological conditions, and genetic/congenital conditions, to be applied to administrative health data containing medication and treatment variables.

METHODS

Design

We used a modified (7) RAND/UCLA appropriateness method (22). This consensus method was developed because the best scientific evidence about the benefits of treatments or medications within a specific population is often lacking. The method combines the best available scientific evidence (e.g. from literature review) with the collective judgment of purposely selected experts to produce informed evaluations regarding appropriateness. Indicators are scored and discussed in two rounds by expert and accepted if there is sufficient

consensus about suitability.

Definitions and Criteria

Quality indicators. We defined quality indicators as “explicitly defined measurable items referring to the outcomes, processes, or structure of care [that] can indicate either poor or good quality in relevant care domains" (7,9,23-24). An indicator had to be measurable with Belgian available administrative data. It had to express a ratio level of potentially appropriate or inappropriate care, i.e. a percentage that can increase or decrease on a population level. Furthermore, the concept measured with an indicator had to be applicable to the majority of the full population of children of the illness group. E.g., adequate nausea management after chemotherapy is not relevant for most children with genetic and congenital conditions on a population level. Relatedly, the measured treatment, medication or administrative act had to occur or had to be estimated to occur in 5 to 95% of the children in the illness group.

Appropriate care. We defined appropriate care as treatment and/or medication in which “the expected health benefit” for quality of life of the child (e.g. pain or anxiety relief, improved family bonding) “exceeds the expected negative consequences” for quality of life of the child (e.g. morbidity, dyspnea, school time lost) “by a sufficiently wide margin that the procedure is worth doing, exclusive of cost” (7,11-14). Inappropriate care was defined as the inverse.

Illness groups. We defined cancer as all malignant and benign tumors that could cause the death of a child from one to 17 years old within the current medical context. We defined neurological conditions as brain and spinal cord malformations, intellectual disability, central nervous system degeneration and diseases, infantile cerebral palsy, epilepsy, other conditions of the central nervous system, occlusion of cerebral arteries, muscular dystrophies and myopathies, and movement diseases (25) that could cause the death of a child from one to 17 years old within the modern medical context. We defined genetic and congenital conditions as cardiovascular, respiratory, renal, urologic, gastro-intestinal, hematological, immunological, and metabolic conditions, and other conditions such as chromosomal anomalies and bone and joint anomalies, and other congenital anomalies (25) that could cause the death of a child from 1 to 17 years old within the modern medical context.

Study and Data Collection Procedures

Step 1: Literature search. We performed a systematic review and scoping review to respectively identify health care interventions associated with increasing or decreasing quality of life in children at the end of life and previously suggested similar indicators (26). The systematic literature review was published previously (26). See Appendix 1 online for additional information on the literature search.

Step 2: Interviews with relevant experts. We conducted interviews to identify additional potential indicators. We conducted interviews between September 2019 and November 2019 with 36 unique experts. See Table 1 for details on the type of experts and inclusion criteria, and Table 2 online for topic guide questions. Experts were asked to suggest potential indicators, including a numerator, denominator, possible exclusion criteria, and reasoning as to why the indicators should be included. One author extracted indicators from all interviews; students extracted indicators to validate the extraction. Extracted indicators were sent to the experts individually via mail for verification and adjusted for comments.

Step 3: Expert evaluation of potential quality indicator sets We used the literature search and interviews as a base to construct the indicator sets and create a list of all potential indicators per illness group. From these lists, the authors selected all indicators that met the pre-determined criteria. We combined similar indicators and adjusted adult indicators to fit the context of children's care. See Appendix 2 online for the rationale and evidence base per indicator. Three sets of potential quality indicators were made: One for children with cancer, one for children with neurological conditions, and one for children with genetic and congenital conditions.

We presented the quality indicator sets to three expert panels - one for each illness group. The expert rating per panel consisted of an individual rating of indicators through an electronic survey, and a group discussion and re-rating of indicators in a collective online expert discussion. Every participating expert was sent a survey with the quality indicator set of the selected patient population. We asked experts to score the quality indicators on a scale of 1–9, where '1' means this indicator is very unsuitable and '9' means this indicator is very suitable to evaluate potential appropriateness or inappropriateness of end-of-life care in children (10,22). See Appendix 3 online for an overview of all questions per indicator. We calculated the ratings and summarized the comments. The calculations were done with the Interpercentile Range Adjusted for Symmetry formula (See Table 3 online). The indicator was either accepted (experts agreed), rejected (expert agreed about withdrawal), or undecided and needed to be discussed in an expert discussion (no expert agreement). We held an online expert discussion for each illness group in late 2020. After discussion, experts voted for the indicator to be rejected, adapted and taken into the final set, or taken into the final set without adaptations, with option to withhold. The decision that received a majority of the votes decided on the outcome. See Appendix 4-6 online for an overview of ratings and reasons for refusal and acceptance.

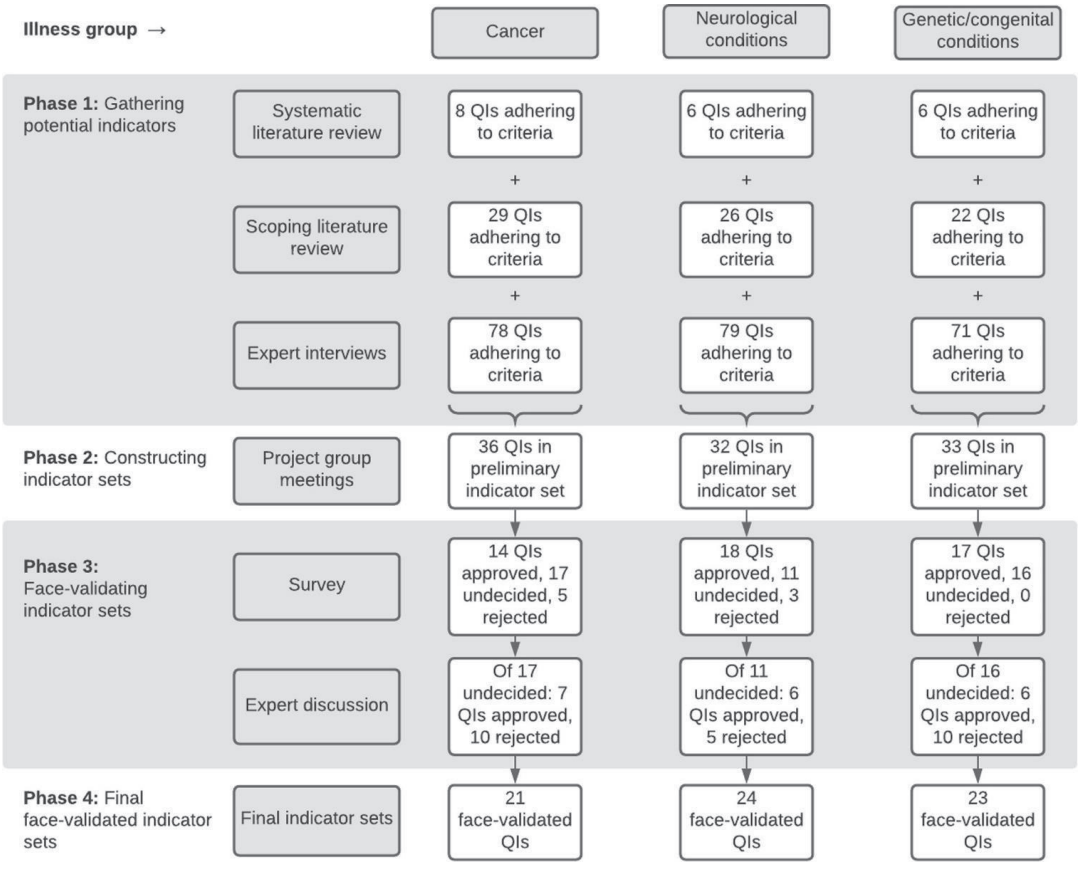
Ethical approval

The study was approved by the Medical Ethics Committee of the University Hospital Brussels, Belgium as the Central commission (reference no. B.U.N. 143201949420).

RESULTS

Figure 1 displays an overview of indicators resulting from each step throughout the development and validation process.

Figure 1: Overview of The Quality Indicator Development Process



We identified 115 potential indicators for cancer, 111 for neurological conditions, and 99 for genetic/congenital conditions through systematic literature review, scoping review and expert interviews. Two thirds of the potential indicators were identified through the expert interviews,

one third resulted from literature review (See Figure 1, Phase 1).

In order to construct the candidate indicator set for expert scoring and evaluation, we combined overlapping and redundant indicators. This resulted in a preliminary indicator set of 36 indicators for cancer, 32 indicators for neurological conditions, and 33 indicators for genetic/congenital conditions (See Figure 1, Phase 2).

Experts then rated the preliminary indicator sets through an electronic survey, group discussion and second rating (one per illness group; three electronic surveys, three group discussions, and three second ratings in total). In the electronic survey, there was agreement between experts to immediately accept roughly half of all indicators for each illness group. There was agreement between experts to immediately reject a small portion of the indicators. The remaining indicators did not immediately reach expert agreement for acceptation or rejection and were therefore taken to the group discussion and the second rating (See Figure 1, Phase 3 - Survey).

In the group discussions, 17 indicators for cancer, 11 for neurological conditions, and 16 for genetic/congenital conditions were discussed and rated again. There was agreement for some indicators to be accepted ultimately, sometimes with adjustments (Appendix 4-6 online). The indicators for which there was agreement to reject or no agreement in the second rating, were all deleted from the sets (See Figure 1, Phase 3 – Expert Discussion).

Indicators were categorized as: 1. Treatment, medication and monitoring, 2. Place of care and death, 3. Care services and providers, and 4. Administrative measures.

Appendix 7: Final Set of 21 Face-Validated Quality Indicators for Children with Cancer

Indicator	Numerator (number of children that died of cancer in which*)	Denominator (*number of children that died of cancer)	Time period before death (in days before death)
	Appropriate care		
Treatment, medication, and monitoring*			
Physiotherapy***	*physiotherapy was prescribed in the last 30,14, 7, or 2 days before death	*	30, 14, 7, 2
(Off-label) Comfort medication***	*there were prescriptions for hyoscine butylbromide, dexmedetomidine, fentanyl, gabapentin, ketamine, ketorolac, lidocaine, midazolam, ondansetron, or scopolamine inthe last 30, 14, 7, or 2 days before death	*	30, 14, 7, 2
Pain control according to World Health Organization steps***	*there were prescriptions from the third World Health Organization step, i.e. morphine, fentanyl, methadone, oxycodone, or hydromorphone, and these were preceded, inthe last 2 years before death, by prescriptionsfrom the first World Health Organization step, i.e. paracetamol, non-steroidal anti-inflammatory drugs or aspirin, and from the second World Health Organization step, i.e. codeine, tramadol, or buprenorphine	*with prescriptions fromthe third World Health Organization step, i.e. morphine, fentanyl, methadone, oxycodone, or hydromorphone in the last 3 months before death	730/ 90
Place of care and death*			
Home death	*there was a home[a] death	*	Not applicable
Follow-up by hospital***	*there was at least 1 consultation in a hospital[b], or with a specialist physician[c] fromthe start of the palliative status onwards	*	from the start of the official palliative status onwards
Care services and providers*			
Contact with general	*there were at least 3 house visits of, prescriptions of, or consultations with a general	*	30

physician***	physician in the last 30 days before death		
Continuous care relationships***	*there was at least 1 prescription, visit, consultation, or treatment from the same[a] physician (general or specialist[b]) in the last 30days before death, as in the last year before death	*	30
Professional care provision***	*there were more than 2 prescriptions, home visits, treatments, consultations of physiciansor paramedics, or a visit to a care institute in the last 30 or 14 days before death	*	30, 14
Palliative home care team***	*there was at least 1 visit of a mobile palliativehome care team[c] within the last 2 years beforedeath	*	730
Multidisciplinary oncological consult	*at least 1 multidisciplinary oncological consultwas done for the child in the last 30 days before death	*	30
Multidisciplinarityof care***	*there was a total of 5 or more prescriptions, treatments, visits, or advices, from 2 or more ofthe following care providers: general physicians, pediatricians, specialist physicians[a] or paramedics[b] in the last 30 days before death	*	30
Administrative measures*			
Palliative status***	* who received a palliative status (i.e. a supportive financial measure to facilitate palliative home care)	*	720
	Inappropriate care		
Treatment, medication, and monitoring*			
Diagnostics and monitoring***	*received 2 or more X-rays, magnetic resonance imaging scans, or Computed Tomography scans in the last 30, 14, 7, or 2 days before death		30, 14, 7, 2
Excessive magnetic resonance imaging monitoring***	*received more than 1 magnetic resonance imaging scan in the last 30, 14, 7, or 2 days before death	*	30, 14, 7, 2
Gastrostomy placement	*a gastrostomy was placed in the last 30, 14,7, or 2 days before death	*	30, 14, 7, 2
Starting dialysis***	* dialysis was started in the last 14, 7, or 2 days before death or from receiving palliativestatus onwards	*	14, 7, 2 or from receiving palliative status onwards
Installing port-a-caths	*a port-a-cath was installed in the last 14, 7, or 2 days before death	*	14, 7, 2
Surgeries***	*a surgery was performed in the last 14, 7, or 2days before death	*	14, 7, 2
Drawing blood***	*there was at least 1 blood drawing in the last7 or 2 days before death	*	7, 2

Place of care and death			
Hospital transfers	*there were 1 or more hospital tranfers[b] in thelast 30, 14, 7, or 2 days before death	*	30, 14, 7, 2
Emergency Room visits	*there was at least 1 Emergency Room visit inthe last 14, 7, or 2 days before death	*	14, 7, 2

[a] Long term palliative care trajectory is defined as: receiving palliative status or visits from a home care team, no sepsis primary cause of death, no transplant or stem cell transplant in the day before death; [b] Hospital transfer is defined as: there is a treatment from another hospital with another unique hospital code number than was previously recorded; ** Categories were defined after development of the indicators; *** Indicator that occurs for all three illness groups

Appendix 8: Final Set of 24 Face-Validated Quality Indicators for Children with Neurological Conditions

Indicator (short title)	Numerator (number of children that died of neurological conditions in which*)	Denominator (*number of children that died of neurological conditions)	Time period before death (in days before death)
	Appropriate care		
Treatment, medication, and monitoring*			
Physiotherapy***	*physiotherapy was given in the last 30 before death	*	30
(Off-label) Comfort medication***	*there were prescriptions for hyoscine butylbromide, dexmedetomidine, fentanyl, gabapentin, ketamine, ketorolac, lidocaine, midazolam, ondansetron, or scopolamine in the last 30, 14, 7, or 2 days before death	*	30, 14, 7, 2
Pain control according to World Health Organization steps***	*there were prescriptions from the third World Health Organization step, i.e. morphine, fentanyl, methadone, oxycodone, or hydromorphone, and these were preceded, in the last 2 years before death, by prescriptions from the first World Health Organization step, i.e. paracetamol, non-steroidal anti- inflammatory drugs or aspirin, and from the second World Health Organization step, i.e. codeine, tramadol, or buprenorphine	*with prescriptions from the third World Health Organization step, i.e. morphine, fentanyl, methadone, oxycodone, or hydromorphone in the last 3 months before death	730/ 90
Place of care and death*			
Follow-up by hospital***	*there was at least 1 consultationin a hospital[a], or with a specialist physician[b] from the start of the palliative status onwards	*	from the start of the palliative status onwards*
Care services and providers*			
Contact with general physician***	*there were at least 3 house visitsof, prescriptions of, or consultations with a general physician in the last 30 days before death	*	30
Continuous care relationships***	*there was at least 1 prescription, visit, consultation, or treatment from the same[c] physician	*	30

	(general or specialist[d]) in the last 30 days before death, as in the last year before death		
Professional care provision***	*there were more than 2 prescriptions, house visits, treatments, consultations of physicians or paramedics, or a visit to a care institute in the last 30 or 14 days before death	*	30, 14
Palliative home care team***	*there was at least 1 visit of a palliative home care team[e] within the last 2 years before death	*	730
Care services and providers*			
Multidisciplinarity of care***	*there was a total of 5 or more prescriptions, treatments, visits, or advices, from 2 or more of the following care providers: general physicians, pediatricians, specialist physicians[b] or paramedics[f] in the last 30 days before death	*	30
Involvement of specialist physicians	*there was at least 1 prescription, visit of or consultation with at least 1 specialist physician [a] in the last 30 days before death		30
Administrative measures*			
Palliative status***	* who received a palliative status	*	720
Increased child benefits	* there were increased child benefits assigned to the family within 2 years before death	*	720
Reimbursed prescriptions	*ondansetron 8mg was prescribed within 2 years beforedeath	* and that received prescriptions of ondansetron within 2 years before death	Within 2 year before death
	Inappropriate care		
Treatment, medication, and monitoring*			
Excessive monitoring***	*received 2 or more X-rays, magnetic resonance imaging scans, or Computed Tomographyscans per day in the last 30, 14, 7, or 2 days before death	*	30, 14, 7, 2
Diagnostics and monitoring***	*received 2 or more X-rays, magnetic resonance imaging scans, or Computed Tomography scans in the last 30, 14, 7, or 2 days before death	*	30, 14, 7, 2
Starting dialysis***	* dialysis was started in the last 30, 14, 7, or 2 days before deathor from receiving palliative status onwards	*	30, 14, 7, 2
Old-generation prescriptions nausea	*domperidone or metoclopramide was prescribed in the last 30, 14,or 7 days before death	*with prescriptions for nausea-treating medication	30, 14, 7, 2
Surgeries***	*a surgery was performed in the	*	2

	last 2 days before death		
New antidepressant	*at least 1 new antidepressant was started in the last 14 days before death	*	14
Late palliative care provision	*there was a first registration of a palliative home care team[e] or palliative status within the last 14 or 7 days before death	*	14, 7
Treatment, medication, and monitoring*			
Drawing blood***	*there was at least 1 blood drawing in the last 7 or 2 days before death	*	7, 2
Place of care and death*			
Pediatric Intensive Care Unit admissions	*there were 1 or more hospital admissions at the Pediatric Intensive Care Unit in the last 14,7, or 2 days before death	*	14, 7, 2
Care setting transfers	*there were 4 or more different care settings (home[g], hospital[a] or other setting[h]) in the last 30, 14, 7 or 2 days before death	*	30, 14, 7, 2
Transfers from medical-pedagogical institute to intensive care	* there were 1 or more transfers from a medical-pedagogical institute to an intensive care wardin the last 7 or 2 days before death	*and resides in a medical-pedagogical institute	7, 2

[a]Hospital is defined as: code number with the category hospital as defined within the obtained mutuality data; [b]Specialist physicians are defined as: all specialist physicians that have a qualification to provide prescriptions as defined within the obtained mutuality data, excluding the specialist physician for geriatrics;[c]The same is defined as: having the same unique code number as defined within the obtained mutuality data; [d]Specialist physicians are defined as: all specialist physicians that have a qualification to provide prescriptions as defined within the obtained mutuality data, excluding the specialist physician for geriatrics;[e]Palliative home care team is defined as: all database codes that point to a Palliative home care team as defined within the obtained data; [f]Paramedics are defined as: physiotherapist, dietician, speech therapist, occupational therapist, bandagist, optician, hearing prosthetist, clinical biologist, nursing staff, home care nurses, psychologists; [g]Home is defined as: remaining category, there are no data that indicates a hospitalstay or other care setting as defined within the obtained data; [h]Other care setting is defined as: a code number or a pseudocode that indicates stay in a (medical-pedagogical) institute other than the hospital;**Categories were defined after development of the indicators; *** Indicator that occurs for all threeillness groups

Appendix 9: Final Set of 23 Face-Validated Quality Indicators for Children with Genetic and Congenital Conditions

Indicator (short title)	Numerator (number of children that died of genetic or congenital conditions in which*)	Denominator (*numberof children that died of genetic or congenital conditions)	Time period before death (in days before death)
	Appropriate care		
Treatment, medication, and monitoring*			
Physiotherapy***	*physiotherapy was given in the last 30, 14, 7, or 2 days before death	*	30, 14, 7, 2
(Off-label) Comfort medication***	*there were prescriptions for hyoscine butylbromide, dexmedetomidine, fentanyl, gabapentin, ketamine, ketorolac, lidocaine, midazolam, ondansetron, or scopolamine in the last 30, 14, 7, or 2 days before death	*	30, 14, 7, 2
Pain control according to World Health Organization steps***	*there were prescriptions from the third World Health Organization step, i.e. morphine, fentanyl, methadone, oxycodone, or hydromorphone, and these were preceded, in the last 2 years before death, by prescriptions from the first World Health Organization step, i.e. paracetamol, non-steroidal anti- inflammatory drugs or aspirin, and from the second World Health Organization step, i.e. codeine, tramadol, or buprenorphine	*with prescriptions from the third World Health Organization step, i.e. morphine, fentanyl, methadone, oxycodone, or hydromorphone in the last 3 months before death	730/ 90
Continuing anti-epileptic medication	*there was at least 1 prescriptionof an anti-epileptic medication[a] in the last 30 days before death	*and in the last 3 months before death received at least 2 prescriptions for anti-epileptic medication	30
Place of care and death*			
Follow-up by hospital***	*there was at least 1 consultationin a hospital[b], or with a specialist physician[c] from the start of the palliative status onwards	*	from the start of the palliative status onwards*
Care services and providers*			
Contact with general physician***	*there were at least 3 house visitsof, prescriptions of, or consultations with a general physician in the last 30 days before death	*	30
Continuous care relationships***	*there was at least 1 prescription, visit, consultation, or treatment from the same[d] physician	*	30

	(general or specialist[c]) in the last 30 days before death, as in the last year before death		
Professional care provision***	*there were more than 2 prescriptions, house visits, treatments, consultations of physicians or paramedics, or a visit to a care institute in the last 30 or 14 days before death	*	30, 14
Palliative home care team***	*there was at least 1 visit of a palliative home care team[e] within the last 2 years before death	*	730
Care services and providers*			
Multidisciplinarity of care***	*there was a total of 5 or more prescriptions, treatments, visits, or advices, from 2 or more of the following care providers: general physicians, pediatricians, specialist physicians[b] or paramedics[f] in the last 30 days before death	*	30
Administrative measures*			
Palliative status***	* who received a palliative status	*	720
	Inappropriate care		
Treatment, medication, and monitoring*			
Diagnostics and monitoring***	*received 2 or more X-rays, magnetic resonance imaging scans, or CT scans in the last 30, 14, 7, or 2 days before death		30, 14, 7, 2
Excessive magnetic resonance imaging monitoring***	*received 1 or more magnetic resonance imaging scans in the last 30, 14, 7, or 2 days before death	*	30, 14, 7, 2
Starting dialysis***	* dialysis was started in the last14, 7, or 2 days before death orfrom receiving palliative status onwards	*	30, 14, 7, 2
Treatment, medication, and monitoring*			
Surgeries***	*a surgery was performed in the last 2 days before death	*	2
Late palliative care provision	*there was a first registration of a palliative home care team[e] or palliative status within the last 14or 7 days before death	*	14, 7
New placement central venous catheter	*there was placement of a central venous catheter in the last 7 or 2 days before death	*	7, 2
Drawing blood***	*there was at least 1 blood drawing in the last 7 or 2 days before death	*	7, 2
Place of care and death*			
Hospital transfers	*there were 1 or more hospital tranfers[g] in the last 30, 14, 7, or 2 days before death	*	30, 14, 7, 2

Care setting transfers	*there were 4 or more different care settings (home[h], hospital[b] or other setting[i]) in the last 30, 14, 7, or 2 days before death	*	30, 14, 7, 2
Transfers from medical-pedagogical institute to intensive care	* there were 1 or more transfers from a medical-pedagogical institute to an intensive care wardin the last 7 or 2 days before death	*and resides in a medical-pedagogical institute	7, 2
Care services and providers			
Care stop after receiving palliative status	*there were less than 3 prescriptions of, visits of, or consultations with a general physician or a specialist physicianor a visit to a care institute from the start of the palliative status onwards	*	from the start of the palliative status onwards
Involvement of specialist physicians	*there was at least 1 prescription, visit of or consultation with at least 1 specialist physician in the last 30 days before death		30

[a]brivaracetam, carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, primidone, rufinamide, stiripentol, sulthiame, topiramate, valproate natrium, vigabatrin or zonisamide; [b]Hospital is defined as: codenumber with the category hospital as defined within the obtained mutuality data; [c]Specialist physicians are defined as: all specialist physicians that have a qualification to provide prescriptions as defined within the obtained mutuality data, excluding the specialist physician for geriatrics; [d]The same is defined as: having the same unique code number as defined within the obtained mutuality data; [e]Palliative home care team isdefined as: all database codes that point to a Palliative home care team as defined within the obtained data;[f]Paramedics are defined as: physiotherapist, dietician, speech therapist, occupational therapist, bandagist, optician, hearing prosthetist, clinical biologist, nursing staff, home care nurses, psychologists; [g] Hospital transfer is defined as: there is a treatment from another hospital with another unique hospital code number than was previously recorded; [h]Home is defined as: remaining category, there are no data that indicates a hospital stay or other care setting as defined within the obtained data; [i]Other care setting is defined as: a code number or a pseudocode that indicates stay in a (medical-pedagogical) institute other than the hospital; **Categories were defined after development of the indicators; *** Indicator that occurs for all three illness groups

Experts accepted 21 quality indicators for cancer (See Appendix 7 online), 24 quality indicators for neurological conditions (See Appendix 8 online), and 23 quality indicators for genetic and congenital conditions (See Appendix 9 online). There are 15 quality indicators that are equal for all 3 illness groups (See indicators indicated with *** in Appendix 7-9 online).

In total, 19 experts participated in the interviews and expert ratings for the cancer population, 21 experts for the neurology population, and 17 experts for the genetic and congenital population (See Table 1).

Table 1: Experts Included in Panels per Phase[a,b]

Profession	Illness group		
	Cancer	**Neurological conditions**	**Genetic and congenital conditions**
Interviews			
Pediatricians (nr.)	5	7	3
Pediatric hospital, home, or liaison nurse (nr.)	6	9	8
Other (psychologist, physiotherapist, pharmacologist, care coordinator, general practitioner, social worker) (nr.)	8	5	3
Total (nr.)	19	21	14
Survey			
Pediatricians (nr.)	5	6	4*
Pediatric hospital, home, or liaison nurse (nr.)	4	9	6
Other (psychologist, physiotherapist, pharmacologist, care coordinator, social worker) (nr.)	6	4	2
Total (nr.)	15	19	12
Group discussion			
Pediatricians (nr.)	3	5	3*
Pediatric hospital, home, or liaison nurse (nr.)	3	4	4
Other (psychologist, physiotherapist, pharmacologist, care coordinator, social worker) (nr.)	4	3	2*
Total (nr.)	10	12	9

*Additional experts were added in this phase to the indicated category within this illness group, compared to the previous phase (total of 3 additional experts)

[a] Some experts participated in panels for multiple illness groups; [b] All experts were required to work in Belgium,have at least 1 year of experience in caring for children at the end of life (excluding residency training), and tospeak and write Dutch or English.

DISCUSSION

We developed 3 sets of quality indicators for measurement of appropriateness of end-of-life care at a population level for children with cancer, neurological conditions, and genetic and congenital conditions. Consensus was reached in multidisciplinary pediatric expert panels on 21 quality indicators for cancer, 24 quality indicators for neurological conditions, and 23 quality indicators for genetic and congenital conditions; 15 indicators were communal for all 3illness groups. Indicators surfaced in four domains; 1) Treatments, medication and monitoring, 2) Place of care and death, 3) Use of services and providers, 4) Administrative measures and benefits received.

We used a stringent method to develop the quality indicators: The RAND/UCLA appropriateness method. Multiple methodologies ensured triangulation, individual and collective rounds counter bias, and a validated consensus formula was used. Starting from a systematic review (26) was a strength as it resulted in an initial selection of indicators with an evidence base for their impact on quality of life. The round of expert interviews was a strength for the identification of quality indicators in a domain where there is little previous research. The involvement of a relatively large panel of pediatric health care professionals, highly experienced in pediatric end-of-life care from various settings (hospital, home care, general practice), from various professions, and different regions within Flanders and Brussels, increases the validity of the consensus-based selection. Our focus on measurability with routinely collected administrative data made for limitations in the type of quality indicators that could be selected; Aspects such as psychosocial outcomes or treatment intention could not be included in the sets. We did not include children and families during the quality indicator development: Multi-case medical and administrative knowledge was indispensable to evaluate the population quality indicators.

Our results align with previous qualitative studies and opinion pieces that identified important themes to be included in quality indicators for children's end-of-care (27,28). In our study, home death was approved as a quality indicator for children with cancer, confirming the careful preference for home death expressed by bereaved parents in a previous qualitative study (27). Continuation of care, mentioned in the same qualitative study, is also reflected prominently in our indicators 'continuous care relationships', 'contact with general physician', and 'palliative home care teams'. The notion of families feeling "abandoned by (the) medical team [at the end of life]" (27), surfaced regularly in our study as well; the importance of avoiding medical abandonment is reflected in our indicators 'follow-up by hospital', and 'professional care provision'. The importance of policies and programs that allow families to spend as much time

as possible with their child (26) was reflected in our indicators 'palliative status', 'increased child benefits', and 'reimbursed prescriptions'. Our study seems to confirm the notion that "although rates of Intensive Care Unit admission, intubation, cardiopulmonary resuscitation, and hemodialysis at the end of life may be important to evaluate with quality measures, antineoplastic therapy may not be" (27); the indicator 'chemotherapy' was immediately rejected as an indication of potentially inappropriate care by cancer experts, while 'Pediatric Intensive Care Unit admissions' and 'starting dialysis' were approved. Our set of indicators for the cancer illness group can be compared with another set of recently published quality indicators for children with cancer at the end of life (29). Many similar indicators arose: dying at home, emergency room visits, chemotherapy, dialysis, palliative care involvement, and indicators referencing financial help. In both studies, experts rejected the use of the indicator of chemotherapy, despite the indicator being used often in current population studies to evaluate children's end-of-life care. In both panels, experts agreed that palliative care involvement, receiving financial support and emergency room visits were important indicators. In our study, however, dialysis and home death were accepted as an indicator, whereas they were rejected in Johnston et al. A published commentary on the indicator development by Johnston et al. also encouraged the use of an indicator for home death.[31] Johnston and other previous studies have pleaded for the indicator 'death at the location of preference' rather than 'home death' (28). The latter indicator also came up in our expert interviews but was not eligible for inclusion as patient preferences are not routinely collected in administrative data registries. Indicators referring to care providers, continuity of and multidisciplinary care, and specific treatments such as physiotherapy, magnetic resonance imaging scans, gastrostomy, surgery, and blood drawing did not surface in Johnston et al., while our set did not include indicators related to intubation, intensive care unit death, preference of place of death, and bereavement programs and sibling care as stated in Johnston. Difference in the sets may be due to the differing focus of quality of life (entire family versus quality of life of child), differing focus of measurement (undefined versus health care data), or region (US versus Belgium).

Fifteen final indicators were common for all 3 illness groups. Comfort treatments and care relationships seem central to potential appropriateness for all three groups, as illustrated by the common indicators '(off-label) comfort medication' and 'contact with a general physician'. Common indicators of potentially inappropriate care were 'diagnostics and monitoring', 'starting dialysis', 'blood drawing', and 'surgeries'. These curative treatments were all deemed generally inappropriate to apply in children with a known terminal trajectory at the end of life. Cancer indicators seem to differ most from the other 2 illness groups. Some differing indicators, such as 'home death', 'gastrostomy placement', and 'emergency room visits', reflect the

increasing emphasis on home treatments and palliative support in children known to be dying with cancer (26). Indicators for children with neurological and genetic/congenital conditions emphasize specialized care even more than the other illness groups, e.g. including the indicator 'involvement of specialist physicians', which could stem from the multi-modal symptomatology (31,32). A need for specialized support in children with neurological and genetic/congenital conditions is indeed reported in previous studies (33-39). Our indicators differ from previously constructed adult end-of-life care indicators.[7] Indicators' time periods in adults are longer than in children, as death in a child often only becomes apparent in the last weeks or days (11). Indicators for adults also centered more around inappropriate and aggressive care (7). Our pediatric-specific indicators seem to focus more oncontinuity of care, multidisciplinary care, and sustained provision of care by trusted health careproviders. The differences reinforce our assumptions about why quality indicator sets specifically for children's end-of-life care are needed.

A number of recommendations for research and policy can be made based on our developed set of quality indicators. It should be kept in mind that indicators can only provide indications, and no definitive conclusions about the quality of care. Indicators should be a starting point for further comprehensive analysis of the quality of end-of-life care and not be used as performance standards (7). We would argue against using indicators as a reward-and-punish system or definitive benchmarks (7). To optimize attributional validity, taking into account children-specific risk adjustments is advised (38). Other important topics, such as symptom monitoring, training of medical staff, and family and sibling care are best assessed additionally. To move from knowing to improving care, responsible authorities could integrate the quality indicators within learning and improvement strategies.

Future research can apply the indicators to measure potential appropriateness of children's end-of-life care in population-level data registries. Results of potential inappropriateness are best complemented with qualitative data in order to uncover underlying rationales of families, children, and staff.

In conclusion, the 3 sets of quality indicators we developed provide a basis to evaluate the quality end-of-life care in children with serious illness using available administrative health claims data.

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Appendix 10: Online Only, Potential Indicators Not Used for Construction of the Indicator Sets [a]

Category [b]	Suggested indicator: Proportion of children*
	1. Systematic literature review
Appropriate care	*in which the parents received 24/7 practical support
	*that received breathing therapy
	2. Scoping review
Appropriate care	* who received each type of opioid (morphine, fentanyl, methadone, hydromorphone, oxycodone, codeine, and tramadol) in last 72 hours of life
	* who received each type of nonopioid analgesic/adjuvant (nonsteroidal anti-inflammatory drugs, ketamine, dexmedetomidine) in last 72 hours of life
	* with increased medication use in last 72 hours of life
	* who received opioids in last 48 hours of life
	* who received opioids in last four days of life
	* who received opioids in last month of life
	* who received benzodiazepines in last four days of life
	* who received benzodiazepines in last month of life
	* that received morphine in combination with neuropathic medication
	* that died at home or in a medical-pedagogical institute
Inappropriate care	* that received blood transfusions in the last month before death
	* in which there was a reanimation 2 weeks before death
	* in which there was treatment from a neurologist in the last month before death
	* in which statins were given and not decreased in the last 12, 6, 1 month before death
	* in which stomach protection was given in the last 6 months before death
	* in which calcium or vitamin D was provided in the last 6, 3, 1 months before death
	* in which novel anticoagulants or vitamin K antagonists were given in the last 3 months before death
	* in which selective serotonin reuptake inhibitors were prescribed in the last 3 months before death
	* who died in hospital vs other
	* who died in hospital vs home
	* who died in Neonatal Intensive Care Unit/Pediatric Intensive Care Unit vs. general unit vs. Emergency Department
	* who died in Pediatric Intensive Care Unit vs. general ward
	* who died in Neonatal Intensive Care Unit/Pediatric Intensive Care Unit vs. general unit vs. home
	* who died in Pediatric Intensive Care Unit vs. other location
	* who received a neuromuscular blocker in last hours of life
	* who received a neuromuscular blocker in last 48 hours of life
	3. Expert interviews

Monitoring	
Appropriate care	* that was monitored for quality of life * in which palliative sedation was registered in most children * that received pain measurements at home * that was monitored via heart monitoring, neuro-imaging, … in the last days before death * in which it was systematically noted that there was play therapy provided
Palliative care (education)	
Appropriate care	* in which palliative care was started from diagnosis onwards * in which the care professionals at the ward followed a course on pediatric palliative care * in which the ward has a physician or nurse who is specialized in palliative care
Inappropriate care	* in which no guidelines for general physicians were present for symptoms * that received palliative care from a palliative team for adults
General care/symptom control	
Appropriate care	* for who dyspnea was controlled * in which non-medicinal pain control was applied * in which life-lengthening care was provided at the intensive care unit in which there was an acute situation * in which a large variety of medication was found over all children * in which a second opinion was sought * that is free of symptoms * that was free of pain * in which diarrhea was treated * in which multiple aspects of care were inspected * in which medical procedures were aimed at comfort, not life-prolonging in the last days before death * in which pain medication was given for families with an immigrant background * in which a diagnosis was determined * in which additional guidance was provided via services such as the neuromuscular reference center or a rehabilitation center
Inappropriate care	* in which no pain control was given * in which the same exact medication and treatment protocol was repeatedly applied * in which children had to wait very long for symptom control * in which guidelines for medication within pediatric palliative care (Dutch guidelines) were not followed * that was suffering from stuffiness or was oxygen dependent * in which children were in the same position the entire day * in which there was no increase of home care, mobile teams, general physicians, physiotherapy, home care nurses, with a decrease of hospital visits * in which curative treatments were done while there was no communication from the child anymore * in which invasive treatments were given to children with acute events * in which other care was given than was decided with the Do Not Resuscitate policy
Psychological support/state	
Appropriate care	*with parents for who psychotherapy was provided

	* in which a different psychologist was used for parents and adolescents
	* in which psychological support is organized in a systematic manner, also within home care
	* in which younger children received more play therapy, and adolescents more talk therapy
	* in which a psychologist was involved if the child ended up on intensive care
	* in which a child psychiatrist was involved
	* in which existential fears are countered
	* in which action is undertaken if the child is not calm anymore
	* in which a pedagogical and psychological staff member gave play therapy
	* in which a psychologist was involved
	* in which psychotherapy was provided to some parents
Inappropriate care	* who are afraid to go to the hospital
	* that was restless
	* in which psychological support was not organized in a systematical manner, also within home care
	* in which no play therapy was given
<u>Specific treatments/medication</u>	
Appropriate care	* in which sufficient variation in treatment was present
	* in which antibiotics were provided when suffering from an infection
	* in which palliative sedation was provided
	* in which relaxants were used in combination with pain control
	* in which doses higher than the maximum dose as prescribed for children were given for pain and consciousness control, e.g. with morphine
	* in which fentanyl, remifentanil, and/or thiopental sodium was given
	* in which palliative chemotherapy was provided
	* in which opioids were combined with laxatives
	* in which pregabalin was provided for neuropathic pain
	* in which diclofenac sodium was provided for inflammatory pain
	* in which dormicum and morphine were provided
	* in which morphine was given according to the Pharmacotherapeutical Compass or Childrens's Formularium
	* in which doses higher than the advised maximum doses of ibuprofen and paracetamol were given
	* in which no antibiotics were given in the last week
	* in which catheters were kept if they were placed in a curative phase in most children
	* in which also other, newer medication than pregabalin was used against neuropathic pain
	* in which the portal catheter was used for symptom control, if it was placed already
	* in which opioids were given
	* in which was started with a continuous morphine intravenous drip
	* in which palliative radiotherapy was given, i.e. provided a maximum of five consecutive times
	* with bone tumors in which cortisones were provided
	* in which morphine was given if the child has a tumor which blocks the airways
	* in which different forms of pain medication were given to the whole group
	* in which laxatives were given
	* in which chemotherapy, if given, was given orally

* in which pain control was provided in the form of a band aid
* in which anti-epileptics were given
* in which medication against itching was provided
* in which ibuprofen was provided
* in which physiotherapy was provided at least 2 times a week
* in which physiotherapy was provided at least 2 times a week within the last 1/3rd period of the palliative period
* with leukemia in which blood transfusions were given
* that received anti-emetics
* that received laxatives
* with anemia that received blood transfusions
* in which ondansetron was prescribed more often than alizapride or domperidone
* in which the children's psychiatrist was involved
* which did not receive food anymore within the last days before death
* in which the carb intake was restricted
* in which maximum 1 life-prolonging treatment was given in the palliative phase in most children
* in which relaxants were given in case of spasms
* in which botulism injections were given for excessive saliva
* in which glycopyrronium was given in case of mucus
* in which glycopyrronium bromide was given
* in which morphine and fentanyl were started quickly
* in which morphine was given and this medication was increased often
* in which a continuous morphine drip was given
* in which propofol was given in the last days
* in which scopolamine was given
* in which pain patches instead of intravenous therapy were given
* in which oxygen was provided
* in which hypertensives were decreased
* in which morphine or fentanyl were not given in the long term
* in which bone marrow transplantation was not applied in cases of leukodystrophy
* in which propofol was only given in the last hours
* in which stomach protection was given
* in which loop diuretics were given in the terminal phase
* in which genetic testing was done
* in which no food was given
* in which tubefeeding and especially fluids were given to children with metabolic disorders
* in which conventions were followed
* in which morphine was regularly prescribed
* in which morphine or fentanyl were not given on the long term
* in which at least 2 times a week physiotherapy was provided
* in which play therapy was provided at home
* in which children came back to the hospital when they got an infection
* in which innocent procedures such as weighing the child were still continued

	* in which echo was done as usual
Inappropriate care	* in which tube feeding was continued
	* in which rescue medication was not available at home
	* in which heavy physiotherapy was provided
	* in which no antidepressants were prescribed
	* in which cortisones were given in high amounts
	* in which leg protheses were provided in the last days before death
	* with a gastrostomy who still received tube feeding
	* in which the majority of children received tube feeding or nasogastric feeding
	* in which daily physiotherapy was done if the child had an infection
	* in which concentrated food was given
	* in which antibiotics were given within the last week of life
	* in which dialyses were abruptly stopped
	* in which the same protocol was always applied
	* in which artificial ventilation was given for years on end
	* in which heart functions were done
	* in which domperidone was given
	* in which metoclopramide was given
	* in which multiple sedatives were being combined
	* in which different medications were combined of the same class, i.e. working on the same pathways
	* in which enzyme replacement therapy was used when they were already mentally very affected
	* in which peroral medication was given, this was increased, and suppositories were given
	* in which intravenous pain control was given
	* in which pain medication was stopped very quickly
	* in which there were a lot of reanimations when there was a Do Not Resuscitate policy
<u>Administrative/practical measures</u>	
Appropriate care	* above 12 in which a hospital bed was requested
	* in which the 'PAPAS' score was used to start the palliative status (own tool developed by children's palliative care team)
	* in which helping devices such as glasses, wheelchair were provided
	* in which a Do Not Resuscitate policy was written down
	* in which the percentage of disability was admitted was 100%
	* in which the disability wage was provided
	* in which the 'maximum invoice' was requested
	* in which the parents were recognized as the official caretaker
	* in which transport was arranged by the social nurse
	* in which there was an observation file about end of life in the patient record, shared between care providers
	* in which social services or a social nurse were involved
	* in which the parents were given practical information on where to obtain medication
	* in which the use of diapers was registered
	* in which the Do Not Resuscitate code was revised sometimes

	* in which there was a Do not resuscitate code
Inappropriate care	* under 6 that could not be indicated as completely dependable in the insurance codes
	* in which no registration was possible for pediatric home care
	Percentage of cured children that still received heightened child benefits
	* in which there was no Do Not Resuscitate code
	* in which a Do Not Resuscitate code was given only after an acute event
Place of/manner of care/death	
Appropriate care	* that died at a place that was known and trusted
	* who died in a calm, warm environment
	* in which someone was near when the child died
	* which were taken care of in a medical-pedagogical institute in the last year before death
	* in which there were no long hospitalizations
Inappropriate care	* that died unexpectedly at intensive care
	* in which there were too many hospitalizations (>30) in the last year before death
	* that died at intensive care
	* that died in the hospital
	* that ended up on intensive care while a palliative trajectory was started
	* that was hospitalized at the end of life
	* in which there was a small number of hospitalizations (<2) in the year before death
	* that stayed at the liaison service for more than 2 years
	* in which children were admitted for a non-acute event
Care providers + care coordination	
Appropriate care	* in which a physician did the coordination of care, preferable a physician that is known to the child
	* in which there were moments of conversation and planning at home with the caretakers of the first line
	* in which there was regular, daily follow-up by home nurses
	* in which a social nurse or a social assistant was included in the care
	* in which there were house visits by a psychologist
	* in which an occupational therapist performed home visits
	* in which the family asked for the same caretaker
	* in which there was a visit at home from a caretaker every day
	* with spinal muscular atrophy or trisomy diagnosis in which there was immediately contact with a liaison team
Inappropriate care	* in which there were multiple visits from care professionals at home every day
	* in which not enough home visits were made by the home care team or the general physician
	* in which a children's psychiatrist was never involved
	* in which only specialists were involved in care provision, no coordination by family physician or liaison team or home nurses
Continuity/intensity of care	
Appropriate care	* in which the head caretaker came to visit most children every day in the hospital
	* in which the liaison team provided a visit 2 to 3 times a year
	* in which the parents got the chance to build a trust bond with the liaison team, by already seeing the liaison team in the hospital
	* in which there is a good proportion for intensity of care: there was a systematic continuation of care, but not too intense

	* in which the trusted psychologist stayed the same during the trajectory * that already knows the liaison team or the specialist pediatric home care team, thanks to already seeing the team in the curative period * that gets nurses that also took care of them during the curative phase
	* in which the general physician or other care professionals were available /7
Relationship between different care providers	
Appropriate care	* in which the liaison team stayed second line and did not replace the first line of care * in which intensive care is necessary and intensivists start a new care trajectory and the head caretaker or the general physician is contacted * in which there was a good proportion between the amount of visits by the general physician and visits by the home care team * in which there is communication between the general physician and the home care team * in which a nurse was present at the multidisciplinary meetings * in which euthanasia was provided and there was a lot of multidisciplinary activity * in which a multidisciplinary consult was done when the child ended up on intensive care * in which a multidisciplinary meeting was done at the start of the trajectory and not only at the end
Inappropriate care	* that received an operation, in which no multidisciplinary meeting before the decision was made to do an operation
Vulnerable groups	
Appropriate care	* in which an intercultural intermediary and/or interpreter was provided to families with a non-Belgian background or language issues * in which there were requests for medical regularization
Inappropriate care	* in which no interpreter was provided for families with a migrant background
Parents and family, care supporters	
Appropriate care	* in which the parent knew they could get help 24/7 * in which appropriate care and support were present for parents, brothers, sisters, and classmates * in which emotional support is provided for the care professionals * in which the families or parents could visit a respite house * in which the parents did not have questions anymore * in which parents feel safe to go home with the child * in which parents came back to visit the ward to thank the care professionals after the death of the child * in which there was there was day care for brothers and sisters * with parents with a 'saving mechanism' (withholding care), in which together with the parents it was determined what the balance is * in which brothers and sisters could say goodbye * in which parents after the death of the child have found rest and accept the death * in which within the family there was open communication about death and dying * in which there was open communication within the family * in which psychological support was provided for the environment * in which parents accepted the help of a liaison team

	* in which there was a consult with a psychologist in the last week before death
	* in which there was sufficient support for caretakers after the death of a child
Inappropriate care	* in which there are parents with borderline or psychological problems
	* in which parents made debt due to hospitals costs
	* in which absenteeism due to disease in the parents was high
	* in which poignant social situations happened during the palliative trajectory
	* in which there was little supervision/framework for families
Routines	
Appropriate care	* Bednet (remote access digital school system) was used
	* in which certain routine activities were kept, such as school, hobby's, …
	* in which continuously an effort was made to give courage and a sense of normality to the child
	* in which a teacher came by or Bednet was installed
Inappropriate care	* in which there was no teacher who visited or no Bednet that was installed
Timing	
Appropriate care	* in which home care nurses were provided before the palliative period was started
	* that received palliative status in time
ACP	
Appropriate care	* in which the values, needs, and wishes of the child and family were surveyed, evaluated, and was mapped what was realistic
	* in which the care trajectory is also discussed with the child
	* in which there is communication to the child that if the symptoms get too bad, they can be put to sleep
	* that was in an advanced care trajectory
	* in which conversations were held about the end of life

Indicators from the three illness groups were put together for clarity and brevity, [b] made retrospectively

PART 2
Measuring pediatric-specific indicators using big data

CHAPTER 3

Population-level analysis of the appropriateness of end-of-life care in children with neurological conditions

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ABSTRACT

Objectives To measure the appropriateness of end-of-life care for children who diedwith neurological conditions.

Study design Based on linked routinely collected databases, we conducted a population-level decedent cohort study of children who died in Belgium with neurological conditions between 2010 and 2017. We measured a set of 22 face-validated quality indicators. The set concerns 12 indicators of potentially appropriate end-of-life care (e.g. specialized comfort medication, physician contact, continuous care) and 10 indicators of potentially inappropriate end-of-life care (e.g. diagnostics, drawing blood). We performed analysis of variance for predictors (age, sex, disease category, nationality, having siblings, year of death) for scales of appropriate and inappropriate care.

Results Between 2010 and 2017, 139 children died with neurological conditions in Belgium. For potentially appropriate care, in the last 30 days 76% of children received clinical care, 55% had continuous care relationships, 17% had contact with a general physician, 8% of children received specialized comfort medication, and 14% received care from a palliative care team. For potentially inappropriate care, in the last 14 days 45% had blood drawn, and 27% were admitted to ICU.

Conclusions Our study found indications of appropriate as well as inappropriate end-of-life care for children who died with neurological conditions. Findings seem to imply a substantial margin for quality improvement, for the themes of palliative care provision, multidisciplinary care, financial support, specialized comfort medication, clinical follow-up, general physician contact, diagnostics and blood drawing.

INTRODUCTION

One in five children dying with neurological and neuromuscular complex chronic conditions are reported to suffer a high symptom burden at the end of life (1). Such conditions, such as cerebral palsy (2) and muscular dystrophy (3), are often incurable and progressive, with treatment focusing on long-term symptom control instead of cure (4). In the final stages of life, children with neurological and neuromuscular conditions can suffer from muscle tone problems such as spasticity and dystonia, spine and chest deformations, pain and other symptoms such as headaches, sleep problems, respiratory complications, digestive problems, psychological problems (agitation), excessive salivation and convulsions (5-10). Neurological conditions have been reported in several cohort studies to be the most common diagnoses of children referred to paediatric palliative care teams (2-3,11-15), and parents of children with neurological conditions report less satisfaction with end-of-life management than parents of children with cancer and heart conditions (16,17). An extensive evaluation of the quality of end-of-life care for children with neurological conditions at the level of the entire healthcare system is missing.

Prior to this study, we developed a set of quality indicators that measure aspects of care that may indicate potentially appropriate or inappropriate care at the end of life in children with neurological conditions (18). The quality indicators were developed for a population level, using administrative health data. Appropriate end-of-life care has been defined as care, such as treatments or medications, for which there is more expected health benefit (e.g. improved quality of life, pain relief) than possible negative consequence (e.g. symptom burden, mortality) on a group level. Inappropriate care was seen as the opposite, i.e. more expected negative consequences than benefits on a group level. To signal that the constructed categories are only indicative and do not provide a definite value judgement for care provision on an individual level, the term 'potentially' is placed alongside the terms appropriateness and inappropriateness.

This study aims to: 1) measure these quality indicators in 6 linked administrative healthcare databases of children who died with neurological conditions in Belgium between 2010 and 2017; and 2) identify risk factors of appropriate and inappropriate end-of-life care (i.e. to identify whether certain clinical or socio-demographic variables show different outcomes for appropriateness – for example, for younger as opposed to older children).

METHODS

Study design

We conducted a decedent cohort study of all insured children who died with neurological conditions in Belgium between 2010 and 2017. Health insurance is mandatory in Belgium and, therefore, our data are expected to include practically the full population.

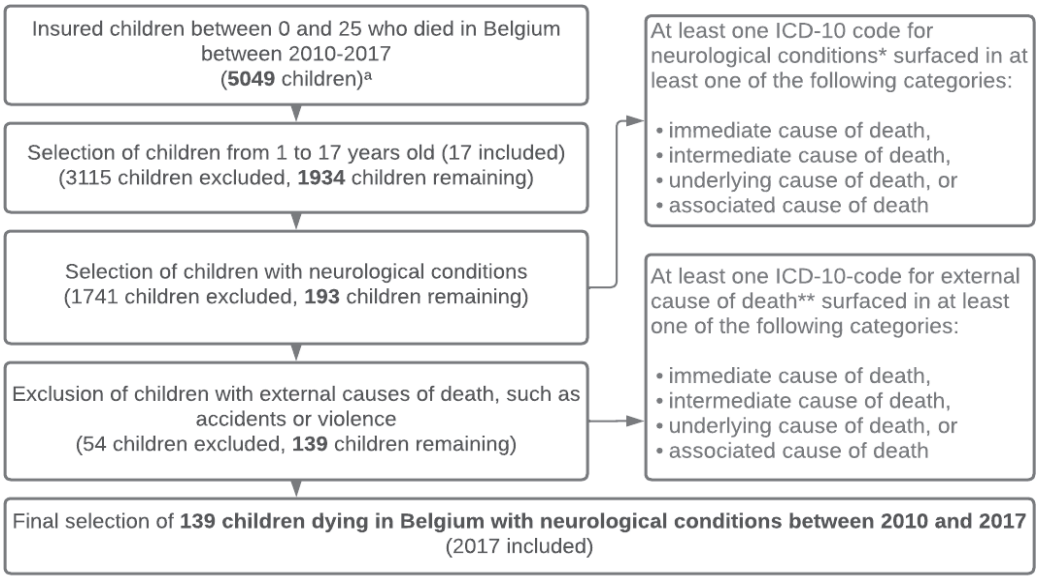
Data sources

We used data from 6 linked Belgian governmental databases. See also Table 1 (Online).

Population

Children, 1-17 years old, who died with neurological conditions within the years 2010 to 2017 were selected using death certificate data (see Figure 1).

Figure 1: Flow chart describing cohort selection



[a] Selection was started from the population database of the Intermutualistic Agency Database, as the deaths recorded in this database result from national death certificates, which were seen as the most reliable source. Variations in number of deaths were present over all databases, due to differing age and death definitions and selection by the different governmental agencies preparing the data.
*ICD-10-codes as defined in Feudtner (2014): Q00-Q07, G90.1, F71-F73, E75.0, E75.2, E75.4, F84.2, G11.1-G11.4, G11.8, G11.9, G12.0-G12.2, G12.8, G12.9, G31.01, G31.09,G31.8, G31.89, G32.89, G93.8, G93.9, G94, G91.1, G31.9, G25.3, G95.19, G95.89, G90.9, Q85.1, G80, G40.311, G40.301, G40.211, G40.219, G40.411, G40.419, G93.1, G93.5, R40.3, I63.30, I63.50, G71, G72, G10, G20, G21.0, G21.11, G21.19, G21.8, G23.0-G23.2, G23.8, G24.02, G24.8, G25.3-G25.5, G25.81-G25.83, G25.89, G25.9, G80.3
**ICD-10 codes were taken from the general ICD-10 framework: S00-T08 (Injury, poisoning and certain other consequences of external causes), U00-U85 (Codes for special purposes), and V00-Y99 (External causes of morbidity)

Newborns or children between 0 and 1 were not included, as this age group is treated in neonatology and differs in treatment approach, disease and trajectory. We selected the ICD-10 codes as defined in the framework of complex chronic conditions (19). Neurological and neuromuscular conditions are defined as brain and spinal cord malformations, intellectual disability, central nervous system degeneration and diseases, infantile cerebral palsy,

epilepsy, other conditions of the central nervous system, occlusion of cerebral arteries, muscular dystrophies and myopathies, and movement diseases (19). We selected neurological conditions for any cause of death – i.e. either underlying, intermediate, immediate or associated cause of death. Therefore, overlap is present for children with other conditions, such as children with brain tumours who developed a neurological condition. Sensitivity analysis was done for underlying cause of death (see Table 2 (Online)).

Context and setting

The Belgian government recognizes 9 neuromuscular reference centers that work to provide multidisciplinary help to children and adults with neuromuscular diseases. Most of these reference centers are connected to a university hospital.

In Belgium, healthcare insurance is mandatory. For most health claims, there is an out-of-pocket amount and an amount that is either reimbursed or covered through third-party payment arrangements. The out-of-pocket amount can vary depending on the characteristics of the insured person or the household – such as socio-economic status, or having an official 'palliative care status'. These reimbursed healthcare expenditures are registered by governmental institutions in large population databases.

Data

We used available data on healthcare use, including data on medication and treatments, admissions to hospitals, and socio-demographic data.

Quality indicators

Based on previously validated quality indicators, we measured 12 indicators for potentially appropriate and 10 indicators for potentially inappropriate end-of-life care (18). Two other previously developed indicators – 1. having reimbursed prescriptions, and 2. having transfers from a medical-pedagogical institute to intensive care – were not measured, as we could not measure the concepts validly based on the available data. We made slight changes to the original indicator 'paediatric intensive care unit admissions', instead measuring intensive care unit admissions, as no code was available for the paediatric intensive care unit. A summary table of the measured indicators can be found in Table 3.

Statistical analysis

We used descriptive statistics to describe the characteristics of children who died with neurological conditions and to measure the quality indicators.

Table 3. Measured indicators with numerator, denominator, period(s) and operationalization

Nr	Title	Numerator (number of children that died of neurological conditions in which*)	Denominator (*Number of children that died of neurological conditions)	Period(s)
		Potentially appropriate care		
1	Prescriptions of physiotherapy	*Physiotherapy was given	*	30 days before death
2	Prescription of specialized comfort medication	*There were prescriptions for hyoscine butylbromide, dexmedetomidine, fentanyl, gabapentin, ketamine, ketorolac, lidocaine, midazolam, ondansetron, or scopolamine	*	30, 14, 7, 2 days before death
3	Pain control according to WHO steps	*There were prescriptions from the third World Health Organization step, i.e. morphine, fentanyl, methadone, oxycodone, or hydromorphone, and these were preceded, in the last 2 years before death, by prescriptions from the first World Health Organization step, i.e. paracetamol, non-steroidal anti-inflammatory drugs or aspirin, and from the second World Health Organization step, i.e. codeine, tramadol, or buprenorphine	*with prescriptions from the third World Health Organization step, i.e. morphine, fentanyl, methadone, oxycodone, or hydromorphone in the last 3 months before death	90/120 days before death
4	Follow-up visits at the hospital	*There was at least 1 consultation in a hospital, or with a specialist physician	*	From palliative status onwards
5	Contact with general physician	*There were at least 3 house visits of, prescriptions of, or consultations with a general physician	*	30 days before death
6	Continuous care relationships	*There was at least 1 prescription, visit, consultation, or treatment from the same physician (general or specialist) in the last 30 days before death, as in the last year before death	*	30 days before death
7	Clinical care provision	*There were more than 2 prescriptions, house visits, treatments, consultations of physicians or paramedics, or a visit to a care institute	*	30, 14 days before death
8	Palliative care team	*There was at least 1 visit of a palliative home care team	*	730 days before death (full period available)
9	Multidisciplinary care	*There was a total of 5 or more prescriptions, treatments, visits, or advices, from 2 or more of the following care providers: general physicians, pediatricians, specialist physicians or paramedics	*	30 days before death
10	Involvement of specialist physicians	*There was at least 1 prescription, visit of or consultation with at least 1 specialist physician	*	30 days before death
11	Palliative status	*Receiving a palliative status (administrative notion that patient is palliative, hereby qualifying also for a palliative stipend)	*	730 days before death (full period available)
12	Increased child benefits	*There were increased child benefits assigned to the family	*	730 days before death (full

				period available)
		Potentially inappropriate care		
13	Daily diagnostics	*Received 2 or more X-rays, magnetic resonance imaging scans, or Computed Tomography scans per day	*	30, 14, 7, 2 days before death
14	General diagnostics	*Received 2 or more X-rays, magnetic resonance imaging scans, or Computed Tomography scans	*	30, 14, 7, 2 days before death
15	Starting dialysis	*Dialysis was started	*	30, 14, 7, 2 days before death
16	Old-generation prescriptions nausea	*Domperidone or metoclopramide was prescribed	*with prescriptions for nausea-treating medication	30, 14, 7, 2 days before death
17	Surgeries	*A surgery was performed	*	2 days before death
18	New antidepressant	*At least 1 new antidepressant was started	*	14 days before death
19	Drawing blood	*There was at least 1 blood drawing	*	7, 2 days before death
20	Late palliative care provision	*There was a first registration of a palliative home care team or palliative status	*	14, 7 days before death
21	Intensive Care Unit admissions	*There were 1 or more hospital admissions at the Intensive Care Unit	*	14, 7, 2 days before death
22	Transfers between care settings	*There were 4 or more different care settings (home, hospital or other setting)	*	30, 14, 7, 2 days before death

The second research aim is to identify risk factors for the indicator results. For this purpose, logistic regressions were performed for all 22 separate indicators, with the identified potential confounders as independent variables and the indicator variables (0 vs 1) as dependent. For a more parsimonious presentation of the findings (the 22 logistic regressions models result in a large table), with the aim of data reduction, factor scales were constructed. This identification was first based on theoretical assumptions about thematic consistency (i.e. appropriateness vs. inappropriateness of care). A principal components analysis limited to one factor was then performed for each scale to verify internal consistency. Items with a component loading below 0.50 were removed from the scale. Cronbach alpha analyses were performed for the scales.

The factor scores for the scales were saved, and for each scale and per predictor we performed multi-variable analysis of variance (proc glm) to identify if and which predictors have significantly different scores per scale. To identify the candidate confounders for this analysis, we built directed acyclic graphs, inspired by the evidence synthesis for constructing directed acyclic graphs (ESC-DAGs) (20),following a non-causal theory-driven approach. Based on predictors identified in previous studies, our own assumptions, and mediator/collider analysis, a set of possible confounders was identified: age, sex, disease category, nationality, having

siblings, year of death. Analyseswere conducted with SAS Enterprise Guide, version 7.1, and StataSE, version 17.

Ethics

All data were linked in a secure, ethically responsible manner, guaranteeing anonymity of the deceased. The study was approved by the Belgian Information Safety Committee.

RESULTS

Population characteristics

Between 2010 and 2017, there were 139 children between 1 and 17 years old that died with neurological conditions in Belgium. See Table 4 for socio-demographic and clinical characteristics.

Table 4. Characteristics of children who died with neurological conditions in Belgium,[a] 2010-2017

Characteristic	Percentage (number)
All	139 (100%)
Sex of the child	
Male	67 (48%)
Female	72 (52%)
Age range of the child	
1-5	44 (32%)
>5-9	31 (22%)
>9-15	40 (29%)
>15-17	24 (17%)
Nationality of the child	
Belgian	125 (90%)
Other	14 (10%)
Type of household in which the child lived	
Two-parent household	102 (74%)
Single-parent or other household	36 (26%)
Comfort of the house in which the child lived	
High	39 (28%)
Average	12 (9%)
Low	13 (9%)
Missing information (None, missing, not known or trailer)	75 (54%)
Highest level of education of the child's parents[b]	
Postsecondary 40-60	45 (32%)
High school 30-34	41 (29%)
Junior high school 20-24	26 (19%)
Primary school 10	17 (12%)
Not known or missing	10 (7%)
Urbanicity of municipality of residence of the child's family[c]	
Very high	37 (27%)
High	44 (32%)
Average	42 (30%)
Low	15 (11%)
Net annual taxable income of the child's family[b]	

High (decile 1-3)	49 (35%)
Average (decile 4-6)	32 (23%)
Low (decile 7-10)	35 (25%)
Missing	23 (17%)
Underlying cause of death of the child according to generalICD-10 category[d]	
Diseases of the nervous system	52 (37%)
Diseases of the respiratory system	19 (14%)
Neoplasms	17 (12%)
Endocrine, nutritional and metabolic diseases	12 (9%)
Diseases of the circulatory system	11 (8%)
Congenital malformations, deformations and chromosomal abnormalities	11 (8%)
Certain infectious and parasitic diseases	6 (4%)
Diseases of the blood and blood-forming organs and certaindisorders involving the immune mechanism and Mental, Behavioral and Neurodevelopmental disorders	7 (5%)
Certain conditions originating in the perinatal period	5 (4%)
Categories of neurological and neuromuscular complex chronic conditions[d]	
Brain and spinal cord malformations	11 (8%)
Mental retardation or Movement diseases	10 (7%)
Central nervous system degeneration and diseases	34 (25%)
Infantile cerebral palsy	32 (23%)
Other disorders of central nervous system	47 (34%)
Muscular dystrophies and myopathies	13 (9%)

[a] Due to the use of population-level databases, practically all children who died are expected to be included within the sample. However, the number of children who died may be slightly larger than reported as some IDs did not overlap within the relational database, see Appendix 4.;[b]Highest level of education/income of both parents was selected; [c]Based on the Eurostat degree of urbanization method; [d]Total number exceeds 139 as neurological or neuromuscular complex chronic conditions could surface in more than one cause of death. No children were found with a cause of death for the illness categories of epilepsy or occlusion of cerebral arteries.

Potentially appropriate care at the end of life

In the last 30 days of life, as shown in Table 5, 34% of the children received prescriptions for physiotherapy, 17% ofthe children had contact with a family physician, 75% with hospital specialists, 7% received multidisciplinary care (received care from at least 2 categories of care providers – e.g. a physician and a paramedic), 55% received continuous care (physician seen in the last month before death had also been seen in the year before). Increased child benefits – which in Belgium can be assigned to parents with children under 21 with a disability or serious condition and provided certain requirements are fulfilled – were assigned in 8% of cases. A palliative care service was involved in 14% of the children and 13% received palliative status.

Potentially inappropriate care at the end of life

In the last month before death, or prior, none of the children received dialysis, nor old- generation prescriptions for nausea, and none received a new anti-depressant in the last 2 weeks before death (Table 5). But, diagnostics (MRIs, X-rays and CT scans) were carried out in 26% of the children in the last month before death and in 45% of the children in the last week before death. 4% of the children received a palliative care visit for the first time, or a palliative status, only in the 2 weeks before death. 27% were admitted to an intensive care unit in the last 2 weeks of life.

Table 5a: Indicators for potentially appropriate and inappropriate end-of-life care for children who died with neurological conditions in Belgium, 2010-2017[a]

Indicators of potentially appropriate end-of-life care								
Number of days until death	**2**	**7**	**14**	**30**	**120**	**From palliative status onwards**	**730 (full period available)**	**Denominator (n)[b]**
Treatment, medication, and monitoring								
Prescriptions of physiotherapy				47 (34%)			72 (52%)[c]	139[d]
Prescription of specialized comfort medication	<5 (<4%)*	6 (4%)	8 (6%)	11 (8%)			16 (12%)[c]	139[d]
Pain control according to WHO steps					6 (55%)			11
Place of care								
Follow-up visits at the hospital						0 (0%)		18
Care services and providers								
Contact with general physician				24 (17%)			118 (85%)[c]	139[d]
Continuous care relationships				76 (55%)				139[d]
Clinical care provision			100 (72%)	105 (76%)			118 (85%)[c]	139[d]
Palliative care team							20 (14%)	139[d]
Multidisciplinary care				10 (7%)			60 (43%)[c]	139[d]
Involvement of specialist physicians				104 (75%)			117 (84%)[c]	139[d]
Financial measures								
Palliative status							18 (13%)	139[a]
Increased child benefits							11 (8%)	139[a]

[a]Empty cells indicate that the indicator was not face-validated for this time period; [b]Some indicators were measured on a subset of the population due to the formulation of the indicator, but are still expected to provide an indication for the population through this subset measurement; [c]Indicator does not increase with number of days as number of scans per day (min. 2) were counted; [d]Indicator was not face-validated for this period, but is shown to provide a comparison; [e]Twenty-one children did not have health care claims within the database and were therefore counted as not having received the indicator; [f]Measured with ATC code A03, no children with prescription for drugs for functional gastrointestinal disorders were found for the full population; *Due to privacy guidelines, it was not possible to report exact details of small cells, i.e. cells with fewer than 5 children

Table 5b: Indicators for potentially inappropriate end-of-life care for children who died with neurological conditions in Belgium, 2010-2017[a]

Indicators of potentially inappropriate end-of-life care								
Number of days until death	**2**	**7**	**14**	**30**	**120**	**From palliative status onwards**	**730 (full period available)**	**Denominator (n)[b]**
Treatment, medication, and monitoring								
Daily diagnostics	9 (7%)[c]	<5 (<4%)[c*]	0 (0%)	0 (0%)			0 (0%)[d]	139[e]
General diagnostics	24 (17%)	31 (22%)	34 (25%)	36 (26%)			85 (61%)[d]	139[e]
Starting dialysis	0 (0%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)[d]	139[e]
Old-generation prescriptions nausea	0 (0%)	0 (0%)	0 (0%)	0 (0%)			0 (0%)[d]	0[f]
Surgeries	<5 (<4%)						23 (17%)[d]	139[e]
New antidepressant			0 (0%)				6 (4%)[d]	139[e]
Drawing blood	51 (37%)	63 (45%)					100 (72%)	139[e]
Care services and providers								
Late palliative care provision		<5 (<4%)	5 (4%)				20 (14%)[d]	139[e]
Place of care								
Pediatric Intensive Care Unit admissions	35 (25%)	38 (27%)	38 (27%)				53 (38%)[d]	139[e]
Transfers between care settings	0 (0%)	0 (0%)	0 (0%)	<5 (<4%)			39 (28%)[d]	139[e]

[a]Empty cells indicate that the indicator was not face-validated for this time period; [b]Some indicators were measured on a subset of the population due to the formulation of the indicator, but are still expected to provide an indication for the population through this subset measurement; [c]Indicator does not increase with number of days as number of scans per day (min. 2) were counted; [d]Indicator was not face-validated for this period, but is shown to provide a comparison; [e]Twenty-one children did not have health care claims within the database and were therefore counted as not having received the indicator; [f]Measured with ATC code A03, no children with prescription for drugs for functional gastrointestinal disorders were found for the full population; *Due to privacy guidelines, it was not possible to report exact details of small cells, i.e. cells with fewer than 5 children

Risk factors for potentially appropriate and inappropriate care at the end of life

The 2 constructed scales had standardized Cronbach alpha of 0.85 and 0.61, respectively. The multi-variable analysis of variance revealed statistically significant differences by disease categories: disorders of the central nervous system and movement diseases showed a significantly lower scale score for appropriate care. No associations were found with age, sex,

nationality, having siblings, or year of death.

DISCUSSION

In this decedent cohort study, we evaluated the quality of end-of-life care with population-level quality indicators for potentially appropriate and inappropriate care for 139 children, from 1 to 17 years old, that died with neurological conditions between 2010 and 2017 in Belgium. Indicators for appropriateness of end-of-life care ranged from 0% (e.g. follow-up visits at the hospital) to 76% (clinical care provision). Indicators for inappropriateness of end-of-life care ranged from 0% (e.g. starting dialysis) to 45% (drawing blood in the last week before death). Analyses of variance indicated that disorders of the central nervous system and movement diseases had a significantly lower scale score for appropriate care.

Strengths and limitations

A strength of our study is the use of routinely collected data. In Belgium, health insurance is mandatory, and our database thus includes healthcare use for the full population of insured children who died in Belgium in the studied period. Thus, we avoided a common pitfall in cohort and children's studies: our database includes children that would normally be difficult to recruit for. Furthermore, our quality indicator set was extensively face-validated specifically for the data at hand. Our database is extensive, as 6 different databases were linked, and many clinical and socio-demographic variables are found within the data. To our knowledge, only 1 previous international population-based study has measured similar indicators for children with neurological conditions at the end of life – namely, for dialysis and ICU admissions (21).

A limitation of the study is that our data do not include certain procedures or non-population-level measures for the children or families, such as consultations with a psychologist or quality-of-life measures. Variables were not collected with research questions in mind, and therefore they might lack validity. Our indicators centered on the child, but did not take the family's healthcare use into account. For the identification of relevant risk factors for appropriate or inappropriate care, not all variables identified as relevant through the DAG-ECS method were available from the data.

Interpretation of findings

Our results show varying numbers for indicators involving care providers. Continuity of care and the use of professional and specialist care was found to occur in the majority of cases. This is consistent with continuity of care being reported as a priority for Belgian paediatric liaison teams (22). The involvement of a general practitioner (GP) in the last month of life seemed much lower. Previous studies report general practitioners experience a relatively high distress level during the terminal phase of the death of a child, as well as feelings of sadness and powerlessness around the child's time of death, which may underlie and account for the low percentage (23). The results also seem to indicate that follow-up consultations at the hospital after receiving a palliative status (an administrative notion indicating that the patient needs palliative care) were non-existent. If the measurements are valid, this could lead to families feeling they "missed out on instructions given by nurses or specialists and on contacts with other families confronted with similar problems" (17), per rationale behind the indicator (18). However, it could also be possible that visits to the hospital were not registered or charged, and therefore not registered in the databases. Belgian paediatric liaison teams also report incorporating in-hospital consultations in their work, based on some families' preference for hospital support (22).

The measured indicators carefully seem to signal a low use of palliative care services (14% of the children received reimbursed palliative care provision in the last 2 years before death; 13% received an official palliative status, which entails the removal of several out-of-pocket costs). This seemingly confirms findings from other studies: the specificity of symptoms of children with degenerative disorders has been previously reported to complicate the provision of palliative care (24). It is possible that the reported numbers are an underestimation, as palliative care for children can also be provided with philanthropic funding and, hence, without any official reimbursement. The small body of evidence for palliative care in children with neurological conditions suggests palliative care could be beneficial (25): an Indian cohort study of 60 children with cerebral palsy found all children had palliative care needs (25).

Additionally, financial support measures – such as being given an official palliative status (13%) and increased child benefits (8%; in Belgium, this can be assigned to parents with children under 21 with a disability or serious condition and provided certain requirements are fulfilled) – seemed to be low. Families of children with complex chronic conditions have previously been reported to require "additional social assistance, financial resources, and support for administrative procedures" due to the high family financial burden (22). Administrative support for families could be provided, or awareness campaigns could possibly be set up, to increase

the use of these measures.

Another finding is that diagnostics, drawing blood and intensive care unit admissions seem to occur often in the final weeks of life. This suggests that a proportion of children potentially receive inappropriate care at the end of life, which perhaps could be avoided. Diagnostics may be highly requested as they are effective for prediction of clinical outcomes (e.g. CT scans in cerebral palsy) (28,29), and deterioration to death can be unpredictable (24). A 2004 cohort study on clinical outcomes for children with neuromuscular disease admitted to paediatric intensive care indicated that admissions for children frequently required invasive ventilation (30), while another cohort study indicated breathing difficulties cause the greatest suffering in children with complex chronic conditions and distress for their parents (1).

Risk factors

Certain types of neurological diseases were more at risk: disorders of the central nervous system and movement diseases showed a significantly lower scale score for appropriate care. This could be caused by the combination of the lesser known or predictable pathology and more erratic symptom pattern for these illnesses. This could be caused by the combination of the physicians' unfamiliarity with the disease, unpredictable illness course and more erratic symptom patterns for these illnesses. For instance, juvenile Huntington's, classified as a movement disorder within the used complex chronic conditions framework, is relatively rare and therefore a clinician "managing the patient is often doing so for the first time", with few available evidence-based guidelines (31). Epilepsy is an example of a central nervous system disease symptom that can be unpredictable to manage,(32) for example in case of West syndrome. Our finding also could be connected to a recent analysis by Lindley et al., who found that the population of children with neurological conditions at the end of life can be divided into two classes, namely one with moderate use of health services, and one with high-intensity use of health services (33). The latter category included most of the children with central nervous system disorders (89%). These results mirror our findings and further the hypothesis that certain, possibly lesser-known, neurological conditions, likely justifiably, utilize more health services and clinical settings at the end of life.

Comparison with international findings

Only 1 previous study (in California, on children's deaths between 2000 and 2013) has measured 2 similar indicators for children with neurological conditions at the end of life (21). Therefore, interpretations about whether findings are low or high remain speculative and basedon assumptions. The study in California found that 2.6% of US children with neurological conditions

were reported to receive dialysis in the last month before death, as opposed to nonein Belgium, and 39% received ICU admissions, while 27% received such in Belgium. International case studies provide similar indications for healthcare setting use, for instance describing ICU use at the end of life in a child with neurological impairment for symptom control (26). In contrast, international cohort studies and case studies show differing measurements for some indicators, such as palliative care provision and medication use. For instance, palliative care consultation was observed to be very high for an inpatient US cohort of children with neurological conditions (76,9% for children with neuromuscular disorders), while our numbers indicated low palliative care provision (34). While differing in operationalization from our comfort medication measurements, Canadian and US cohort studies also showed a higher use of comfort medications than our measurements: in one study 57% of children were provided with opioids in the last days of life, and a median of 4 drugs classes was given, while our findings show less than 4% of children received certain specialized comfort medications (35). Such contrasts may signal important differences between hospital and population samples, and it may be looked into further whether this also indicates a care quality difference. Differences could also be present due to care provision differences per region (US vs Belgium), and/or due to measurement differences (reimbursed vs non-reimbursed medications).

Recommendations for research, practice and policy

Our research provided a broad evaluation of the quality of end-of-life care for children with neurological conditions in Belgium, and it can be used as a starting point for further interventions to improve the end of life for these children and the related research. Further steps could involve the design of interventions to target the potential areas of improvement (e.g. courses to increase comfort medication knowledge), after which the quality indicators could be measured again to measure the interventions' impact. Besides educational efforts, other possible system barriers that might be targeted are a lack of incentives for multidisciplinary care provision in children at the end of life, and the lack of a proper evidence base (overview) with potential benefits and downsides of medications and treatments for children with neurological conditions' quality of life at the end of life. Workload indicators and patient-reported outcome measures, amongst others, have been previously suggested for the Belgian context to improve continuity of care for paediatric liaison teams (22), yet analysis of quality improvement evidence and national system mechanics is advisable before development of further quality improvement initiatives.

Additionally, the indicators are best externally validated in further studies. Due to the absence of similar national and international measurements, it is unknown whether the measured

frequencies precisely reflect the true frequencies of the concepts selected for measurement. While some indicators likely provide accurate reflection, other indicators could provide underestimations due to lack of reimbursement, misclassification, or greater concept ambiguity. Highly specialized treatments such as surgeries and specialized comfort medication are likely accurate in measurement as these treatments are always reimbursed in Belgium due to their lack of over-the-counter availability, and free provision based on goodwill of providers is unlikely. On the other hand, care which also could be provided without reimbursement or via goodwill could show undermeasurement, such as palliative care, general physician contact or follow-up by the hospital. Also, concepts which are less concrete and only measurable in part via administrative data, such as multidisciplinary care, could provide undermeasurement. Certain one-time administrative measures, such as palliative status, could have showed low scores due to the availability of data, which was limited to 2 years before death. It is advised that further research is conducted using different sources for indicator estimations in small samples of children at the end of life, in order to further validate the indicators. Parents' and children's evaluation of the quality of end-of-life care might provide further triangulation - previous studies show parents can be highly involved in the care and decision-making on treatments for children with neurological conditions at the end of life (36).

CONCLUSION

This study performed the first evaluation of the quality of end-of-life care for children with neurological conditions, using quality indicators for the appropriateness of end-of-life care for 139 children who died between 2010 and 2017 with neurological conditions in Belgium. Our study found indications of appropriate, as well as inappropriate, end-of-life care for children who died from neurological conditions, with relatively frequent blood drawing and ICU admissions in the final weeks of life and infrequent comfort care, general physician contact, and palliative care service use, but also frequent clinical and continuous care relationships. While further research and international comparison is warranted to develop further interventions, these findings seem to imply a substantial margin for quality improvement in paediatric neurological end-of-life care, especially for the themes of palliative care provision, multidisciplinary care, financial support, specialized comfort medication, clinical follow-up, general physician contact, diagnostics and blood drawing.

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Supplemental information 2: Information on databases (based on De Schreye et al. (37))

Institution	Database	Description
Intermutualistic Agency	Sociodemographic database	Sociodemographic information for all individuals with healthcare insurance, which is legally mandatory in Belgium (37)
	Healthcare database	Outpatient and hospital care provided in Belgium, except medication dispensed in pharmacies, with amongst others date, healthcare provider, setting. (37)
	Pharmaceutical database	Reimbursed medication dispensed in pharmacies in Belgium, with amongst others date of prescription, date of delivery, information on prescriber, setting, for every reimbursed medication delivery (37)
StatBel	Death certificate database	Underlying cause of death, as well as associated and intermediate causes of death on all deaths in Belgium, from Belgian death certificates (37)
	Population registry database	Citizens' household composition and highest attained level of education for every Belgian citizen (37)
	Census database	Data from the last census in Belgium in 2012, such as educational level and housing comfort characteristics (37)

Supplemental information 4: Validation and reliability verifications for identification of bias

Validity database population
Validity
Our database population was compared to population numbers from Statistics Belgium. Statistics Belgium public documentation identified 6050 deaths for children between 1 and 25 years old. Our database includes 5098 deaths for children between 1 and 25 years old, which is 84% of the number of deaths reported by Statistics Belgium. Differing selections for death, time and age by the governmental agencies providing the data may account for the differing number of deaths between databases.
Reliability
The unique IDs within our databases that form the relational database were compared to each other to assess reliability of the databases. The majority of IDs provided overlap. However, some IDs did not overlap with the IDs in other databases for the total amount of children (1-25) who diedof all causes of death: 91 for the databases of the Intermutualistic Agency, 104 for Statistics Belgium (out of 5344 unique codes in total). However, this concerns all children dying of all cause of death, and is therefore expected not to have a large impact on the identified number of childrenwith neurological conditions was found. Further investigation confirmed there was no faulty linkingat the base of the unlinkable IDs.
Validity and reliability indicators
Validity
To our knowledge, no publications are available to compare the percentages found to verify external validity for the Belgian context.
Reliability
To evaluate reliability, measurements were repeated with a different method or by a different researcher for some indicators. For some indicators (physiotherapy, general physician contact, clinical care provision, specialist physician involvement, surgeries, care setting transfers), two different calculation methods were used to verify reliability. Categorical selection and selective selection were applied. Indicators were originally calculated with a selective method, meaning the researcher screened all nomenclature codes and hand-selected the relevant codes. The categorical selection method was used to validate the selective method, meaning the calculations were repeated while selecting categories, e.g. following the structure of the nomenclature codes or practitioner categories. For example, for the indicator 'Prescriptions of physiotherapy', the selective method entailed selecting all individual nomenclature codes of which the description referred to physiotherapy. The categorical method entailed selecting all nomenclature codes that were categorized as prescribed by a physiotherapist by the healthcare funds. For most indicators, results of the two methods were similar, which suggests results are internally reliable. For the indicator care setting transfers, use of different variables gave differing results, which suggests results may not be reliable – however, conversations with the database providers indicate that the more reliable variables were used for final analysis. Some indicators (palliative status, dialysis), were repeated by another researcher. Same resultwere found by the other researcher for these indicators, which suggests the calculations are reliable.

Supplemental information: Sensitivity analyses

For cases excluded based on external cause (ICD S-V)

We conducted a sensitivity analysis on external/acute causes of death, i.e. the cases that were excluded based on ICD-10 codes S to V. This analysis was conducted to verify whether the excluded causes were indeed acute causes and not cases of e.g. palliative sedation or complications of surgeries. Due to privacy reasons, the exact results of this sensitivity analysis cannot be shown, yet sensitivity analysis for causes of death confirmed that the excluded cases all had causes of death related to acute causes, such as traffic accidents, suicide, or drownings, that fell out of the scope of this study.

For underlying neurological conditions only as underlying cause of death

We conducted a sensitivity analysis for children who died from neurological conditions, i.e. neurological conditions only as an underlying cause of death (n=67). No large differences in percentages are present for children dying with and children dying from neurological conditions. The results for the indicators with only children dying from neurological conditions are shown below.

	Number of days before death until death							
Indicator	2	7	14	30	120	From palliative status onwards	730 (full period available)	Denominator (n)[b]
Treatment, medication, and monitoring								
Prescriptions of physiotherapy				22 (33%)			34 (51%)	67
(Off-label) prescription of comfort medication	<5 (<8%)	<5 (<8%)	<5 (<8%)	<5 (<8%)			6 (9%)	67
Pain control according to WHO steps					<5 (50%)			<5
Place of care								
Follow-up visits at the hospital						0 (0%)		10
Care services and providers								
Contact with general physician				13 (20%)			44 (66%)	67
Continuous care relationships				40 (60%)				67
Clinical care provision			47 (70%)*	50 (75%)*			56 (84%)*	67
Palliative care team							11 (16%)	67
Multidisciplinarity of care				<5 (<8%)			31 (46%)	67
Involvement of specialist physicians				48 (72%)			55 (82%)	67
Administrative measures								
Palliative status							10 (15%)	67
Increased child benefits							6 (9%)	67

	Number of days before death until death							
Indicator	2	7	14	30	120	From palliative status onwards	730 (full period available)	Denominator (n)[b]
Treatment, medication, and monitoring								
Daily diagnostics	<5 (<8%)	<5 (<8%)	0 (0%)	0 (0%)			0 (0%)	67
General diagnostics	9 (13%)	13 (19%)	14 (21%)	16 (24%)			39 (58%)	67
Starting dialysis	0 (0%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	67
Old-generation prescriptions nausea	0 (0%)	0 (0%)	0 (0%)	0 (0%)			0 (0%)	0
Surgeries	0 (0%)						12 (18%)	67
New antidepressant			<5 (<8%)				2 (3%)	67
Late palliative care provision		<5 (<8%)	<5 (<8%)				10 (15%)	67
Drawing blood	25 (37%)	31 (46%)					48 (72%)	67
Place of care and death								
Pediatric Intensive Care Unit admissions	15 (22%)	17 (25%)	17 (25%)				23 (34%)	67
Transfers between care settings	0 (0%)	0 (0%)	0 (0%)	<5 (<8%)			20 (30%)	67

For acute vs. chronic trajectory

We conducted a sensitivity analysis for children who died from acute vs. chronic (and therefore known EOL) trajectory. Two variables were taken as proxy for trajectory for these sensitivity analyses: 1. Having received palliative care/palliative status in the last 3 weeks before death (n=5), and 2. Dying at the ICU (n=39). Results from the first proxy contained too many small cells, therefore only the results from the second proxy are shown below, but showed similar results.

Death at ICU

	Number of days before death until death							
Indicator	2	7	14	30	120	From palliative status onwards	730 (full period available)	Denominator (n)[b]
Treatment, medication, and monitoring								
Prescriptions of physiotherapy				20 (51%)			24 (62%)	39
(Off-label) prescription of comfort medication	0 (0%)	0 (0%)	0 (0%)	0 (0%)			1 (3%)	39

Pain control according to WHO steps					0 (0%)			0
Place of care								
Follow-up visits at the hospital						0 (0%)		10
Care services and providers								
Contact with general physician				5 (13%)			25 (64%)	39
Continuous care relationships				28 (72%)				39
Clinical care provision			34 (87%)	34 (87%)			34 (87%)	39
Palliative care team							0 (0%)	39
Multidisciplinarity of care				<5 (<13%)			17 (44%)	39
Involvement of specialist physicians				34 (87%)			34 (87%)	39
Administrative measures								
Palliative status							0 (0%)	39
Increased child benefits							<5 (<13%)	39

	Number of days before death until death							
Indicator	2	7	14	30	120	From palliative status onwards	730 (full period available)	Denominator (n)[b]
Treatment, medication, and monitoring								
Daily diagnostics	7 (18%)	<5 (<13%)	0 (0%)	0 (0%)			0 (0%)	39
General diagnostics	18 (46%)	23 (59%)	25 (64%)	25 (64%)			30 (77%)	39
Starting dialysis	0 (0%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	39
Old-generation prescriptions nausea	0 (0%)	0 (0%)	0 (0%)	0 (0%)			0 (0%)	0
Surgeries	0 (0%)						7 (18%)	39
New antidepressant			0 (0%)				0 (0%)	39
Late palliative care provision		0 (0%)	0 (0%)	0 (0%)			0 (0%)	39
Drawing blood	31 (80%)ùp	31 (80%)					34 (87%)	39

	7m							
Place of care and death								
Intensive Care Unit admissions	34 (87%)*	34 (87%)*	34 (87%)*				34 (87%)*	39
Transfers between care settings	0 (0%)	0 (0%)	0 (0%)	0 (0%)			8 (21%)	39

*Measured on admission, while n=39 was measured on admission and dismissal variables, therefore there is adifference of 5.

Table 8: Logistic regressions per separate indicator

Supplemental file 8.a. Appropriateness indicators[a]

	QI1 (Physiotherapy)		QI2 (Comfort medication)[a]		QI3 (WHO Steps)[b]		QI4 (Follow-up Visits)[b]		QI5 (General physician)[a]		QI6 (Continuous care)[a]	
	Adj. OR (95% CI)	Unadj. OR (95% CI).	Adj. OR (95% CI)	Unadj.OR (95% CI).	N/A	N/A	N/A	N/A	Adj. OR (95% CI)	Unadj. OR (95% CI).	Adj. OR (95% CI)	Unadj .OR (95% CI).
Age												
1-9 (vs. 10-17)	1.24 (0.57-2.70)	1.61 (0.79-3.30)	1.05 (0.32-3.47)	1.01 (0.31-3.35)					1.47 (0.57-3.79)	1.50 (0.61-3.65)	1.54 (0.74-3.21)	1.60 (0.81-3.13)
Sex												
Male (vs.female)	1.37 (0.62-2.99)	1.41 (0.70-2.86)	0.43 (0.13-1.45)	0.35 (0.10-1.30)					0.63 (0.24-1.62)	0.62 (0.26-1.50)	1.32 (0.63-2.76)	1.08 (0.55-2.10)
Disease category												
Mental retardation (vs. Brain andspinal cord malforma tions)	2.29 (0.17-31.32)	1.71 (0.13-22.50)	0.31 (0.02-5.47)	0.33 (0.02-5.41)					2.30 (0.19-27.62)	2.76 (0.24-31.82)	0.95 (0.07-13.53)	0.89 (0.06-12.25)
CNS degeneration and diseases (vs. Brainand spinal cord malformations)	1.29 (0.29-5.67)	1.00 (0.24-4.13)	1.39 (0.15-12.76)	1.80 (0.20-16.47)					9.47 (1.88-47.78)	7.75 (1.64-36.71)	2.13 (0.47-9.80)	1.73 (0.39-7.76)
Infantile cerebral palsy (vs. Brainand spinal cord malforma tions)	1.00 (0.22-4.61)	0.94 (0.22-3.94)	0.62 (0.08-5.04)	0.81 (0.10-6.33)					5.69 (1.20-26.98)	5.26 (1.16-23.92)	1.92 (0.41-9.11)	1.63 (0.36-7.48)
Other disordersof CNS (vs. Brainand spinal cord malformations)	1.62 (0.38-7.01)	1.41 (0.35-5.63)	1.87 (0.21-16.59)	2.49 (0.28-22.51)					8.91 (1.93-41.07)	8.70 (1.96-38.58)	3.43 (0.78-15.06)	3.05 (0.72-13.00)
Muscular dystrophies and myopathies (vs. Brainand spinal cord malformations)	1.17 (0.21-6.72)	0.91 (0.17-4.81)	0.63 (0.05-8.69)	1.19 (0.10-14.60)					3.41 (0.55-21.05)	3.55 (0.63-19.94)	5.71 (0.94-34.52)	4.27 (0.75-24.18)
Moveme nt diseases (vs. Brainand spinal cord malforma tions)	1.83 (0.12-26.99)	1.71 (0.13-22.50)	1.49 (0.04-64.17)	1.29 (0.03-53.23)					9.27 (0.30-289.04)	10.64 (0.33-343.62)	8.77 (0.61-126.47)	8.00 (0.58-110.27)
Nationality												
Other (vs. Belgian)	4.38 (1.23-15.68)	2.94 (0.96-9.05)	1.01 (0.16-6.53)	1.22 (0.19-7.83)					2.84 (0.77-10.50)	2.21 (0.64-7.61)	3.72 (0.94-14.71)	3.39 (0.90-12.72)
Having siblings												
No (vs.yes)	0.20 (0.06-0.68)	0.25 (0.08-0.77)	1.68 (0.44-6.37)	2.44 (0.69-8.60)					1.41 (0.46-4.34)	1.38 (0.50-3.82)	0.89 (0.36-2.23)	0.86 (0.38-1.95)
Year of death												
2010-2014 (vs. 2015-2017)	1.22 (0.51-2.93)	1.03 (0.46-2.31)	6.53 (0.53-80.92)	8.74 (0.48-158.38)					0.79 (0.27-2.28)	0.97 (0.36-2.63)	1.18 (0.51-2.71)	1.19 (0.55-2.57)

[a] Penalized logistic regression was performed due to low counts in the contingency table, [b] Due to low total and cell counts for these indicators, no logistic regression was performed

Supplemental file 8.a. Appropriateness indicators (Continued)

	QI7 (Clinicalcare) [a]		QI8 (Palliativecare) [a]		QI9 (Multidisciplinary care) [a]		QI10 (Specialist physicians) [a]		QI11 (Palliative status)	
	Adj. OR (95% CI)	Unadj. OR (95% CI).	Adj. OR (95% CI)	Unadj.OR (95% CI).	Adj. OR (95% CI)	Unadj. OR (95% CI).	Adj. OR (95% CI)	Unadj. OR (95% CI).	Adj. OR (95% CI)	Unadj .OR (95% CI).
Age										
1-9 (vs. 10-17)	1.67 (0.72-3.85)	1.67 (0.77-3.63)	1.28 (0.49-3.35)	1.31 (0.51-3.38)	1.07 (0.32-3.65)	1.26 (0.36-4.43)	1.80 (0.79-4.11)	1.80 (0.83-3.89)	1.59 (0.58-4.39)	1.77 (0.64-4.91)
Sex										
Male (vs.female)	0.96 (0.41-2.24)	0.81 (0.37-1.76)	0.95 (0.36-2.47)	0.92 (0.36-2.34)	0.88 (0.24-3.16)	1.38 (0.39-4.86)	0.81 (0.35-1.87)	0.76 (0.35-1.63)	0.64 (0.23-1.79)	0.72 (0.27-1.92)
Disease category										
Mental retardation (vs. Brain andspinal cord malforma tions)	0.92 (0.02-38.14)	0.78 (0.02-32.20)	0.76 (0.06-9.55)	0.96 (0.08-11.74)	0.11 (0.01-4.01)	0.10 (0.01-3.90)	0.86 (0.02-36.11)	0.78 (0.02-32.20)	0.76 (0.0 6-9.81)	0.96 (0.08-11.74)
CNS degeneration and diseases (vs. Brainand spinal cord malformations)	2.74 (0.38-19.51)	2.33 (0.33-16.45)	3.04 (0.57-16.25)	2.70 (0.52-13.98)	1.55 (0.06-40.58)	0.94 (0.03-28.01)	3.54 (0.51-24.70)	3.13 (0.45-21.62)	4.63 (0.78-27.44)	3.59 (0.64-20.00)
Infantile cerebral palsy (vs. Brainand spinal cord malforma tions)	2.02 (0.27-15.04)	1.94 (0.26-14.21)	1.76 (0.35-8.75)	1.49 (0.31-7.17)	0.61 (0.03-13.54)	0.48 (0.02-12.18)	1.58 (0.21-12.01)	1.57 (0.21-11.84)	1.68 (0.3 3-8.44)	1.49 (0.31-7.17)
Other disordersof CNS (vs. Brainand spinal cord malformations)	2.52 (0.37-17.20)	2.61 (0.39-17.53)	4.16 (0.79-21.92)	3.80 (0.74-19.39)	0.72 (0.04-14.97)	0.53 (0.02-12.39)	2.33 (0.34-15.83)	2.61 (0.39-17.53)	5.24 (0.92-29.85)	5.00 (0.91-27.49)
Muscular dystrophies and myopathies (vs. Brainand spinal cord malformations)	3.23 (0.36-29.25)	3.32 (0.39-27.97)	2.18 (0.30-15.97)	1.89 (0.28-12.98)	0.17 (0.01-3.70)	0.13 (0.01-3.24)	3.09 (0.35-27.54)	3.32 (0.39-27.97)	2.02 (0.27-15.02)	1.89 (0.28-12.98)
Moveme nt diseases (vs. Brainand spinal cord malforma tions)	19.0 (1.14-314.70)	16.34 (1.01-265.26)	3.49 (0.11-114.58)	3.71 (0.11-124.68)	0.37 (0.01-25.45)	0.39 (0.01-32.08)	17.48 (1.06-288.99)	16.34 (1.01-265.23)	2.91 (0.09-93.34)	3.71 (0.11-124.67)
Nationality										
Other (vs. Belgian)	3.20 (0.55-18.69)	3.26 (0.54-19.55)	1.93 (0.48-7.71)	1.89 (0.50-7.20)	6.40 (1.39-29.46)	4.81 (1.14-20.36)	1.95 (0.44-8.63)	1.81 (0.42-7.80)	2.76 (0.67-11.34)	2.17 (0.56-8.36)
Having siblings										
No (vs.yes)	0.91 (0.32-2.56)	0.99 (0.38-2.54)	1.99 (0.66-6.03)	1.84 (0.65-5.22)	0.42 (0.07-2.62)	0.56 (0.09-3.40)	0.78 (0.29-2.14)	0.83 (0.33-2.08)	1.24 (0.37-4.22)	1.17 (0.37-3.75)
Year of death										
2010-2014 (vs. 2015-2017)	2.33 (0.96-5.66)	2.33 (1.01-5.36)	0.62 (0.21-1.79)	0.73 (0.26-2.03)	0.78 (0.20-3.04)	0.71 (0.19-2.74)	1.88 (0.78-4.56)	1.85 (0.80-4.25)	0.51 (0.17-1.54)	0.61 (0.22-1.75)

[a] Penalized logistic regression was performed due to low counts in the contingency table, [b] Due to low total and cell counts for these indicators, no logistic regression was performed

Supplemental file 8.a. Appropriateness indicatorsa (Continued)

	QI12 (Increased child benefits)	
	Adj. OR (95% CI)	Unadj. OR (95% CI).
Age		
1-9 (vs. 10-17)	0.85 (0.27-2.69)	0.70 (0.21-2.32)
Sex		
Male (vs.female)	1.06 (0.34-3.33)	0.77 (2.55)
Disease category		
Mental retardation (vs. Brain andspinal cord malforma tions)	0.55 (0.04-7.45)	0.61 (0.05-8.16)
CNS degeneration and diseases (vs. Brainand spinal cord malformations)	4.23 (0.52-34.79)	5.70 (0.63-51.90)
Infantile cerebral palsy (vs. Brainand spinal cord malforma tions)	1.42 (0.24-8.44)	1.49 (0.25-8.81)
Other disordersof CNS (vs. Brainand spinal cord malformations)	3.01 (0.49-18.66)	3.20 (0.52-19.83)
Muscular dystrophies and myopathies (vs. Brainand spinal cord malformations)	5.74 (0.25-132.44)	7.16 (0.27-187.09
Moveme nt diseases (vs. Brainand spinal cord malforma tions)	2.73 (0.08-96.78)	2.37 (0.07-84.63)
Nationality		
Other (vs. Belgian)	0.39 (0.03-5.54)	0.34 (0.02-6.77)
Having siblings		
No (vs.yes)	2.30 (0.63-8.40)	2.44 (0.69-8.60)
Year of death		
2010-2014 (vs. 2015-2017)	1.04 (0.26-4.22)	1.33 (0.31-5.77)

[a] Penalized logistic regression was performed due to low counts in the contingency table, [b] Due to low total and cell counts for these indicators, no logistic regression was performed

Supplemental file 8.b. Inappropriateness indicators (Continued)

	QI13 (Daily diagnostics) [b]		QI14 (General diagnostics)		QI15 (Dialysis) b		QI16 (Nauseau prescriptions) b		QI17 (Surgeries)[a]	
	N/A	N/A	Adj. OR (95% CI)	Unadj.OR (95% CI).	N/A	N/A	N/A	N/A	Adj. OR (95% CI)	Unadj .OR (95% CI).
Age										
1-9 (vs. 10-17)			1.24 (0.54-2.83)	1,48 (0,68-3.21)					1.69 (0.27-10.78)	2.60 (0.10-66.47)
Sex										
Male (vs.female)			0.88 (0.39-2.01)	0.78 (0.37-1.67)					0.32 (0.05-2.12)	0.31 (0.01-7.81)
Disease category										
Mental retardation (vs. Brain andspinal cord malformations)			3.31 (0.25-44.08)	2.50 (0.19-32.19)					0.46 (0.01-30.66)	0.39 (0.01-32.07)
CNS degeneration and diseases (vs. Brainand spinal cord malformations)			1.79 (0.43-7.54)	1.67 (0.42-6.70)					3.01 (0.09-104.02)	2.91 (0.05-175.12)
Infantile cerebral palsy (vs. Brainand spinal cord malformations)			2.94 (0.63-13.73)	3.19 (0.72-14.15)					0.61 (0.03-12.28)	0.83 (0.03-24.66)
Other disordersof CNS (vs. Brainand spinal cord malformations)			3.17 (0.75-13.40)	3.33 (0.83-13.43)					2.95 (0.09-93.03)	3.96 (0.07-235.14)
Muscular dystrophies and myopathies (vs. Brainand spinal cord malformations)			2.54 (0.40-15.95)	2.78 (0.48-16.03)					0.71 (0.02-29.76)	1.17 (0.02-75.40)
Moveme nt diseases (vs. Brainand spinal cord malformations)			2.71 (0.20-36.86)	2.50 (0.19-32.19)					0.33 (0.01-19.79)	0.39 (0.01-32.07)
Nationality										
Other (vs. Belgian)			1.37 (0.37-5.07)	1.16 (0.34-3.97)					2.66 (0.23-31.04)	2.86 (0.10-80.43)
Having siblings										
No (vs.yes)			0.37 (0.11-1.23)	0.39 (0.13-1.21)					0.66 (0.07-6.70)	1.24 (0.05-32.60)
Year of death										
2010-2014 (vs. 2015-2017)			2.10 (0.76-5.85)	1.96 (0.74-5.20)					1.20 (0.13-11.55)	1.03 (0.04-26.84)

[a] Penalized logistic regression was performed due to low counts in the contingency table, [b] Due to low total and cell counts for these indicators, no logistic regression was performed

Supplemental file 8.b. Inappropriateness indicators (Continued)

	QI18 (New antidepressants) [b]		**QI19 (Drawing blood)**		**QI20 (Late palliative care)** [a]		**QI21 (ICU admissions)**		**QI22 (Care setting transfers)** [a]	
	N/A	N/A.	Adj. OR (95% CI)	Unadj.OR (95% CI).	Adj. OR (95% CI)	Unadj. OR (95% CI).	Adj. OR (95% CI)	Unadj. OR (95% CI).	Adj. OR (95% CI)	Unadj .OR (95% CI).
Age										
1-9 (vs. 10-17)			1.28 (0.61-2.66)	1.60 (0.82-3.15)	1.27 (0.30-5.44)	1.21 (0.23-6.41)	1.73 (0.77-3.88)	1.96 (0.90-4.26)	2.17 (0.32-14.87)	2.60 (0.10-66.47)
Sex										
Male (vs.female)			1.18 (0.56-2.48)	1.17 (0.60-2.29)	2.60 (0.52-13.14)	2.91 (0.44-19.32)	1.22 (0.55-2.72)	1.21 (0.57-2.56)	2.25 (0.33-15.49)	2.83 (0.11-72.43)
Disease category										
Mental retardation (vs. Brain andspinal cord malformations)			0.79 (0.06-10.81)	0.58 (0.04-7.66)	0.28 (0.02-4.84)	0.33 (0.02-5.41)	1.24 (0.09-17.70)	1.13 (0.08-15.51)	0.11 (0.00-3.43)	0.10 (0.00-3.90)
CNS degeneration and diseases (vs. Brainand spinal cord malformations)			2.67 (0.62-11.52)	2.10 (0.51-8.57)	9.42 (0.47-188.85)	9.57 (0.37-272.99)	0.80 (0.17-3.74)	0.75 (0.17-3.40)	3.15 (0.11-91.06)	2.91 (0.05-175.12)
Infantile cerebral palsy (vs. Brainand spinal cord malformations)			1.98 (0.45-8.79)	1.88 (0.45-7.82)	3.51 (0.33-37.04)	2.71 (0.24-31.32)	1.03 (0.21-5.10)	0.98 (0.21-4.67)	4.06 (0.12-139.20)	2.57 (0.04-155.13)
Other disorders of CNS (vs. Brainand spinal cord malformations)			3.53 (0.84-14.77)	3.17 (0.81-12.50)	5.05 (0.47-54.09)	4.24 (0.37-48.08)	1.24 (0.27-5.78)	1.31 (0.29-5.89)	4.28 (0.14-133.82)	3.96 (0.07-235.14)
Muscular dystrophies and myopathies (vs. Brainand spinal cord malformations)			1.78 (0.32-9.99)	1.50 (0.29-7.75)	2.25 (0.18-28.78)	1.19 (0.10-14.60)	1.02 (0.16-6.47)	0.84 (0.41-4.97)	2.13 (0.06-81.57)	1.17 (0.02-75.40)
Movement diseases (vs. Brainand spinal cord malformations)			5.99 (0.42-85.34)	5.25 (0.40-68.95)	1.34 (0.04-51.44)	1.29 (0.03-53.23)	1.14 (0.08-16.78)	1.13 (0.08-15.51)	0.55 (0.01-32.84)	0.39 (0.01-32.08)
Nationality										
Other (vs. Belgian)			3.37 (0.98-11.62)	2.37 (0.75-7.47)	0.89 (0.06-13.37)	0.76 (0.04-15.82)	1.13 (0.32-4.06)	1.07 (0.32-3.64)	3.18 (0.25-39.74)	2.86 (0.10-80.43)
Having siblings										
No (vs.yes)			0.34 (0.12-0.91)	0.38 (0.16-0.93)	2.73 (0.47-15.99)	1.25 (0.18-8.50)	0.57 (0.19-1.70)	0.49 (0.17-1.38)	2.57 (0.30-22.26)	1.24 (0.05-32.60)
Year of death										
2010-2014 (vs. 2015-2017)			1.55 (0.67-3.61)	1.34 (0.61-2.91)	0.41 (0.08-2.01)	0.46 (0.09-2.50)	1.01 (0.42-2.48)	0.92 (0.39-2.16)	0.69 (0.08-6.29)	1.03 (0.04-26.84)

[a] Penalized logistic regression was performed due to low counts in the contingency table, [b] Due to low total and cell counts for these indicators, no logistic regression was performed

CHAPTER 4

Population-level analysis of the appropriateness of end-of-life care in children with cancer

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To be submitted

ABSTRACT

Background Children who die with cancer might receive suboptimal treatment such as for pain and anxiety resulting in unrelieved symptoms. This study aimed to measure potential (in-)appropriateness of end-of-life care for children who died with cancer.

Methods We conducted a decedent cohort study of all children (1-17) who died with cancer in Belgium between 2010 and 2017, using validated quality indicators. Data from 7 routinely collected population-level databases were linked to measure 20 quality indicators. Children dying with cancer were identified using cause of death as registered on the death certificate. We investigated relationships between in-/appropriateness of care and clinical, sociodemographic and regional factors.

Results Of the 228 children who died with cancer between 2010 and 2017, 53% had continuous care relationships (having reimbursements for the same physician in the last month before death as in the 11 months before), and 14% received reimbursed palliative care in the last 2 years before death. Indicators of inappropriateness of care show that: 31% of the children underwent 2 or more MRIs, CT scans, or X-rays in the last month before death; 45% underwent blood drawings in the last 2 weeks before death; and 18% were admitted to the Intensive Care Unit during the last 2 weeks before death. Appropriateness of end-of-life care differed by province and nationality (children with non-Belgian background received more inappropriate care).

Conclusion Findings suggest improvements are possible in terms of palliative, comfort and multidisciplinary care,care provider contact aside from the , and diagnostics.

INTRODUCTION

While medical treatments are advancing, one third to half of European children who die with complex chronic conditions, do so with cancer (1). Burdensome symptoms can occur for children in the last phase of life, with end-of-life care whose benefits might not exceed disadvantages (2–8). Providing care at the end of life for children dyingwith cancer poses considerable challenges, such as knowing what comfort medication and treatments to use to relieve symptoms (2,3). In adults' end-of-life care research, population-level quality evaluations have previously been performed to measure potentially appropriate and inappropriate medications and treatment at the end of life (9,10). In children, to our knowledge no population-level evaluation of end-of-life cancer has been done for various themes with indicators validated for the data.

Routinely collected population healthcare data can be used as an efficient strategy for the assessment of potential appropriateness of care, which can be defined as care in which the expected health benefit exceeds possible negative outcomes (11). We previously developed and validated a set of quality indicators using a modified RAND/UCLA method, to measure the appropriateness of end-of-life care for children with cancer on a population level using administrative healthcare claims data (11). No population-level quality measures for children's end-of-life care were developed until recently (11–13), and population-level measurement of face-validated indicators is lacking for children with cancer. Additional analyses for clinical and socio- demographic factors can provide more insight into differences for appropriateness of end-of- life care – for example, for age groups – in order to know if quality improvement initiatives should target different sub-populations.

Therefore, the aim of this study was to evaluate the end-of-life care for children dying with cancer. Specific research questions are: 1. What is the quality of end-of-life care on a population level for children who died with cancer using quality indicators for potentially appropriate and inappropriate care? 2. What socio-demographic, clinical and regional factors (age, sex, nationality, having siblings, year of death, disease category, province) are associated with increased or decreased appropriate and inappropriate end-of-life care?

METHODS

Study design

We conducted a population-level decedent cohort study of all insured children who died with cancer in Belgium between 2010 and 2017. Health insurance is mandatory in Belgium, and therefore our data is expected to include almost all children who died with cancer (See Appendix 4 for information on reliability and variability of database population).

Data sources

7 Belgian routinely collected clinical and/or administrative databases were linked. See Supplemental information 2 for details on the databases used. Access was provided with 2-factor authentication. Linking was done by executive researcher V.P.

Population

We selected insured children from 1 to 17 years old who died with cancer in Belgium, with a registered death within the years 2010 to 2017. Selection was done using the causes of death from death certificate data. To select the disease group, we used ICD-10 codes C00–C97, D01-D09, D37-D49 and D3A.0 and Q85.0, as defined in the complex chronic conditions framework (14). Dying with cancer is defined as having cancer as at least one of the 7 registered causes of death (one immediate cause, two intermediate causes, one underlying cause, three associated causes) as registered on the death certificate. A sensitivity analysis was added with a different selection method, namely having a clinical cancer diagnosis as well as cancer as one of the causes of death.

Quality indicators

The development and the final set of quality indicators have been published previously (11). We measured 10 indicators for potentially appropriate end-of-life care, and 9 indicators for potentially inappropriate end-of-life care. See Table 1 for an overview of indicators.

Table 1. Measurement per indicator.[a]

Potentially appropriate end-of-life care		
Indicator	Measurement (number of children that died of cancer for who*)	Timing
1. Physiotherapy	*physiotherapy was prescribed in the last 30, 14, 7, or 2 days before death	30, 14, 7, 2 days before death
2. (Off-label) Comfort medication	*there were prescriptions for hyoscine butylbromide, dexmedetomidine, fentanyl, gabapentin, ketamine, ketorolac, lidocaine, midazolam, ondansetron, or scopolamine in the last 30, 14, 7, or 2 days before death	30, 14, 7, 2 days before death

3. Pain control according to World Health Organization steps	*there were prescriptions from the third World Health Organization step, i.e. morphine, fentanyl, methadone, oxycodone, or hydromorphone, and these were preceded, in the last 2 years before death, by prescriptions from the first World Health Organization step, i.e. paracetamol, non-steroidal anti-inflammatory drugs or aspirin, and from the second World Health Organization step, i.e. codeine, tramadol, or buprenorphine	2 years before death (first or second step); 3 months before death (third step)
4. Home death	*there was a home death	N/A
5. Follow-up by hospital	At least 1 consultation in a hospital, or with a specialist physician after palliative status	From the start of the official palliativestatus onwards
6. Contact with family physician[b]	*there were at least 3 house visits of, prescriptions of, or consultations with a general physician in the last 30 days before death	30 days before death
7. Continuous care relationships	*there was at least 1 prescription, visit, consultation, or treatment from the same physician (general or specialist) in the last 30 days before death, as in the last year before death	30 days before death
8. Palliative care at home[c]	*there was at least 1 visit of a mobile palliative home care team within the last 2 years before death	2 years before death
9. Multidisciplinary care[b]	*there was a total of 5 or more prescriptions, treatments, visits, or advices, from 2 or more of the following care providers: general physicians, pediatricians, specialist physicians or paramedics in the last 30 days before death	30 days before death
10. Palliative status	* who received a palliative status (i.e. a supportive financial measure to facilitate palliative home care)	2 years before death
Potentially inappropriate end-of-life care		
Indicator	Measurement	Timing
11. Excessive magnetic resonance imaging monitoring	*received 2 or more magnetic resonance imaging scans in the last 30, 14, 7, or 2 days before death (per day)	30, 14, 7, 2 days before death
12. Diagnostics and monitoring	*received more than 1 magnetic resonance imaging scan in the last 30, 14, 7, or 2 days before death (for the whole period)	30, 14, 7, 2 days before death

13. Gastrostomy placement	*a gastrostomy was placed in the last 30, 14, 7, or 2 days before death	30, 14, 7, 2 days before death
14. Starting dialysis	* a first dialysis was started in the last 30, 14, 7, or 2 days before death or from receiving palliative status onwards	30, 14, 7, 2 days before death or fromreceiving palliative status onwards
15. Installing port-a-cath	*a port-a-cath was installed in the last 14, 7, or 2 days before death	14, 7, 2 days before death
16. Surgeries	*a surgery was performed in the last 14, 7, or 2 days before death	14, 7, 2 days before death
17. Drawing blood	*there was at least 1 blood drawing in the last 7 or 2 days before death	7, 2 days before death
18. Hospital transfers	*there were 1 or more hospital transfers in the last 30, 14, 7, or 2 days before death	30, 14, 7, 2 days before death
19. Intensive Care Unit admissions[c]	*there was at least 1 Emergency Room visit in the last 14, 7, or 2 days before death	14, 7, 2 days before death

[a] Two indicators (multidisciplinary oncological consult and professional care provision) from the set of validated indicators as published in a previous article,[10] were not included as the measurements were suspected to not be reliable; [b] Name of the indicator, as published in a previous article,[10] was altered to clarify the concept; [c] Name of the indicator, as published in a previous article,[10] was changed as a slightly different concept was measured

Statistical analysis

We used descriptive statistics to describe the characteristics of children who died with cancer and to measure the quality indicators. We combined all years to obtain a sufficiently large sample. To identify associated clinical, socio-demographic and regional factors (age, sex, nationality, having siblings, year of death, disease category, province), we performed analysesof variance on scales for appropriateness and inappropriateness. We performed logistic regressions per indicator (See Supplemental Materials 7). We combined different indicators into Principal Component Analysis (PCA) scales (See Supplemental Materials 8). A PCA was performed distinguishing appropriateness from inappropriateness of care with restriction for 1 factor, and items with a ow component loading (below 0.50) were removed from the scale. We performed multivariable analysis of variance with post hoc tests to identify which clinical, socio- demographic and regional factors were associated with the factor scores for the scales. Clinical, socio-demographic and regional factors were: age, sex, cancer site, nationality, having siblings, year of death and province. The set of possible factors was identified based on factors identified in previous studies and own assumptions (15).Two original indicators – Multidisciplinary oncological consult and Professional care provision – were left out of the sets, as different experts deemed it impossible post-hoc to measure them in a valid manner (multidisciplinary consult) or different experts deemed that they included care that was measured in other indicators (professional care provision).

Additional sensitivity analysis (repetition of the same analyses with another cause of death selection) was performed for diagnosis compared to cause of death selection via death certificates (See Supplemental materials 6). The variable of diagnosis differs in that it is collected via clinical and pathology routes, whereas cause of death is collected via death certificates.

Analyses were conducted with SAS Enterprise Guide, version 7.1 and StataSE, version 17.

Ethics

All data were linked in a secure, ethically responsible manner, guaranteeing anonymity of thedeceased. The study was approved by the International Safety Committee (Reference number 20/226, October 6 2020).

RESULTS

Population characteristics

Our cohort selection identified 228 children aged 1 to 17 who died with cancer in Belgium between 2010 and 2017 (Figure 1). See Table 2 for socio-demographic and clinical characteristics. Most children were male (61%), aged 1-5 (37%), and of Belgian nationality (91%). Most common underlying cause of death was malignant neoplasms of eye, brain andother parts of central nervous system (31%).

Table 2. Characteristics of all children who died with* cancer in Belgium, 2010-2017[a]

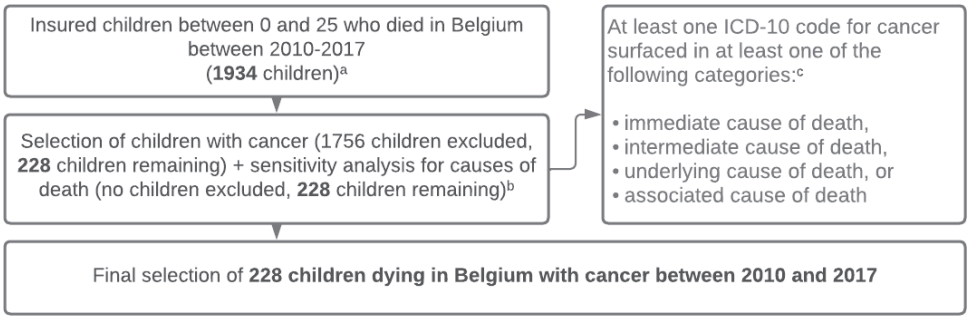
	Number (percentage)
All	228 (100%)
Sex of the child	
Male	139 (61%)
Female	89 (39%)
Age range of the child at the time of death	
1-5	84 (37%)
>5-9	36 (16%)
>9-15	55 (24%)
>15-17	53 (23%)
Nationality of the child	

Belgian	207 (91%)
Other	21 (10%)
Type of household in which the child lived	
Two-parent household	173 (76%)
Single-parent or other household	55 (24%)
Comfort of the house in which the child lived	
High	71 (31%)
Average	25 (11%)
Low	24 (11%)
Trailer, none, not known	13 (6%)
Missing[b]	95 (42%)
Highest level of education of the child's parents[c]	
Postsecondary	98 (43%)
High school	69 (30%)
Junior high school	30 (13%)
Primary school	9 (4%)
No diploma	<5 (<2%)[d]
Not known	<5 (<2%)[d]
Missing	16 (7%)
Urbanicity of municipality of residence of the child's family[e]	
Very high	71 (31%)
High	55 (24%)
Average	72 (32%)
Low	29 (13%)
Missing	<5 (<2%)[d]
Net annual taxable income of the child's family[c]	
High (decile 1-3)	75 (33%)
Average (decile 4-6)	60 (26%)
Low (decile 7-10)	68 (30%)
Missing[b]	25 (11%)
Underlying cause of death of the child according to general ICD-10 category	
Malignant neoplasms (C00-C75)	
Malignant neoplasms of digestive organs (C15-C26)	14 (6%)
Malignant neoplasms of respiratory and intrathoracic organs (C30-C39)	6 (3%)
Malignant neoplasms of bone and articular cartilage (C40-C41)	17 (8%)

Melanoma and other malignant neoplasms of skin, mesothelial and soft tissue (C43-C49)	14 (6%)
Malignant neoplasm of breast, genital organs or urinary tract (C50-C68)	13 (6%)
Malignant neoplasms of eye, brain and other parts of central nervous system (C69-C72)	70 (31%)
Malignant neoplasms of thyroid and other endocrine glands (C73-C75)	<5 (<2%)[d]
Malignant neoplasm of other and ill-defined sites (C76-C80)	6 (3%)
Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue (C81-C96)	65 (29%)
Neoplasms of uncertain or unknown behaviour (D37-D48)	14 (6%)
Other	<5 (<2%)[c]

* Dying with cancer indicates that cancer was at least one of the seven causes of death as registered in the death certificate; [a] Percentages were rounded, therefore could amount to more than 100% or to 99%; Population is expected to contain practically all insured children yet there could be children left out as validation measures showed differing numbers for deaths within other databases and certain unique ids within database could not be matched; [b] Large amount of missing results from the census basis of this variable; [c]Highest level of education/income of both parents was selected for each child; [d]Due to privacy regulations, small cells (smaller than n=5) could not bereported; [e]Based on the Eurostat degree-of-urbanization method

Figure 1. Flow chart illustrating cohort selection



[a] Selection was started from the population database of the Intermutualistic Agency Database, as the deaths recorded in this database result from national death certificates, which were seen as the most reliable source. Variations in number of deaths were present over all databases, due to differing age and death definitions and selection by the different governmental agencies preparing the data.
[b] We conducted sensitivity analyses for causes of death, to ensure that no underlying cause of death was due to an injury, such as e.g. a car accident, as this kind of death would cause differing end-of-life care and therefore bias the results
[c] ICD-10-codes as defined in Feudtner (2014): C00-C96, D01-D09, D3A.0, D37-D49, Q85.0

Potentially appropriate care at the end of life

Table 3 shows results for indicators for appropriateness of end-of-life care for all time periods.

36% of the children had reimbursed physiotherapy prescriptions in the last month before

death.6% of the children had reimbursed prescriptions for off-label comfort medication in the last month before death. 47% of the children died at home, while less than 2% of the 26 children received follow-up visits after palliative registration (having consultations with a hospital specialist after palliative status). 13% of the children had contact with a family physician in the last month before death. 53% of the children had continuous care relationships (having reimbursements from the same physician in the last month before death as in the 11 months before). 14% of the children received reimbursed palliative care and 11% of the children were registered as being palliative ('palliative status', receiving palliative status, an administrative registration that the child is palliative) in the last 2 years before death. 4% of the children received multidisciplinary care in the last month before death (having 5 or more reimbursements from at least 2 types of clinicians or paramedics

Table 3a: Indicators for potentially appropriate end-of-life care for children who died with cancer in Belgium, 2010-2017[a]

Indicators for potentially appropriate end-of-life care								
	Number of days before death							
Indicator	2	7	14	30	90	From palliative status onwards	730 (full period available)	Denominator (n)
Treatment, medication, and monitoring								
Prescriptions of physiotherapy	37 (16%)	62 (27%)	72 (32%)	82 (36%)			119 (52%)	/228
Specialized prescription of comfort medication	<5 (<2%)	<5 (<2%)	8 (4%)	13 (6%)			26 (11%)	/228
Pain control according toWHO steps					9 (50%)			/18*
Place of care and death								
Home death							106 (47%)	/228
Follow-up visits at the hospital						0 (0%)		/26*
Care services and providers								

Contact with family physician				30 (13%)			150 (66%)	/228
Continuous care relationships				120 (53%)				/228
Palliative care team							31 (14%)	/228
Multidisciplinary care				10 (4%)			95 (42%)	/228
Administrative measures								
Palliative status							26 (11%)	/228

[a] Hatched cells indicate that the indicator was not face-validated for this time period. Due to privacy regulations, small cells (smaller than 5) could not be reported; *Indicator that was measured on a subsetof children, not the full population (See also Appendix 3)

Potentially inappropriate care at the end of life

Table 4 shows results forindicators for inappropriateness of end-of-life care for all time periods. Fewer than 2% of thechildren received gastrostomy placement, started dialysis, port-a-cath installation, or receivedexcessive magnetic resonance imaging monitoring scans in the last month before death orprior. 31% of the children underwent diagnostics and monitoring (receiving more than 2 MRIs,CTs, or X-rays) in the last month before death. 45% of the children received blood drawingsin the last week before death, and 40% in the last 2 days before death. 4% of the children hadreimbursed surgeries in the last 2 weeks before death. 6% of the children had transfers to a different hospital in the last month before death. Emergency room admissions occurred in thelast 2 weeks before death for 18% of the children.

Sensitivity analyses, selecting a population that had cancer as a cause of death and as a diagnosis at least 30 days before death (n=200), showed minor differences with the main analysis in terms of indicator results, but did show differences for the amount of children that had died (See Supplemental Information 7).

Table 3b: Indicators for potentially inappropriate end-of-life care for children who died with cancer in Belgium, 2010-2017[a]

Indicators for potentially inappropriate end-of-life care								
	Number of days before death							
Indicator	2	7	14	30	120	From palliative status onwards	730 (full period available)	Denominator (n)

Treatment, medication, and monitoring								
Excessive magnetic resonance imaging monitoring	<5 (<2%)	<5 (<2%)	<5 (<2%)	<5 (<2%)			<5 (<2%)	/228
Diagnostics and monitoring	59 (26%)	62 (27%)	68 (30%)	71 (31%)			132 (58%)	/228
Gastrostomy placement	<5 (<2%)	<5 (<2%)	<5 (<2%)	<5 (<2%)			15 (7%)	/228
Starting dialysis	<5 (<2%)	<5 (<2%)	<5 (<2%)			<5 (<2%)	11 (6%)	/228 /26*
Installing port-a-caths	<5 (<2%)	<5 (<2%)	<5 (<2%)				11 (6%)	/228
Surgeries	5 (2%)	7 (3%)	8 (4%)				33 (15%)	/228
Drawing blood	90 (40%)	102 (45%)					171 (75%)	/228
Place of care and death								
Hospital transfers	<5 (<2%)	7 (3%)	10 (4%)	13 (6%)			66 (29%)	/228
Intensive Care Unit admissions	24 (11%)	37 (16%)	42 (18%)				72 (32%)	/228

[a] Hatched cells indicate that the indicator was not face-validated for this time period. Due to privacy regulations, small cells (smaller than 5) could not be reported; *Indicator that was measured on a subset of children, not the full population (See also Appendix 3)

Clinical, socio-demographic and regional factors

Analyses of variance showed that children with non-Belgian nationality received more potentially inappropriate care significantly more often compared to those with Belgian nationality. One Flemish region showed significantly higher potential appropriateness of care compared to other regions. There were no significant differences between age, sex, cancer type, having siblings, province or year of death for scale scores of (in)appropriateness of care. See Table 4for results of analyses of variance.

Table 4: Analysis of variance for scale scores of appropriate and inappropriate end-of-life care for clinical, socio-demographic and regional factors

Analysis of variance for estimated factor scores for all clinical, sociodemographic and regional factors				
	Scale 1: Potentially appropriate care		Scale 2: Potentially inappropriate care	
	Estimate	P value[a]	Estimate	P value[a]
Age				

1-9 (vs. 10-17)	-.18	0.200	-.22	0.106
Sex				
Male (vs. female)	-.08	0.547	-.16	0.219
Disease category				
Malignant neoplasms of respiratory and intrathoracic organs (vs. Malignant neoplasms of digestive organs)	-.32	0.576	0.54	0.317
Malignant neoplasms of bone and articular cartilage (vs. Malignant neoplasms of digestive organs)	0.75	0.138	0.14	0.768
Melanoma and other malignant neoplasms of skin, mesothelial and soft tissue (vs. Malignant neoplasms of digestive organs)	-.48	0.195	0.27	0.437
Malignant neoplasm of breast, genital organs or urinary tract (vs. Malignant neoplasms of digestive organs)	-.34	0.376	0.44	0.219
Malignant neoplasms of eye, brain and other parts of central nervous system (vs. Malignant neoplasms of digestive organs)	-.58	0.138	0.60	0.100
Malignant neoplasms of thyroid and other endocrine glands (vs. Malignant neoplasms of digestive organs)	-.14	0.641	0.42	0.133
Malignant neoplasm of other and ill-defined sites (vs. Malignant neoplasms of digestive organs)	-.42	0.415	0.29	0.554
Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue (vs. Malignant neoplasms of digestive organs)	0.10	0.838	0.37	0.421
Neoplasms of uncertain or unknown behaviour (vs. Malignant neoplasms of digestive organs)	0.16	0.591	0.26	0.352
Others (vs. Malignant neoplasms of digestive organs)	-.00	0.987	0.59	0.098
Nationality				
Belgian (vs. Other)	0.33	0.173	-.48	0.038*
Having siblings				
No (vs. yes)	0.11	0.507	0.05	0.722
Year of death				
2015-2017 (vs. 2010-2014)	0.23	0.146	0.09	0.529
Province				
Flemish Brabant (vs. Antwerp)	0.13	0.647	-.24	0.600
Walloon Brabant (vs. Antwerp)	-.45	0.253	-.17	0.377
Brussels (vs. Antwerp)	0.29	0.323	0.10	0.653
East Flanders (vs. Antwerp)	-.11	0.698	-.43	0.730
West Flanders (vs. Antwerp)	0.13	0.591	0.26	0.122
Hainaut (vs. Antwerp)	0.33	0.181	-.006	0.264
Liège (vs. Antwerp)	-.30	0.241	0.46	0.980
Limburg (vs. Antwerp)	0.63	0.021*	0.29	0.053
Luxemburg (vs. Antwerp)	-.21	0.640	-.26	0.260
Namur (vs. Antwerp)	0.31	0.341	0.20	0.532

[a] Alpha level below 0.05

Logistic regressions per separate indicator show differences mainly by cancer types: For instance, children with skin cancer were more likely (than children with malignant neoplasms of digestive organs as a reference category) to, , in the last 30 days of life, have had contact with the family physician. See Supplementary Materials 7 for results of logistic regressions per indicator.

The two formed scales each formed a dimension. Scales had a high internal consistency, namely a standardized Cronbach alpha of 0.83 and 0.80. Factor score estimates were saved per scale. See Supplemental Materials 5 for more details on scale construction.

DISCUSSION

In this population-based retrospective cohort study, we measured 19 quality indicators for potential (in)appropriateness of end-of-life care for children dying with cancer between 2010 and 2017 in Belgium. In the last months, weeks and/or days before death, around half of children received continuous care (i.e. having reimbursements from the same physician in the last month before death as in the 11 months before) , but less than one fifth of children received palliative care, multidisciplinary, or comfort care, or had family physician contacts. In general, few children received potentially inappropriate care, yet drawing blood and diagnostics and monitoring in a third to half of children within the last 2 weeks before death: 45% and 27% respectively. Non-Belgian children received significantly more inappropriate care, and children in one province received significantly more potentially appropriate care.

Potentially inappropriate care was indicated to be low, except for some high-scoring indicators. We found that almost half of the children in Belgium die at home, which is relatively high: According to a 2020 systematic review, for example, proportions of home death for children with cancer vary from 7% to 45% between regions in international studies (17).Measurements for potentially inappropriate care were generally low and seem to align with international population-level findings. While our sample showed 18% of children with cancer had Intensive Care Unit admissions in the last month before death, US and Canadian population-level studies for children and adolescents dying with cancer show a range of 18% to 21.7% of patients admitted to the Intensive Care Unit within the last month before death (6,7,17). Our sample also showed 0% of gastrostomy placement and start of dialysis in the last month before death. A US sample showed 1.0% of patients in the same period before death received gastrostomy placement and 3.4% received hemodialysis (which includes continuation of dialysis where our study only evaluated initiation) (6).

Our study showed there may be a low involvement of specialized palliative and comfort care at the end of life of children in Belgium dying with cancer: 14% received reimbursed support

from palliative care services and 11% received the official palliative care status (entitling them for full reimbursement of home care). This score falls on the low end of the 10%-90% reported range of palliative care initiation in children with cancer found in a systematic review of international studies (18). However, pediatric palliative care in Belgium is partly charity-based, so not all palliative care support may have been recorded in routinely collected data. Pediatric liaison teams in Belgium are structurally funded by the Belgian Federal Government of Health, but also receive substantial funding from non-profit organizations and charities (19,20). Our findings also showed a low physiotherapy and off-label comfort medication provision at the end of life, which may be caused by a lack of involvement from specialized pediatric palliative care providers.

Children with Belgian nationality received less inappropriate care than children with a non-Belgian nationality. While the precise nationality of this group is not provided due to data protection concerns, the majority of this group concerns children with Italian, Turkish and unspecified non-European nationality. This result aligns with previous studies on race disparities in end-of-life care for children with cancer (21,22). While different from our measurement of nationality, findings for race disparities provide some comparison, and qualitative studies suggest responsible mechanisms could be amongst others language barriers and culturally differing expectations of end-of-life care (24).

Children in one province (Limburg) received significantly more appropriate end-of-life care – i.e. more (off-label) comfort medication, palliative care, and palliative status. This could be an indicationof better quality of end-of-life care for certain children in the healthcare system, but non-controlled differences in the population could also be present.

The design of our study best leads to careful interpretation of the indicators, as we did not know the actual end-of-life period of the children within our population. Indicators are measured on the population of children who died, but no distinction can be made within the

databases for children that died acutely (following an unpredictable end-of-life trajectory) and those that died with a predicted death. This means healthcare use with a justifiable curative intent could have been measured with our indicators. There might be seriously ill children who still have high chances for curation even in the last month or days before death, especially due to overall high survival rates in the cancer population. Children with acute lymphoblastic leukemia, for example, have an estimated 5-year survival rate of 90% in high-income countries (91), and death of the child can be acute and occur in a matter of days. If diagnostics would be discouraged overall as a public health measure for this population, some children may suffer from worsened care or increased mortality. It is therefore important to first further investigate the populations and characteristics of children that could still benefit from diagnostics, and those who do not, which is best done by prospective or retrospective designs in which the duration of the end-of-life period is recorded.

Other studies can apply our indicators to provide comparative measurements in other countries. Some indicators showed very low levels in our measurements (follow-up visits at the hospital, excessive magnetic resonance imaging monitoring, gastrostomy placement, starting dialysis, installing port-a-caths), and therefore may need to be removed from the indicator set, as an indicator was defined to best show a result between 5% and 95% (10). Further studies can also measure additional indicators in retrospective or prospective chart or cohort studies – psychosocial care, for example – and take guardian/family and sibling perspectives into account. Findings suggest improvements may be particularly possible in terms of the use of palliative care services, multidisciplinary care, (off-label) comfort medication, family physician contact, diagnostics and monitoring, and blood drawing. Education trajectories may be provided for comfort procedures ((off-label) comfort medication, physiotherapy). Physicians are advised to communicate possibilities to families for financial support measures such as palliative status. Diagnostics and monitoring and drawing blood may be overly aggressive at the end of life. To remedy this and aid in correct timing, pediatric palliative care professionals may use prognostic indicators for a child being at the end of life as defined in previous research, such as progressive decline in disease trajectory or increased

chest infections (24).

A strength of our study is the use of routinely collected data. In Belgium, health insurance is mandatory, and our database therefore includes healthcare use for most children who died in Belgium in the studied period. Our database thus includes children that would normally be difficult to recruit for, or retain within, studies and does not suffer from selection bias. The database also is extensive. Our quality indicator set was face-validated for the data at hand by care professionals from the studied care settings and regions.

A limitation of this study is that our data does not include non-reimbursed or certain relevant clinical variables such as psychologist visits or comorbidities. Only reimbursed medications and treatments are measured: over-the-counter medications and treatments are not included in thenumbers. Procedures provided in the context of clinical trials, frequent in children's cancer care, are not included in claims data. Certain subpopulations that are not insured but still received care, or did not submit documents to their sickness funds for reimbursement, could be absent from the data. Indicators might not capture the full spectrum of a measured concept: for example, multidisciplinary care contains many facets of which only one was measured. Furthermore, there is no recording of indication for the medication or treatment. Big data may be vulnerable to misclassification bias: administrative mistakes may be present and not all databases aligned. Analyses of variance may not be robust due to small sample sizes, and certain factors could not be corrected for, as they were not present in the datasets. Logistic regressions were performed on small cells, furthering careful interpretation.

Conclusion

Our findings suggest possible directions for the improvement of end-of-life care in children with cancer in terms of palliative and comfort care, follow-up by professionals outside the hospital and paramedics, financial support for families, and diagnostics.

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Supplemental information 2: Additional information on databases

Institution	Database	Description
Intermutualistic Agency	Sociodemographic database	Sociodemographic informationfor all individuals with healthcare insurance, which is legally mandatory in Belgium (10)
	Healthcare database	Outpatient and hospital care provided in Belgium, except medication dispensed in pharmacies, with amongst others date, healthcare provider, setting. (10)
	Pharmaceutical database	Reimbursed medication dispensed in pharmacies in Belgium, with amongst others date of prescription, date of delivery, information on prescriber, setting, for every reimbursed medication delivery (10)
StatBel	Death certificate database	Underlying cause of death, as well as associated and intermediate causes of death on all deaths in Belgium, from Belgian death certificates (10)
	Population registry database	Citizens' household composition and highest attained level of education for every Belgian citizen (10)
	Census database	Data from the last census in Belgium in 2012, such as educational level and housing comfort characteristics. (10)
Belgian Cancer Registry (BCR)	Cancer Incidences in Belgium	Population-based cancer registration of all newly diagnosed tumors in Belgium

Supplemental information 3: Validation and reliability verifications for identification of bias

Validity database population
Validity
Our database population was compared to population numbers from Statistics Belgium. Statistics Belgium public documentation identified 6050 deaths for children between 1 and 25 years old. Our database includes 5098 deaths for children between 1 and 25 years old, which is 84% of the number of deaths reported by Statistics Belgium. Differing selections for death, time and age by the governmental agencies providing the data may account for the differing number of deaths between databases. Our database population was also compared to population numbers from the Belgian National Cancer Registry, which uses a different selection method, namely clinical selection such as biopsies. The Belgian National Cancer Registry selection based on diagnosis shows 200 deaths due to cancer in children aged 1 to 17 It is important to note that this number (n=200) results from a linking with cause of death selection, and that the actual selection based on diagnosis might be larger.
In order to verify the reliability of our ID selection, we compared the amount of children deaths between our different databases. Between databases of IMA and Statistics Belgium, there was around a 2% difference in children's deaths. Between the databases of the Belgian Cancer Registry and IMA/Statistics Belgium a larger difference was present of 12% - this likely occurred due to the different selection method (Belgian Cancer Registry uses a clinical selection method). This 12% difference was also started from the death certificate selection and the full sample of 1-17 year olds for the diagnosis selection method is not known. Death certificate method was the only selection method which provided healthcare data for the selection.
Validity and reliability indicators
Validity
To our knowledge, no publications are available to compare the percentages found to verify external validity.
Reliability
To evaluate reliability, measurements were repeated with a different method or by a different researcher for some indicators. For some indicators (physiotherapy, family physician contact, specialist physician involvement, surgeries, care setting transfers), two different calculation methods were used to verify reliability. Categorical selection and selective selection were applied. Indicators were originally calculated with a selective method, meaning the researcher screened all nomenclature codes and hand-selected the relevant codes. The categorical selection method was used to validate the selective method, meaning the calculations were repeated while selecting categories, e.g. following the structure of the nomenclature codes or practitioner categories. For example, for the indicator 'Prescriptions of physiotherapy', the selective method entailed selecting all individual nomenclature codes of which the description referred to physiotherapy. The categorical method entailed selecting all nomenclature codes that were categorized as prescribed by a physiotherapist by the healthcare funds. For most indicators, results of the two methods were similar, which suggests results are internally reliable. For the indicator care setting transfers, use of different variables gave differing results, which suggests results may not be reliable – however, conversations with the database providers indicate that the more reliable variables were used for final analysis. Some indicators (palliative status, starting dialysis), were repeated by another researcher. Same results were found by the other researcher for these indicators, which suggests the calculations are reliable.

Supplemental information 5: Additional information and tables for scale construction and analyses of variance

Scale construction

Initial scale selection
We grouped variables per category of appropriateness and inappropriateness. We used the last-30-days-version of the indicators where that time interval was relevant. When no 30-day-version was available, a shorter time interval was used, for example surgeries was only validated for the last 2 days before death.

Scale optimalization
Per group of variables, we performed a principal component analysis with the number of factors limited to 1, on a correlation matrix of the variables, to see which variables were highly correlated with each other. We also performed Cronbach Alpha analysis. We deleted variables that did not load highly together with the other variables in the principal component loadings.

Assumption tests
Prior to the PCA, a Kaiser–Meyer–Olkin (KMO) test was performed to verify whether there was sufficient Measure of Sampling Adequacy (MSA) . In order to obtain a sufficient matrix, some variables which consisted of full or near zeroes were deleted (e.g. dialysis, gastrostomy).

Final scales
The final scale for appropriateness of care included the variables: (off-label) comfort medication, palliative care, and palliative status.

The final scale for appropriateness of care included the variables: diagnostics andmonitoring, blood drawings, Intensive Care Unit admissions.

Analyses of variance

General
We performed analyses of variance with post hoc tests with the SAS General Linear Model (GLM) procedure, with least squares to fit method, for each scale.
Analyses were done for confounders (age, sex, disease category, nationality, having siblings, year of death), for time (year of death), and region (province and Flemish health care regions).

Initial variable selection
Estimated factor scores for each scale from the PCA (see above) were used as thedependent variable.

Confounders: Independent variable selection was based on literature review. We first identified possible confounders through literature review. Out of the identified variables, we selected the variables that were 1. reliably measurable with our data, 2. likely confounders, 3.did not have missings within our data, and 4. based on DAGs, were not the same or interfering with measured indicators. We selected the variables age, sex, disease category, nationality, having siblings, and year of death as possible confounders. Some variables were

categorized, such as year of death, others were already categorized within the data.

Time/region: Uncategorized year of death was chosen as independent variable for time analysis, for difference in region provinces and Flemish health care regions were looked at.

Model construction
We included all independent variables. To avoid coincidental statistical relationships to befound, we did not use stepwise method, but used expert opinion and previous theoretical arguments in literature to construct our model.[35]

Cut-off score
The alpha level of 0.05 defined statistical significance.

Supplemental Materials 6: Logistic regressions for appropriateness and inappropriateness according to clinical and sociodemographic factors

6.a. Appropriateness indicators[a]

	QI1: Physiotherapy		QI2: (Off-label) comfort medication		QI3: Pain control according to World Health Organizationsteps [b]		QI4: Home death [a]		QI5: Contact with family physician[a]	
	Adj. OR (95% CI)	Unadj. OR (95% CI).	Adj. OR (95% CI)	Unadj.OR (95% CI).	N/A	N/A	Adj. OR (95% CI)	Unadj. OR (95% CI).	Adj. OR (95% CI)	Unadj .OR (95% CI).
Age										
1-9 (vs. 10-17)	1.63 (0.89-2.99)	1.57 (0.91-2.71)	0.71 (0.25-2.02)	0.77 (0.26-2.28)			1.11 (0.61-2.05)	1.02 (0.60-1.71)	1.45 (0.64-3.26)	1.39 (0.64-3.02)
Sex										
Male (vs.female)	1.18 (0.65-2.14)	1.28 (0.73-2.23)	1.11 (0.40-3.11)	0.99 (0.33-3.02)			1.53 (0.84-2.80)	1.60 (0.93-2.75)	0.76 (0.35-1.66)	0.70 (0.32-1.50)
Disease category (vs. Malignant neoplasms of digestive organs)										
Malignant neoplasms of respiratory and intrathoracic organs	0.06 (0.00-0.86)	0.04 (0.00-0.54)	0.06 (0.00-1.69)	0.06 (0.00-1.79)			0.43 (0.05-3.55)	0.56 (0.08-3.99)	0.21 (0.02-2.53)	0.20 (0.02-2.24)
Malignant neoplasms of bone and articular cartilage	0.15 (0.02-1.45)	0.14 (0.02-1.36)	1.27 (0.03-62.63)	1.21 (0.02-73.47)			0.30 (0.06-1.47)	0.33 (0.07-1.52)	0.98 (0.09-11.10)	1.22 (0.11-14.18)
Melanoma and other malignant neoplasms of skin, mesothelial and soft tissue	0.13 (0.01-1.28)	0.10 (0.01-1.02)	0.81 (0.02-41.08)	1.00 (0.02-61.98)			1.20 (0.26-5.66)	1.31 (0.30-5.79)	3.17 (0.12-87.87)	3.22 (0.11-96.61)
Malignant neoplasm of breast, genital organs or urinary tract	0.17 (0.02-1.79)	0.17 (0.02-1.82)	1.33 (0.03-71.03)	0.93 (0.02-58.16)			0.77 (0.16-3.68)	0.65 (0.14-2.98)	0.22 (0.03-1.85)	0.24 (0.03-1.91)
Malignant neoplasms of eye, brain and other parts of central nervous system	0.17 (0.02-1.37)	0.15 (0.02-1.20)	0.33 (0.02-5.78)	0.34 (0.02-7.08)			0.59 (0.18-1.91)	0.63 (0.20-2.00)	0.94 (0.14-6.16)	0.94 (0.14-6.32)
Malignant neoplasms of thyroid and other endocrine glands	0.15 (0.01-2.25)	0.12 (0.01-1.73)	0.42 (0.01-28.13)	0.38 (0.01-28.23)			1.75 (0.21-14.26)	1.40 (0.18-11.03)	1.49 (0.04-54.09)	1.22 (0.03-45.64)
Malignant neoplasm of other and ill- defined sites	0.42 (0.02-8.32)	0.39 (0.02-7.40)	0.11 (0.00-3.30)	0.13 (0.00-4.23)			3.53 (0.38-32.81)	3.67 (0.40-33.55)	0.47 (0.04-6.44)	0.41 (0.03-5.58)
Malignant neoplasms, stated or presumed to be primary, of- lymphoid, haematopoietic and related tissue	0.13 (0.02-1.03)	0.12 (0.01-0.94)	0.58 (0.03-11.08)	0.62 (0.03-13.85)			2.98 (0.89-10.01)	3.00 (0.91-9.85)	0.57 (0.09-3.59)	0.59 (0.09-3.80)
Neoplasms of uncertain or unknown behaviour	0.11 (0.01-1.08)	0.10 (0.01-1.02)	0.30 (0.01-7.54)	0.31 (0.01-9.31)			1.39 (0.30-6.49)	1.73 (0.38-7.82)	0.24 (0.03-1.91)	0.26 (0.03-2.09)
Nationality										
Other (vs. Belgian)	2.80 (1.02-7.70)	2.61 (1.05-6.49)	0.73 (0.12-4.57)	1.14 (0.19-6.86)			0.32 (0.10-1.01)	0.35 (0.13-0.98)	0.84 (0.19-3.73)	0.81 (0.20-3.29)
Having siblings										
No (vs.yes)	0.63 (0.31-1.30)	0.75 (0.40-1.40)	0.75 (0.21-2.73)	0.57 (0.14-2.34)			0.62 (0.31-1.26)	0.47 (0.25-0.86)	0.64 (0.24-1.70)	0.54 (0.20-1.45)
Year of death										
2010-2014 (vs.2015-2017)	1.01 (0.53-1.92)	1.05 (0.58-1.88)	0.60 (0.21-1.73)	0.69 (0.23-2.0)			0.80 (0.42-1.52)	0.78 (0.45-1.37)	1.20 (0.51-2.86)	1.04 (0.45-2.37)

[a] Penalized logistic regression was performed due to low counts in the contingency table, [b] Due to low total and cell counts for these indicators, no logistic regression was performed

6.a. Appropriateness indicators[a] (Continued)

	QI6: Continuous care relationshipsa		QI7: Palliative care [a]		QI8: Multidisciplinary care [a]		QI9:Palliative status [a]			
	Adj. OR (95% CI)	Unadj. OR (95% CI).	Adj. OR (95% CI)	Unadj.OR (95% CI).	Adj. OR (95% CI)	Unadj. OR (95% CI).	Adj. OR (95% CI)	Unadj. OR (95% CI).		
Age										
1-9 (vs. 10-17)	1.11 (0.63-1.98)	1.22 (0.73-2.06)	1.43 (0.64 -3.19)	1.48 (0.69-3.19)	1.20 (0.35 -4.10)	0.90 (0.27-3.03)	1.50 (0.64 -3.50)	1.771 (0.76-4.10)		
Sex										
Male (vs.female)	1.11 (0.63-1.95)	1.06 (0.62-1.81)	0.71 (0.33 -1.55)	0.74 (0.35-1.59)	0.34 (0.11 -1.07)	0.43 (0.12-1.47)	1.22 (0.53 -2.81)	1.21 (0.52-2.81)		
Disease category (vs. Malignant neoplasms of digestive organs)										
Malignant neoplasms of respiratory and intrathoracic organs	0.05 (0.00-1.43)	0.05 (0.00-1.20)	0.18 (0.02-1.64)	0.20 (0.02-1.68)	1.66 (0.02-163.99)	0.45 (0.01-31.82)	0.32 (0.03-3.14)	0.36 (0.04-3.19)		
Malignant neoplasms of bone and articular cartilage	0.87 (0.20-3.78)	0.81 (0.19-3.47)	1.71 (0.19-15.73)	2.20 (0.24-20.28)	1.34 (0.02-85.95)	1.21 (0.02-73.47)	6.38 (0.27-48.54)	7.00 (0.28-174.50)		
Melanoma and other malignant neoplasms of skin, mesothelial and soft tissue	1.08 (0.23-5.14)	1.00 (0.22-4.65)	4.64 (0.20-109.64)	5.80 (0.23-147.95)	1.24 (0.02-71.61)	1.00 (0.02-61.98)	5.31 (0.22-126.34)	5.80 (0.23-147.95)		
Malignant neoplasm of breast, genital organs or urinary tract	0.53 (0.11-2.51)	0.50 (0.11-2.34)	6.63 (0.26-166.48)	5.40 (0.21-139.13)	1.00 (0.02-55.21)	0.93 (0.02-58.16)	6.32 (0.25-157.07)	5.40 (0.21-139.13)		
Malignant neoplasms of eye, brain and other parts of central nervous system	0.69 (0.21-2.27)	0.65 (0.20-2.12)	1.36 (0.28-6.61)	1.47 (0.30-7.14)	1.04 (0.05-22.08)	0.95 (0.04-22.79)	1.64 (0.33-8.11)	1.69 (0.34-8.38)		
Malignant neoplasms of thyroid and other endocrine glands	0.88 (0.11-7.16)	0.81 (0.10-6.51)	2.73 (0.09-85.99)	2.20 (0.07-70.63)	0.46 (0.01-31.37)	0.38 (0.01-28.23)	2.93 (0.09-92.53)	2.20 (0.07-70.62)		
Malignant neoplasm of other and ill- defined sites	0.05 (0.00-1.22)	0.05 (0.00-1.20)	0.36 (0.04-3.32)	0.36 (0.04-3.19)	0.56 (0.01-38.08)	0.45 (0.01-31.82)	0.74 (0.07-8.23)	0.73 (0.07-8.12)		
Malignant neoplasms, stated or presumed to be primary, of- lymphoid, haematopoietic and related tissue	0.39 (0.12-1.29)	0.37 (0.11-1.21)	0.71 (0.15-3.29)	0.78 (0.17-3.59)	0.37 (0.02-7.07)	0.38 (0.02-7.99)	0.83 (0.18-3.87)	0.86 (0.18-3.98)		
Neoplasms of uncertain or unknown behaviour	0.47 (0.10-2.17)	0.44 (0.10-2.02)	0.90 (0.12-6.48)	1.00 (0.14-7.30)	0.47 (0.02-14.21)	0.31 (0.01-9.31)	0.82 (0.11-5.96)	1.00 (0.14-7.30)		
Nationality										
Other (vs. Belgian)	0.72 (0.16-3.32)	0.78 (0.19-3.16)	6.28 (1.27-31.03)	5.06 (1.27-20.08)	0.53 (0.09-3.10)	0.52 (0.09-3.00)	0.72 (0.16-3.32)	0.78 (0.19-3.16)		
Having siblings										
No (vs.yes)	0.91 (0.47-1.75)	0.91 (0.50-1.63)	0.62 (0.23-1.64)	0.52 (0.20-1.38)	0.33 (0.07-1.55)	0.79 (0.19-3.37)	0.60 (0.21-1.70)	0.51 (0.71-1.47)		
Year of death										
2010-2014 (vs. 2015-2017)	0.90 (0.49-1.66)	0.95 (0.54-1.67)	0.61 (0.27-1.39)	0.78 (0.36-1.72)	1.19 (0.33-4.34)	0.98 (0.26-3.61)	0.69 (0.29-1.64)	0.82 (0.35-1.92)		

[a] Penalized logistic regression was performed due to low counts in the contingency table, [b] Due to low total and cell counts for these indicators, no logistic regression was performed

6.a. Inappropriateness indicators[a] (Continued)

	QI10: Excessive magnetic resonance imaging monitoring [b]		QI11: Diagnostics and monitoring		QI12: Gastrostomy placement b		QI13: Starting dialysis a		QI14: Installing port- a-caths b	
	N/A	N/A	Adj. OR (95% CI)	Unadj.OR (95% CI).	N/A	N/A	Adj. OR (95% CI)	Unadj. OR (95% CI).	N/A	N/A
Age										
1-9 (vs. 10-17)			1.44 (0.78 2.65)	1.46 (0.83- 2.57)			1.18 (0.29- 4.88)	0.90 (0.15- 5.33)		
Sex										
Male (vs.female)			1.36 (0.74 2.50)	1.37 (0.77- 2.46)			0.70 (0.19- 2.53)	0.64 (0.11- 3.78)		
Disease category (vs. Malignant neoplasms of digestive organs)										
Malignant neoplasms of respiratory and intrathoracic organs			1.05 (0.09- 12.57)	0.73 (0.07- 8.12)			1.17 (0.02- 93.20)	0.45 (0.01- 31.82)		
Malignant neoplasms of bone and articular cartilage			0.51 (0.09- 2.96)	0.46 (0.08- 2.60)			1.78 (0.04- 83.51)	1.21 (0.02- 73.47)		
Melanoma and other malignant neoplasms of skin, mesothelial and soft tissue			0.31 (0.05- 1.86)	0.26 (0.05- 1.52)			2.45 (004- 148.15)	1.00 (0.02- 61.98)		
Malignant neoplasm of breast, genital organs or urinary tract			0.33 (0.05- 2.00)	0.31 (0.05- 1.86)			0.86 (0.02- 39.38)	0.93 (0.02- 58.16)		
Malignant neoplasms of eye, brain and other parts of central nervous system			0.42 (0.09- 1.88)	0.38 (0.09- 1.68)			0.94 (0.05- 16.64)	0.67 (0.03- 14.95)		
Malignant neoplasms of thyroid and other endocrine glands			0.35 (0.04- 3.42)	0.28 (0.03- 2.70)			0.38 (0.01- 22.19)	0.38 (0.01- 28.23)		
Malignant neoplasm of other and ill- defined sites			0.38 (0.04- 3.42)	0.36 (0.04- 3.19)			0.52 (0.01- 27.54)	0.45 (0.01- 31.82)		
Malignant neoplasms, stated or presumed to be primary, of- lymphoid, haematopoietic and related tissue			0.61 (0.14- 2.79)	0.55 (0.12- 2.51)			2.05 (0.10- 44.24)	1.48 (0.05- 41.97)		
Neoplasms of uncertain or unknown behaviour			0.28 (0.05- 1.63)	0.26 (0.05- 1.52)			1.86 (0.04- 86.23)	1.00 (0.02- 61.98)		
Nationality										
Other (vs. Belgian)			2.06 (0.76- 5.61)	1.77 (0.71- 4.41)			5.99 (1.20- 29.88)	10.54 (1.68- 66.24)		
Having siblings										
No (vs.yes)			0.76 (0.37- 1.56)	0.82 (0.43- 1.56)			1.55 (0.35- 6.90)	2.78 (0.47- 16.62)		
Year of death										
2010-2014 (vs.2015-2017)			0.84 (0.44- 1.59)	0.83 (0.46- 1.52)			0.95 (0.22- 4.06)	1.07 (0.15- 7.44)		

[a] Penalized logistic regression was performed due to low counts in the contingency table, [b] Due to low total and cell counts for these indicators, no logistic regression was performed

6.a. Appropriateness indicators[a] (Continued)

	QI15: Surgeries b		QI16: Drawing blood		QI17: Hospital transfers a		QI18: Intensive Care Unit admissions			
	N/A	N/A	Adj. OR (95% CI)	Unadj.OR (95% CI).	Adj. OR (95% CI)	Unadj. OR (95% CI).	Adj. OR (95% CI)	Unadj. OR (95% CI).		
Age										
1-9 (vs. 10-17)			2.48 (1.32-4.64)	1.96 (1.16-3.33)	1.41 (0.49-4.08)	1.42 (0.47-4.32)	1.43 (0.65-3.13)	1.25 (0.64-2.46)		
Sex										
Male (vs.female)			1.24 (0.67-2.28)	1.23 (0.72-2.11)	0.42 (0.15-1.15)	0.39 (0.13-1.19)	1.74 (0.81-3.75)	1.54 (0.75-3.16)		
Disease category (vs. Malignant neoplasms of digestive organs)										
Malignant neoplasms of respiratory and intrathoracic organs			0.08 (0.01-1.15)	0.06 (0.00-0.66)	0.19 (0.01-7.27)	0.13 (0.01-4.23)	0.08 (0.01-1.15)	0.06 (0.00-0.66)		
Malignant neoplasms of bone and articular cartilage			0.65 (0.12-3.62)	0.50 (0.10-2.52)	1.20 (0.02-68.69)	1.21 (0.02-73.47)	0.65 (0.12-3.62)	0.50 (0.10-2.52)		
Melanoma and other malignant neoplasms of skin, mesothelial and soft tissue			0.45 (0.08-2.60)	0.27 (0.05-1.42)	0.20 (0.01-4.98)	0.17 (0.01-4.40)	0.45 (0.08-2.60)	0.27 (0.05-1.42)		
Malignant neoplasm of breast, genital organs or urinary tract			0.17 (0.03-0.97)	0.23 (0.04-1.25)	1.16 (0.02-64.83)	0.93 (0.02-58.16)	0.14 (0.01-1.56)	0.17 (0.02-1.82)		
Malignant neoplasms of eye, brain and other parts of central nervous system			0.53 (0.13-2.16)	0.41 (0.11-1.60)	0.35 (0.02-6.38)	0.34 (0.02-7.08)	0.33 (0.04-2.74)	0.26 (0.03-2.14)		
Malignant neoplasms of thyroid and other endocrine glands			0.51 (0.05-4.86)	0.41 (0.05-3.68)	0.43 (0.01-29.54)	0.38 (0.01-28.23)	0.13 (0.01-2.04)	0.12 (0.01-1.73)		
Malignant neoplasm of other and ill- defined sites			0.36 (0.04-2.98)	0.27 (0.04-2.11)	0.47 (0.01-30.12)	0.45 (0.01-31.82)	0.47 (0.02-9.42)	0.39 (0.02-7.41)		
Malignant neoplasms, stated or presumed to be primary, of- lymphoid, haematopoietic and related tissue			0.40 (0.10-1.62)	0.32 (0.08-1.25)	0.61 (0.03-11.99)	0.62 (0.03-13.85)	1.01 (0.11-9.31)	0.76 (0.08-6.83)		
Neoplasms of uncertain or unknown behaviour			0.16 (0.03-0.94)	0.15 (0.03-0.81)	0.41 (0.02-11.01)	0.31 (0.01-9.31)	0.23 (0.02-2.51)	0.19 (0.02-2.00)		
Nationality										
Other (vs. Belgian)			17.16 (3.57-82.46)	14.19 (3.22-62.55)	3.47 (0.86-14.00)	5.37 (1.55-18.66)	3.64 (1.21-10.95)	3.13 (1.21-8.13)		
Having siblings										
No (vs.yes)			1.14 (0.56-2.32)	1.40 (0.78-2.52)	0.89 (0.26-3.11)	1.31 (0.41-4.20)	1.02 (0.42-2.45)	1.12 (0.53-2.36)		
Year of death										
2010-2014 (vs. 2015-2017)			1.15 (0.59-2.23)	1.16 (0.66-2.04)	0.51 (0.17-1.48)	0.69 (0.23-2.10)	1.40 (0.61-3.21)	1.16 (0.56-2.43)		

[a] Penalized logistic regression was performed due to low counts in the contingency table, [b] Due to low total and cell counts for these indicators, no logistic regression was performed

Supplemental Materials 7: Operationalization of indicators

Indicator	Operationalization (Nomenclature codes, ATC codes or pre-categorized variables used)
Physiotherapy	Nomenclature codes: 560011,560033,560055,560092,560114,560151,560195,560210,560232,560254,560291 ,560313,560335,560350,560394,560416,560431,560453,560501,560523,560534,560545 ,560556,560560,560571,560593,560615,560652,560674,560696,560711,560733,560755 ,560770,560792,560814,560836,560851,560873,560895,560910,560932,560954,560976 ,560991,561013,561035,561050,561072,561094,561116,561131,561153,561175,561190 ,561212,561245,561260,561282,561304,561315,561326,561330,561341,561352,561374 ,561396,561411,561433,561455,561470,561492,561514,561540,561551,561562,561573 561595,561610,561632,561654,561676,561702,561713,561724,562332,562354,562376 ,562391,562413,562435,562450,562472,563010,563032,563054,563076,563091,563113 ,563135,563150,563172,563194,563216,563231,563253,563275,563290,563312,563334 ,563356,563371,563393,563415,563430,563452,563474,563496,563511,563533,563555 ,563570,563581,563603,563614,563651,563673,563695,563710,563732,563754,563776 ,563791,563813,563850,563872,563894,563916,563953,563975,563990,564012,564056 ,564071,564093,564130,564152,564174,564185,564211,564233,564255,564270,564292 ,564314,564336,564351,564373,564395,564410,564432,564454,564476,564491,564513 ,564535,564550,564572,564594,564616,564631,564653,564675,564701,564756,564771 ,564793,564815,564830,564852,564874,564896,564911,564933,564955,564970,639332 639354,639376,639391,639413,639435,639446,639450,639461,639472,639494,639516 ,639531,639553,639575,639590,639601,639612,639623,639634,639656,639671,639693 ,639715,639730,639752,639774,639785,639796,639811,639833,639855,639866,639870 ,639881,639892,558014,558025,558051,558062,558095,558106,558132,558143,558176 ,558180,558390,558423,558434,558445,503005,503020,503042,503064,503086,503101 ,503123,503145,503160,503182,503204,504313,504335,504350,504372,504394,504416 ,504431,504453,504475,504490,504512,505315,505330,505352,505374,505396,505411 ,505433,505455,505470,505492,505514,506612,506634,506656,506671,506693,506715 ,506730,506752,506774,506796,506811,510016,510031,510053,510075,510090,510112 ,510134,510156,510252,510414,510436,510451,510473,510495,510510,510532,510554 510613,510635,510716,510731,510753,510775,510790,510812,510915,510930,511000 ,511022,511044,511066,511081,511103,511125,511140,511243,511416,511431,511453 ,511475,511490,511512,511534,511556,511652,511674,511696,511814,511836,511851 ,511873,511895,511910,511932,511954,512013,512035,512050,512212,512234,512256 ,512271,512293,512315,512411,512433,512455,512606,512621,512643,512665,512680 ,512702,512724,512746,512842,512864,512886,513015,513026,513030,513041,513052 ,513063,513074,513085,513096,513100,513111,513122,513133,513144,513155,513166 ,515104,515115,515130,515196,515200,515211,515233,515266,515292,515314,515336 ,515395,515712,515734,515911,515922,515933,515944,515955,515970,515992,516106 ,516110,516132,516154,516202,516213,516235,516250,516401,516412,516434,516456 516714,516736,516751,516773,516795,516821,516913,516924,516935,516946,516950 ,516972,516994,517016,517112,517311,517414,517510,517613,517705,517720,517812 ,517823,517834,517845,517856,517871,517904,517915,517930,517952,517974,517985 ,517996,560011,560033,560055,560092,560114,560136,560151,560195,560210,560232 ,560254,560291,560313,560335,560350,560394,560416,560431,560453,560501,560523 ,560534,560545,560556,560560,560571,560593,560615,560652,560674,560696,560711 ,560733,560755,560770,560792,560814,560836,560851,560873,560895,560910,560932 ,560954,560976,560991,561013,561035,561050,561072,561094,561116,561131,561153 ,561175,561190,561212,561245,561260,561282,561304,561315,561326,561330,561341 ,561352,561374,561396,561411,561433,561455,561470,561492,561514,561540,561551 561562,561573,561595,561610,561632,561654,561676,561702,561713,561724,561735 ,561750,561772,561794,561816,561831,561853,561875,561890,561912,561934,561956 ,561971,561993,562015,562030,562052,562074,562096,562111,562133,562155,562170 ,562192,562214,562236,562251,562273,562295,562306,562310,562321,562332,562354 ,562376,562391,562413,562435,562450,562472,563010,563032,563054,563076,563091 ,563113,563135,563150,563172,563194,563216,563231,563253,563275,563290,563312 ,563334,563356,563371,563393,563415,563430,563452,563474,563496,563511,563533 ,563555,563570,563581,563592,563603,563614,563636,563651,563673,563695,563710 ,563732,563754,563776,563791,563813,563835,563850,563872,563894,563916,563931 ,563953,563975,563990,564012,564034,564056,564071,564093,564115,564130,564152 564174,564185,564196,564200,564211,564233,564255,564270,564292,564314,564336 ,564351,564373,564395,564410,564432,564454,564476,564491,564513,564535,564550

(Off-label) Comfort medication	ATC codes: A03BB01,A03DB04,QA03BB01,N05CM18,N01AH01,N02AB03,N01AH51,N01AX14,N06AX27,N01AX03,N03AX12,M01AB15,S01BC05,S01FB51,C01BB01,C05AD01,D04AB01,N01BB02,R0AD02,S01HA07,S02DA01,N01BB52,N05CD08,A04AA01,A04AD01,N05CM05,S01FA02,A04A D51
Pain control according to World Health Organization steps	ATC codes: N02AA01,N02AA03,N02AA04,N02AA05,N02AA10,N02AA11,N02AA51,N02AA53,N02AA55,N02AA56,N02AB03,QN02AB53,QN02AB73,N02AC52,QN02AC90,N02AE01,N02AG01,N02AG04 N02AJ17,N02AJ18,N02AX06
Continuing anti-epileptic medication	ATC codes: N03AA-N03AX
Home death	Pre-categorized variable: Place of death
Contact with family physician[a]	Nomenclature codes: 101010,101032,101054,101076,103412,103434,103110,104215,104230,104252,104510,104532,104554,109045,109701,109723,103132,103213,103235,109060,109082,102410,102432,102454,102476,102771,103316,103331,103353,103515,103530,103552,103913,103935,103950,104215,104230,104252,104274,104296,104311,104333,104355,104370,104392,104414,104436,104451,104510,104532,104554,104576,104591,104613,104635,104650,104672,104694,104716,104731,104753,109045,109060,109082,109701,109723,109734,423032,423043,215014,215025,215036,215040,215051,215062,215073,215084,216016,216020,216031,216042,216053,216064,216075,216086,350232,590015,590030,590052,590100,590531,590575,590612,590656,590693,590730,590774,590811,107015,107052,107096,107133,109955,426893,775876,775880,775935,775946,777954,777965,783414,783425,784350,787894,787905
Continuous care relationships	Pre-ategorized variable: Practitioner category
Professional care provision	Pre-categorized variable: Practitioner category Ward of admission
Palliative care service[A]	Nomenclature codes: 109701,427011,427033,427055,427070,427092,427114,427136,427151,427173,427195,597763,599782,599804,768143,768445,768762,768784,768806,768821,774056,774071,784092,426510,426532,426554,426871,426893,426915,426930,426952,740213,768143,768445,768762,768784,768806,768821,774056,774071,774093,775530,775541,775611,775622,775633,775644,777630,777652,784092,785234,785245
Multidisciplinary oncological consult	Nomenclature codes: 350276,350280,350291,350302,350372,350383,350394,350405,350416,350420,350453,350464,350475,350486,350232,350254,350265,350276,350280,350291,350302,350372,350383,350394,350405,350416,350420,350453,350464,350475,350486
Multidisciplinary care[a]	Pre-categorized variable: Practitioner category
Palliative status	Nomenclature code: 740213
Increased child benefits	Nomenclature code: 740051
Diagnostics and monitoring	Nomenclature codes: 459395, 459406, 459410, 459421, 459476, 459480, 459491, 459502, 459513, 459524, 459535, 459546, 3070, 16, 307020, 307031, 307042, 307053, 307064, 307075, 307086, 307112, 307123, 307134, 307145, 377016, 37, 7020, 377031, 377042, 377053, 377064, 377112, 377123, 377134, 377145, 450015, 450026, 450170, 450181, , 450516, 450520, 450774, 450785, 451010, 451021, 451032, 451043, 451054, 451065, 451076, 451080, 4511, 13, 451124, 451135, 451146, 451150, 451161, 451172, 451183, 451194, 451205, 451216, 451220, 451290, 45, 1301, 451312, 451323, 451334, 451345, 451356, 451360, 451371, 451382, 451393, 451404, 451415, 451426, , 451430, 451441, 451452, 451463, 451474, 451485, 451496, 451500, 451511, 451522, 451533, 451544, 4515, 55, 451566, 451570, 451581, 451592, 451603, 451636, 451640, 451651, 451662, 451695, 451706, 451710

Excessive monitoring	Nomenclature codes: 1721, 451732, 451743, 451754, 451765, 451791, 451802, 451872, 451883, 452690, 452701, 452712, 452723, 452734, 452745, 452793, 452804, 452815, 452826, 452830, 452841, 453014, 453025, 453036, 453040, 453051, 453062, 453250, 453261, 455011, 455022, 455033, 455044, 455055, 455066, 455070, 455081, 455092, 455103, 455114, 455125, 455136, 455140, 455151, 455162, 455173, 455184, 455195, 455206, 455210, 455221, 455232, 455243, 455254, 455265, 455276, 455280, 455291, 455302, 455313, 455324, 455335, 455346, 455350, 455361, 455372, 455383, 455394, 455405, 455416, 455420, 455431, 455442, 455453, 455464, 455475, 455486, 455490, 455501, 455512, 455523, 455534, 455545, 455556, 455560, 455571, 455582, 455630, 455641, 455652, 455663, 455674, 455685, 455696, 455700, 455792, 455803, 455814, 455825, 455836, 455840, 455851, 455862, 455873, 455884, 456013, 456024, 456035, 456046, 456050, 456061, 456072, 456083, 456116, 456120, 456131, 456142, 456190, 456201, 456212, 456223, 456934, 456945, 458172, 458183, 459071, 459082, 459104, 461510, 461521, 462431, 462442, 462512, 462523, 462711, 462722, 462755, 462766, 463691, 463702, 463713, 463724, 463794, 463805, 463831, 463842, 466012, 466023, 466034, 466045, 466056, 466060, 466071, 466082, 466093, 466104, 466115, 466126, 466130, 466141, 466152, 466163, 466174, 466185, 466196, 466200, 466211, 466222, 466233, 466244, 466255, 466266, 466270, 466281, 466292, 466303, 466314, 466325, 466336, 466340, 466351, 466362, 466373, 466384, 466395, 466406, 466410, 466421, 466476, 466480, 466535, 466546, 466631, 466642, 466690, 466701, 466793, 466804, 467935, 467946, 468171, 468182, 469070, , 469081, 469103, 451931, 451942, 442396, 442400, 442514, 442525, 442396, 442400, 442514, 442525, 442595, 442606, 442654, 442665, 442676, 442680, 442691, 442702, 442713, 442724, 442735, 442746, 442750, 442761, 442971, 442982, 450531, 450542, 451570, 451581, 456514, 456525, 456536, 456540, 56551, 456562, 456573, 456584, 456595, 456606, 456610, 456621, 456632, 456643, 456654, 456665, 456676, 456680, 456691, 456702, 456713, 456724, 456735, 456746, 456750, 456761, 456772, 456783, 456794, 456805, 456816, 456820, 456831, 456842, 456853, 456864, 456875, 456886, 456890, 456901, 456912, 456923, 458452, 458463, 458570, 458581, 458592, 458603, 458614, 458625, 458636, 458640, 458651, 458662, 458673, 458684, 458695, 458706, 458710, 458721, 458732, 458743, 458754, 458765, 458776, 458780, 458791, 458802, 458813, 458824, 458835, 458846, 458850, 458861, 458872, 458883, 458894, 458905, 459550, 459561, 459572, 459583, 459594, 459605, 459616, 459620, 459631, 459642, 459675, 459686, 459690, 459701, 459852, 459863, 459874, 459885, 459896, 459900, 459911, 459922, 460740, 460762, 461532, 461543, 458511, 458522, 458533, 458544, 458555, 458566
Excessive magnetic resonance imaging and monitoring	Nomenclature codes: 459395,459406,459410,459421,459476,459480,459491,459502,459513,459524,459535,459546
Gastrostomy placement	Nomenclature codes: 241695,241706,243316,243320,355950,355961,473911,473922,682570,682581,733095,733106,738076,738080,155654,155665,155676,155680,
Installing port-a-caths	Nomenclature codes: 354362,354351
Starting dialysis	Nomenclature codes: 235174, 235185, 238254, 238265, 244672, 244683, 354336, 354340, 470072, 470083, 470105, 470120, 470131, 470142, 470374, 470385, 470400, 470422, 470433, 470444, 470455, 470466, 470470, 470481, 470492, 470503, 474714, 474725, 611715, 611726, 611752, 611763, 684176, 684180, 684191, 684202, 715934, 715945, 720871, 720882, 158336, 158340, 161070, 161081, 161571, 161582, 172314, 172325, 740272, 740283, 751413, 761272, 761283, 761456, 761471, 761493, 761515, 761526, 761530, 761552, 761574, 761596, 761655, 761670, 761946, 761972, 761983, 780813
Old-generation prescriptions nausea	ATC codes: A03FA03,A03FA01
Surgeries	Nomenclature codes: (due to the large volume of codes, not all are shown) 221130, 221141, 227150, 227161, 227172, 227183, 227334, 227345, 228012, 228023, 228056, 228060, 228071, 228082, 228233, 228244, 229014, 229025, 229036, 229040, 229390, 229401, 229412, 229423, 229515, 229526, 229530, 229541, 229596, 229600, 230252, 230263, 231475, 231486, 232514, 232525, 232750, 232761, 232772, 232783, 235211, 235222, 241172, 241183, 241511, 241522, 241710, 241721, 242351, 242362, 244053, 244064, 244156, 244160, 244252, 244263, 244436, 244440, 244451, 244462, 244532, 244543, 244635, 244646, 246610, 246621, 247155, 247166, 247170, 247181, 247634, 247645, 247656, 247660, 251753, 251764, 251775, 251786, 255150, 255161, 255371, 255382, 255835, 255846, 258134, 258145, 260772, 260783, 277793, 277804, 277815, 277826, 281934, 281945, 353290, 353301, 431911, 431922, 476630, 476641, 589094, 589105, 589190, 589201, 589455, 589466, 226914, 226925, 226936, 226940, 227216, 227220, 227253, 227264, 227371, 227382, 229585, 229611, 229622, 229633, 229644, 227636, 227640, 227651, 227662, 227673, 227684, 227695, 227706, 227710, 227721, 227732, 227743, 227754, 227765, 227776, 227780, 227791, 227802, 227813, 227824, 227835, 227846, 228115, 228126, 228174, 228185, 229574, 230473, 230484, 231033, 231044, 241415, 241426

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New antidepressants	ATC codes: N06AA-N06AX
Drawing blood	Nomenclature codes: 121516, 121520, 122710, 122721, 120153, 120164, 120175, 120186, 120190, 120201, 121516, 121520, 122710, 122721, 123034, 123045, 123056, 123060, 123071, 123082, 123093, 123104, 123115, 123126, 123130, 123141, 123152, 123163, 123174, 123185, 123196, 123200, 124014, 124025, 124051, 124062, 124515, 124526, 124530, 124541, 125156, 125160, 125171, 125182, 125193, 125204, 125915, 125926, 126556, 126560, 126711, 126722, 126733, 126744, 126755, 126766, 127035, 127046, 127050, 127061, 127072, 127083, 127094, 127105, 127116, 127120, 127131, 127142, 127153, 127164, 127175, 127186, 127190, 127201, 128015, 128026, 128052, 128063, 128516, 128520, 128531, 128542, 130056, 130060, 130071, 130082, 130093, 130104, 131036, 131040, 131515, 131526, 132016, 132020, 132031, 132042, 132075, 132086, 132090, 132101, 132112, 132123, 132134, 132145, 132156, 132160, 132171, 132182, 132193, 132204, 132215, 132226, 132230, 132241, 132252, 132263, 132274, 132285, 133011, 133022, 133033, 133044, 133254, 133265, 133276, 133280, 133291, 133302, 134072, 134083, 134094, 134105, 134116, 134120, 134131, 134142, 134153, 134164, 135052, 135063, 135074, 135085, 135096, 135100, 136032, 136043, 136511, 136522, 137012, 137023, 137034, 137045, 137071, 137082, 137093, 137104, 137115, 137126, 137130, 137141, 137152, 137163, 137174, 137185, 137196, 137200, 137211, 137222, 137233, 137244, 137255, 137266, 137270, 137281, 138014, 138025, 138036, 138040, 138250, 138261, 138272, 138283, 138294, 138305, 139031, 139042, 139075, 139086, 139090, 139101, 139112, 139123, 139134, 139145, 139156, 139160, 437010, 437021, 437032, 437043, 437054, 437065, 437076, 437080, 437091, 437102, 437113, 437124, 438115, 438126, 445130, 445141, 445152, 445163, 445174, 445185, 445196, 445200, 445211, 445222, 446014, 446025, 446036, 446040, 446051, 446062, 446073, 446084, 446095, 446106, 446110, 446121, 540035, 540046, 540374, 540385, 540433, 540444, 540455, 540466, 540514, 540525, 540536, 540540, 540654, 540665, 540676, 540680, 540713, 540724, 540735, 540746, 540816, 540820, 541634, 541645, 541715, 541726, 541811, 541822, 542032, 542043, 542076, 542080, 542091, 542102, 542150, 542161, 542172, 542183, 542290, 542301, 542415, 542426, 542430, 542441, 543012, 543023, 543071, 543082, 543115, 543126, 543270, 543281, 543336, 543340, 543395, 543406, 543432, 543443, 543616, 543620, 543756, 543760, 543815, 543826, 543896, 543900, 544110, 544121, 544132, 544143, 544154, 544165, 544272, 544283, 546770, 546781, 547352, 547363, 547374, 547385, 547396, 547400, 547514, 547525, 547794, 547805, 547816, 547820, 547831, 547842, 547875, 547886, 547890, 547901, 549010, 549021, 549032, 549043, 549894, 549905, 550056, 550060, 550071, 550082, 550093, 550104, 550211, 550222, 550233, 550244, 550292, 550303, 550454, 550465, 550476, 550480, 550491, 550502, 550513, 550524, 550535, 550546, 550550, 550561, 550572, 550583, 550594, 550605, 550616, 550620, 550653, 550664, 550690, 550701, 550712, 550723, 550734, 550745, 550771, 550782, 550793, 550804, 550830, 550841, 550852, 550863, 550896, 550900, 550911, 550922, 550933, 550944, 550970, 550981, 551014, 551025, 551036, 551040,

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Late palliative care provision	Nomenclature codes: 109701,427011,427033,427055,427070,427092,427114,427136,427151,427173,427195,597763,599782,599804,768143,768445,768762,768784,768806,768821,774056,774071,784092,426510,426532,426554,426871,426893,426915,426930,426952,740213,768143,768445,768762,768784,768806,768821,774056,774071,774093,775530,775541,775611,775622,775633,775644,777630,777652,784092,785234,785245
New placement catheter	Nomenclature codes: 354255,354266,355552,355563,211665,211680,354196,354200,354255,354266,474692,474703,613992,614003
Hospital transfers, care transfers	Pre-categorized variable: Hospital admissions
Care stop after receiving palliative status	Pre-categorized variable: Practitioner category Category of stay
Involvement of specialist physicians	Pre-categorized variable: Practitioner category
Intensive Care Unit admissions	Pre-categorized variable: Ward of admission

CHAPTER 5

Population-level analysis of the appropriateness of end-of-life care in children with genetic and congenital conditions

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To be submitted

ABSTRACT

Objective Children with genetic and congenital conditions may receive intense treatments at the end of life, such as hemodialysis and transplants, that can negatively impact their quality of life. This study evaluates appropriateness of end-of-life care for children with genetic and congenital conditions.

Design Decedent cohort study.

Setting We used 6 linked, Belgian, routinely-collected, population-level databases.

Patients Children (1-17) who died with genetic and congenital conditions in Belgium between 2010 and 2017.

Main outcome measures We measured 21 validated quality indicators. We performed analyses of variance for provinces and healthcare regions.

Results In the 8-year study period, 200 children were identified to have died with genetic and congenital conditions. Concerning appropriateness of care, in the last month before death 79% of the children had contact with specialist physicians, 17% had contact with a family physician, and 5% received multidisciplinary care. Palliative care was used by 17% of the children. Concerning inappropriateness of care, 51% of the children received blood drawings in the last week before death, and 29% received diagnostics and monitoring (2 or more MRIs, CT scans, or X-rays) in the last month. There was more appropriate care in the regions of Brussels, Genk, and Ghent, and less inappropriate care in Brussels.

Conclusions This study presents the first population-level analysis of end-of-life care for children who died with genetic and congenital conditions. Findings suggest quality can be improved in terms of palliative care, family physician and paramedics contact, and diagnostic interventions.

What is already known on this topic Children with genetic and congenital conditions may receive intense treatments at the end of life, such as hemodialysis and transplants, that lower quality of life at the end of life. A quality evaluation of appropriateness of end-of-life care for children with genetic and congenital conditions is lacking.

What this study adds This study provides an evaluation of the appropriateness of end-of-life care for children who died in Belgium with genetic and congenital conditions between 2010 and 2017, using administrative healthcare data and validated quality indicators. We provide a description of medication and treatments that are provided on a population level, and could be potentially appropriate or inappropriate, which is currently lacking.

How this study might affect research, practice or policy Our study suggests that improvements could be made in the provision of palliative care provision, contact with care providers next to their specialist physician, and use of diagnostictesting (e.g. MRIs, CT scans). Further research could investigate healthcare use in other countries using administrative databases.

INTRODUCTION

Children with genetic and congenital complex chronic conditions suffer from a variety of disorders impacting various body systems: respiratory conditions such as cystic fibrosis; cardiovascular conditions such as cardiomyopathies; renal, urologic and gastrointestinal conditions such as congenital anomalies; immunologic and hematologic conditions such as polyarteritis nodosa; metabolic conditions such as amino acid disorders; and other congenital or genetic defects, such as monosomies (1). These conditions represent a large proportion of children dying with complex chronic conditions, with a third of children with non-cancer and non-cardiac complex chronic conditions shown to experience high suffering at the end of life (2).

While treatments and trajectories can vary due to variation in underlying pathologies, similar challenges for the provision of end-of-life care have been identified for children with genetic and congenital conditions. End-of-life care was rated as poor or fair by half of the bereaved parents of children who died with non-cancer and non-cardiac complex chronic conditions between 2006 and 2015 in the US (2). Almost one-third of the parents reported that the children suffered a lot to a great deal in the final 2 days of life (2). Studies on individual conditions report that intense treatments can be given at the end of life that can reduce health-related quality of life, such as hemodialysis in children dying with renal disease (5) and transplants in children dying with heart failure or cystic fibrosis (6,7). Few studies look into end-of-life care for children with genetic and congenital complex chronic conditions. A population-level evaluation with validated indicators for appropriateness of care can provide an overview of appropriateness of end-of-life care, and provide further hypotheses and options for improvements through research and practice. To provide such evaluation, we previously developed and validated a set of quality indicators that measures aspects of care that may indicate potentially appropriate or inappropriate care at the end of life in children with genetic and congenital conditions (8). The quality indicators were developed to be measured at a population level, using administrative health data.

This study aimed to measure the quality indicators in children who died with genetic and congenital conditions in Belgium between 2010 and 2017. Additionally, the study aimed to verify whether there was a difference between provinces and healthcare regions for appropriateness or inappropriateness of end-of-life care.

METHODS

Study design

We conducted a population-level decedent cohort study of all children who died with genetic and congenital conditions in Belgium between 2010 and 2017. Selection was done from death certificates in Belgium and our data is therefore expected to include practically all insured children who died with genetic and congenital conditions.

Data sources

6 Belgian routinely collected clinical and/or administrative databases were linked. See Appendix 2 for details on the databases used. Databases included sociodemographic information for all individuals with healthcare insurance in Belgium, and healthcare data such as outpatient and hospital care or reimbursed medication provided in Belgium, and death certificate data.

Population

We selected children between 1 and 17 years old who died with genetic and congenital conditions within the given time period, and resided in Belgium, with a registered death within the year 2010 to 2017, based on death certificate data. We defined genetic and congenital conditions as cardiovascular, respiratory, renal, urologic, gastrointestinal, hematologic, immunologic, and metabolic conditions, and other conditions such as chromosomal anomalies and bone and joint anomalies, and other congenital anomalies (1) that could cause the death of a child from 1 to 17 years old within the modern medical context. ICD-10 codes were used as defined in the framework of complex chronic conditions (See Figure 1) (1). After sensitivity analysis, 5 deaths were deleted from the selection due to external causes of death (such as self-harm or drowning), despite also having a genetic or congenital condition. Childrenbetween 0 and 1 were not included, as care for this age group differs considerably from care for children over the age of 1.

Quality indicators of potentially appropriate and inappropriate end-of-life genetic and congenital conditions care

We measured 22 quality indicators, which were published previously (8). One indicator from the original set was not included: professional care provision was deleted, as some professional care provision was already included in another indicator (ICU admissions). We measured 10 indicators for potentially appropriate care and 10 for potentially inappropriate care. Each indicator was validated and measured for appropriateness of end-of-life care and specific time periods (8). One originally validated indicator (8), transfers from medical-pedagogical institute to intensive care, was not measured, as the concept of medical-

pedagogical institute could not be identified in the database. One indicator, involvement of specialist physicians, was moved to the category of potentially appropriate care from inappropriate care due to a mistake in categorization. See Table 1 for an overview of the operationalization of the quality indicators.

Table 1. Operationalization of all 20 end-of-life care quality indicators

Potentially **appropriate** end-of-life care		
Indicator	Operationalization (number of children that died of genetic or congenital conditions in which…)	Timing
1 Physiotherapy	Physiotherapy was given	Last 30, 14, 7, or 2 days before death
2 Off-label comfort medication	There were prescriptions for hyoscine butylbromide, dexmedetomidine, fentanyl, gabapentin, ketamine, ketorolac, lidocaine, midazolam, ondansetron, or scopolamine	Last 30, 14, 7, or 2 days before death
3 Pain control according to World Health Organization steps	There were prescriptions from the third World Health Organization step, i.e. morphine, fentanyl, methadone, oxycodone, or hydromorphone, and these were preceded, in the last 2 years before death, by prescriptions from the first World Health Organization step, i.e. paracetamol, non-steroidal anti-inflammatory drugs or aspirin, and from the second World Health Organization step, i.e. codeine, tramadol, or buprenorphine	Last 30/90 days before death
4 Continuing anti-epileptic medication	There was at least 1 prescription of an anti-epileptic medication in the last 30 days before death (for children who in the last 3 months before death received at least 2 prescriptions for anti-epileptic medication)	Last 30 days before death
5 Contact with family physician	There were at least 3 house visits of, prescriptions of, or consultations with a family physician	Last 30 days before death
6 Follow-up by hospital after palliative status	At least 1 consultation in a hospital, or with a specialist physician after palliative status	From palliative status onwards
7 Continuous care relationships	There was at least 1 prescription, visit, consultation, or treatment from the same physician (family physician or specialist) in the last 30 days before death, as in the last year before death	Last 30/365 days before death
8 Palliative care team	There was at least 1 visit of a palliative care team	Last 2 years before death

9 Multidisciplinary care	There was a total of 5 or more prescriptions, treatments, visits, or advices, from 2 or more of the following care providers: family physicians, pediatricians, specialist physicians or paramedics	Last 30 days before death
10 Palliative status	Received a palliative status	Last 2 years before death
11 Involvement of specialist physicians	There was at least 1 prescription, visit of or consultation with at least 1 specialist physician	Last 30 days before death
Potentially **inappropriate** end-of-life care		
Indicator	Operationalization (number of children that died of genetic or congenital conditions in which…)	Timing
1 Excessive magnetic resonance imaging monitoring (Daily MRIs)	Received 1 or more magnetic resonance imaging scans per day	Last 30, 14, 7, or 2 days before death
2 General diagnostics and monitoring	Received 1 or more magnetic resonance imaging scans	Last 30, 14, 7, or 2 days before death
3 Starting dialysis	Dialysis was started	Last 14, 7, or 2 days before death or from receiving palliative status onwards
4 Surgeries	A surgery was performed	Last 2 days before death
5 Late palliative care provision	There was a first registration of a palliative care team or palliative status	Last 14 or 7 days before death
6 New placement central venous catheter	There was placement of a central venous catheter	Last 7 or 2 days before death
7 Drawing blood	There was at least 1 blood drawing	Last 7 or 2 days before death
8 Hospital transfers	There were 1 or more hospital transfers	Last 30, 14, 7, or 2 days before death
9 Care setting transfers	There were 4 or more different care settings (home, hospital or other setting)	Last 30, 14, 7, or 2 days before death
10 Care stop after receiving palliative status	There were less than 3 prescriptions of, visits of, or consultations with a family physician or a specialist physician or a visit to a care institute	From the start of the palliative status onwards

Statistical analysis

We used descriptive statistics to describe the characteristics of children who died with genetic and congenital conditions, and to measure the quality indicators. We combined all years to obtain a sufficiently large sample.

To identify differences in appropriateness for region, we first constructed scales for data reduction. Scale construction (See Appendix 5) was based on previous theoretical assumptions, i.e. appropriateness vs. inappropriateness of care, as the 21 quality indicators belong to previously categorized domains of appropriateness vs. inappropriateness. A principal components analysis was performed for each scale with restriction for 1 factor, and items with a low component loading (below 0.50) were removed from the scale. The factor scores for both scales were saved. For each scale we performed 2 analyses of variance with post hoc tests: one for province and one for Flemish healthcare regions. Analysis of variance was performed separately for Flemish care regions, as the factor was only applicable to half of all children, as only Flemish and no Walloon healthcare regions are registered within the databases. The reference categories were the province of Namur (for province) and the healthcare region of Antwerp (for Flemish healthcare regions). Healthcare regions were only looked into for Flemish regions, as no data was available for Walloon healthcare regions – this is not recorded in administrative databases.

Belgium consists of 10 provinces, which are sub-regions with their own governance boards. Flanders, a sub-region of Belgium, also provides a healthcare region subdivision in addition to the province division. Healthcare region subdivision differs from province subdivision in that healthcare subdivision focuses on aggregating the regional concentrations of healthcare provision, such as hospitals.

Analyses were conducted with SAS Enterprise Guide, version 7.1 and StataSE, version 17.

Ethics

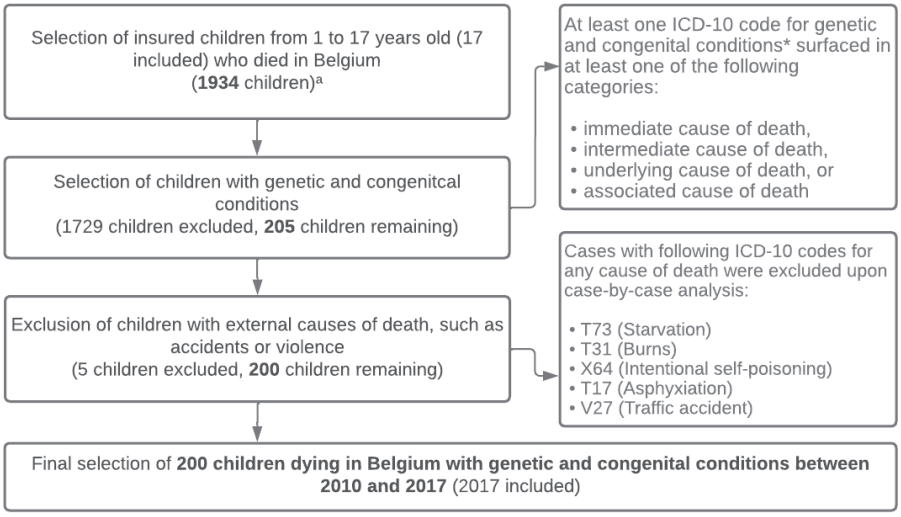
All data was linked in a secure, ethically responsible manner, guaranteeing anonymity of the deceased. The study was approved by the International Safety Committee.

RESULTS

Population characteristics

Our cohort selection identified 200 children aged 1 to 17 who died with genetic and congenital conditions in Belgium between 2010 and 2017 (Figure 1). See Table 2 for socio-demographic and clinical characteristics. The largest disease group was children who suffered from congenital malformations, deformations and chromosomal abnormalities (24%). The largest age group was between 9 and 15 (35%).

Figure 1: Flow chart of the cohort selection



[a] Selection was started from the population database of the Intermutualistic Agency Database, as the deaths recorded in this database result from national death certificates, which were seen as the most reliable source. Variations in number of deaths were present over all databases, due to differing age and death definitions and selection by the different governmental agencies preparing the data.
*ICD-10 codes as defined in Feudtner (2014): B20-24, D55-28, D60-61, D66, D682, D6941, D6942, D6949,D700,D704,D71, D720, D761-D763, D80-89,D841, D869, E009, E222, E230, E232, E233, E237,E240, E242-243, E248-249, E2681, E250, E258-259, E343, E700, E702-704, E708, E710-715, E720-724, E728-729, E740-744, E748-749, E75, E760-763, E770-771, E780-789, E791, E798, E804-807, E830-831, E833-834, E84-85, E88, E881, E888, G4735, G834, H498, I270-272, I2781-2782, I2789, I279, I340, I348, I360, I368, I370, I378, I42-45, I47-48, I490-492, I493-495, I498-499, I509, I515, I517, I5181, I63139, I63239, I820, J84112, J9500-9504, J9509, J95850, J9620, K449, K50-51, K551, K562, K593, K73-74, K754, K760-763, K765, K768, K9420, K9422-9423, K9429, M300, M303, M310-311, M3130, M314, M316, M3210, M3390, M340-341, M349, M359, M410, M412, M4130, M418-419, M4330, M965, N18, N312, N319, P280, Q20, Q212-214, Q218-219, Q22-24, Q251-259, Q26, Q282-283, Q289, Q30-34, Q390-394, Q41-45, Q60-64, Q722, Q750, Q752, Q759-762, Q764-767, Q77, Q780-784, Q788-795, Q799, Q7959, Q81, Q871-873, Q8740, Q8781, Q8789, Q897, Q899, Q909, Q913-914, Q917, Q928, Q93, Q950, Q969, Q97-98, Q998-999, Q992, R001

Table 2. Characteristics of all insured children who died with genetic and congenital conditions in Belgium, 2010-2017[a]

	Percentage (number)
All	200 (100%)
Sex of the child	
Male	105 (53%)
Female	95 (48%)
Age range of the child	
1-5	60 (30%)
>5-9	37 (19%)
>9-15	69 (35%)
>15-17	34 (17%)
Nationality of the child	
Belgian	170 (85%)
Other	30 (15%)
Type of household in which the child lived[b]	
Two-parent household	146 (73%)
Single-parent or other household	50 (25%)
Comfort of the house in which the child lived[b]	
High	65 (33%)
Average	11 (6%)
Low	24 (12%)
Trailer, none, not known	11 (6%)
Highest level of education of the child's parents[b,c]	
Postsecondary	66 (33%)
High school	70 (35%)
Junior high school	22 (11%)
Primary school	16 (8%)
No diploma	<5 (<3%) [d]
Not known	6 (3%)
Urbanicity of municipality of residence of the child's family[b,e]	
Very high	59 (30%)
High	49 (25%)
Average	59 (30%)
Low	30 (15%)

Net annual taxable income of the child's family[b]	
High (decile 1-3)	82 (41%)
Average (decile 4-6)	37 (19%)
Low (decile 7-10)	51 (26%)
Underlying cause of death of the child according to general ICD-10 category	
Congenital malformations, deformations and chromosomal abnormalities	47 (24%)
Endocrine, nutritional and metabolic diseases	37 (19%)
Neoplasms	31 (16%)
Diseases of the circulatory system	30 (15%)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	14 (7%)
Diseases of the nervous system	14 (7%)
Diseases of the musculoskeletal system and connective tissue	6 (3%)
Certain infectious and parasitic diseases	5 (3%)
Diseases of the digestive system	5 (3%)
Diseases of the respiratory system	<5 (<3%) [d]
Diseases of the genitourinary system	<5 (<3%) [d]
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified, Injury, poisoning and certain other consequences of external causes	<5 (<3%) [d]

[a]Percentages were rounded, therefore could amount to more than 100% or to 99%. Some variables donot amount to 100% because of missings (see [b]); [b]Missings resulted from the census basis of these variables, namely <5 (<3%) for type of household, 89 (45%) for comfort of the house, 17 (9%) for highestlevel of education of the parents, <5 (<3%) for urbanicity, and 30 (15%) for net annual income; [c]Highest level of education/income of both parents was selected for each child; [d]Due to privacy regulations, smallcells (smaller than 5) could not be reported; [e]Based on the Eurostat degree-of-urbanization method

Potentially appropriate care at the end of life

Table 3 shows the measurements for the quality indicators of potentially appropriate care, with different time periods shown in the columns. 57% of the children had continuous care relationships (having reimbursements from the same physician in the last month before death as in the 11 months before) in the last month of life. In 17% of the children, there was contact with a family physician in the last month before death. 16% of the children received palliative status and 17% palliative care.

Table 3a: Quality indicators for potentially appropriate end-of-life care for children who died with genetic and congenital conditions in Belgium, 2010-2017[a]

Quality indicators of potentially **appropriate** end-of-life care								
	Time period: Number of days before death							
	Quality indicator denominator (n)	2days	7days	14days	30days	90days	From palliative status onwards	730days (full period available)
Treatment, medication, and monitoring								
Continuing anti-epileptic medication	/32[b]				28 (88%)			
Pain control according to World Health Organization steps (receiving step 1 and/or 2 before step 3)	/20[b]					13 (65%)		
Physiotherapy	/200[c]	42 (21%)	60 (30%)	68 (34%)	73 (37%)			108 (54%)
(Off-label) Comfort medication	/200[c]	0 (0%)	8 (4%)	8 (4%)	12 (6%)			27 (14%)
Care services and providers								
Involvement of specialist physicians	/200[c]				157 (79%)			177 (89%)
Continuous care relationships (Having reimbursements from the same physician in the last month before death as in the eleven months before)	/175[b]				113 (57%)			
Palliative care team	/200[c]							34 (17%)
Contact with family physician	/200[c]				33 (17%)			136 (68%)
Follow-up visits at the hospital	/31[b]						0 (0%)	
Multidisciplinary care (Having =>5 reimbursements from at least two types of clinicians)	/200[c]				10 (5%)			89 (45%)
Administrative measures								
Palliative status (Receiving a palliative status (i.e. a supportive financial measure to facilitate palliative home care))	/200[c]							31 (16%)

[a] Empty cells indicate that the quality indicator was not face-validated for this time period. Due to privacy regulations, small cells (smaller than 5) could not be reported; [b] Quality indicator that was measured on a subset of children due to the nature of the quality indicator, not the full population. The quality indicator is still supposed to make an indication for the full population; [c] 180 cases were present in the database for medication and treatment, missing cases were interpreted as not having received reimbursed care. 151 cases were presentin the database for inpatient and outpatient care, missing cases were interpreted as not having received inpatient or outpatient care

Potentially inappropriate care at the end of life

Part 2 of Table 3 shows the measurements for the quality indicators of potentially inappropriate care at the end of life, for different time periods. 51% of the children had blood drawings in the last week before death. 29% received diagnostic and monitoring (at least 2 reimbursed MRIs, X-rays or CT scans) during the last month before death. 6% transferred to another hospital in the last month before death.

Table 3b: Quality indicators for potentially inappropriate end-of-life care for children who died with genetic and congenital conditions in Belgium, 2010-2017[a]

Quality indicators of potentially **inappropriate** end-of-life care								
	Time period: Number of days before death							
	Quality indicator denominator (n)	2days	7days	14days	30days	120days	From palliative status onwards	730days (full period available)
Treatment, medication, and monitoring								
Drawing blood	/200[c]	86 (43%)	101 (51%)					148 (74%)
Diagnostics and monitoring	/200[c]	45 (23%)	52 (26%)	54 (27%)	58 (29%)			116 (58%)
New placement central venous catheter	/200[c]	12 (6%)	21 (11%)					59 (30%)
Late palliative care provision	/200[c]		6 (3%)	8 (4%)				33 (17%)
Excessive (magnetic resonance imaging) monitoring	/200[c]	0 (0%)	0 (0%)	0 (0%)	0 (0%)			<5 (<3%)
Starting dialysis	/200[c]	0 (0%)	0 (0%)	0 (0%)	0 (0%)			5 (3%)
Surgeries	/200[c]	0 (0%)						27 (14%)
Place of care and death								
Care stopped after receiving palliative status	/31[b]						<2 (<16%)	
Hospital transfers	/200[c]	0 (0%)	5 (3%)	7 (4%)	12 (6%)			50 (25%)
Care setting transfers	/200[c]	0 (0%)	0 (0%)	0 (0%)	0 (0%)			68 (34%)

[a] Empty cells indicate that the quality indicator was not face-validated for this time period. Due to privacy regulations, small cells (smaller than 5) could not be reported; [b] Quality indicator that was measured on a subset of children due to the nature of the quality indicator, not the full population. The quality indicator is still supposed to make an indication for the full population; [c] 180 cases were present in the database for medication and treatment, missing cases were interpreted as not having received reimbursed care. 151 cases were present in the database for inpatient and outpatient care, missing cases were interpreted as not having received inpatient or outpatient care

Differences in appropriateness per region

Analyses of variance showed no significant differences for appropriateness or inappropriateness of end-of-life care for different Belgian provinces. However, there were significant differences for 3 Flemish healthcare regions: there was more appropriate care in the regions of Brussels, Genk, and Ghent, there was less inappropriate care in Brussels, and more inappropriate care in Genk compared to the reference category of Antwerp. See Table 4 for details on analyses of variance.

Table 4: Results for analyses of variance for province and Flemish healthcare regions on scales for appropriateness and inappropriateness

Province (n=198)				
	Scale 1: Potentially appropriatecare		Scale 2: Potentially inappropriate care	
	Estimated factor scores	P value[a]	Estimated factor scores	P value[a]
Province				
Antwerp (vs. Namur)	-.2764430129	0.4134	-0.392515223	0.2466
Flemish Brabant (vs.Namur)	0.1230197763	0.7355	-0.033609367	0.9266
Walloon Brabant (vs.Namur)	0.4006266641	0.3787	0.171708558	0.7061
Brussels (vs. Namur)	0.0111877051	0.9764	-0.069061877	0.8552
East Flanders (vs. Namur)	-.1024238384	0.7963	-0.279828822	0.4816
West Flanders (vs. Namur)	0.0873032610	0.8021	-0.060513678	0.8623
Hainaut (vs. Namur)	-.0198591797	0.9534	-0.057057766	0.8667
Liège (vs. Namur)	0.2926244495	0.4389	0.038332528	0.9193
Limburg (vs. Namur)	0.2032921104	0.5627	0.116592880	0.7402
Luxemburg (vs. Namur)	0.3395378853	0.4555	0.297458067	0.5138
Flemish health care regions (n=108)				
	Scale 1: Potentially appropriatecare		Scale 2: Potentially inappropriate care	
	Estimate	P value[a]	Estimate	P value[a]
Flemish health region				
Ostend (vs Antwerp)	0.334360799	0.5787	0.158826419	0.7919
Sint-Niklaas (vs Antwerp)	-0.322808989	0.5458	-0.387238023	0.4690
Brussels (vs Antwerp)	1.105391924	0.0047*	0.955906984	0.0141*
Genk (vs Antwerp)	1.443896470	0.0181*	1.514395135	0.0133*
Kortrijk (vs Antwerp)	0.428612860	0.4229	0.420440452	0.4319
Brugge (vs Antwerp)	1.866586561	0.0614	1.557430487	0.1176
Aalst (vs Antwerp)	0.406989528	0.3734	0.367481001	0.4214
Roeselare (vs Antwerp)	-0.136627596	0.7799	-0.259315205	0.5961
Mechelen (vs Antwerp)	0.440040699	0.3091	0.261389942	0.5451
Turnhout (vs Antwerp)	0.115070121	0.8139	0.059761727	0.9027
Leuven (vs Antwerp)	-0.118783857	0.7643	-0.149477672	0.7060
Hasselt (vs Antwerp)	0.480075777	0.1322	0.442722599	0.1647
Gent (vs Antwerp)	0.757468777	0.0310*	0.648118004	0.0641

Logistic regressions (dependent variable was the separate indicator, independent variable was province or healthcare region, regression performed separately due to different n) per indicator showed higher odds for certain indicators of appropriate care for certain healthcare regions, similar to the analyses of variance: there were higher odds for continuing anti-epileptic

medication and contact with a family physician in the Brussels healthcare region and higher odds for multidisciplinary care (having =>5 reimbursements from at least 2 types of clinicians) for the Ghent and Leuven healthcare regions. Provinces showed certain regions had higher odds of palliative care and palliative status (children received a palliative status – i.e. a supportive financial measure – to facilitate palliative home care), namely the Brussels, Flemish Brabant and Luxembourg provinces. Inappropriate care showed higher odds for some provinces: Antwerp, Walloon Brabant and Liège showed higher odds for new placement of a central venous catheter. See Appendix 6 for the results of the logistics regressions.

DISCUSSION

Main results of the study

In this population-based retrospective cohort study, we measured 21 quality indicators for potential appropriateness and potential inappropriateness of end-of-life care for children dying with genetic and congenital conditions between 2010 and 2017 in Belgium. In the last months, weeks and/or days before death, the children received possible appropriate care by having frequent specialist (79%) and continuous care relationships (57%), continuing anti-epileptic medication (88%), and pain control according to World Health Organization steps (65%), yet infrequent multidisciplinary care, palliative and comfort care, and family physician contact. Our results suggest that few children received potentially inappropriate care, yet diagnostics and monitoring and drawing blood were present for over one third of all children.

Interpretation of main findings and comparison with previous studies

It was remarkable that almost 4 out of 5 children received contact with their specialist physician in the final month before death – as is deemed appropriate – but that less than 1 in 5 in their final month of life had contact with a family physician (17%) and/or less than 1 in 10 received multidisciplinary care (5%, i.e. there was reimbursed care from at least 2 different types of health carers). The involvement of other health carers, such as the family physician, physiotherapists, especially at the end of life, could be further explored.

Palliative care provision for this group of children seems low: only about 1/5th received palliative care or a palliative status, an administrative registration of a palliative patient. Our measurements are similar to previous national studies: for example, a 2019 cohort study that was performed in Belgium for referrals to pediatric liaison teams, which in Belgium are responsible by governmental decree for the provision of palliative care and end-of-life care. They found for a similar period using Brussels hospital data, that 5% of children with genetic and congenital complex chronic conditions were referred to a pediatric liaison team (12). Both studies therefore indicate pediatric palliative care provision might be low in Belgium.

The highest scoring indicators for inappropriateness of care were the drawing of blood in the last week before death (51%) and diagnostics and monitoring (MRI, CT or X-ray) in the last month before death. Our measurements for some other indicators of inappropriate care were very low, yet match previous international population-level decedent studies for children with genetic and congenital complex chronic conditions. For example, our results showed that no one received a new dialysis in the last month before death. A 2019 population-level study that selected children aged 1 to 21 who died from complex chronic conditions between 2000 and 2013 in California, showed that children with genetic and congenital complex chronic conditions received hemodialysis in an average of 7% of cases in the last month of life (13). Measurements in our study may be smaller because we only measured a first dialysis, or because dialysis was provided less frequently. The drawing of blood and imaging may be provided as a reassurance to parents and to prepare them for the upcoming death of the child, but could also be administered earlier in the trajectory, and efforts could be made to decrease the diagnostics.

Our results showed that 3 healthcare regions in Belgium show a significantly higher scalescore of appropriateness. 2 of these 3 healthcare regions represent the regions with a pediatric liaison team anchored into the care system, which may explain the higher rate ofappropriate end-of-life care, and may provide an argument for pediatric liaison teams.

Strengths and limitations

Our study has various strengths. In Belgium, health insurance is obligatory, and therefore our database includes healthcare use for most children who died in Belgium in the studied period. Our design avoids selection bias, as the use of population data includes children that would normally be difficult to recruit for, or retain within, trials or prospective studies. The database is extensive, as 6 databases were linked, and contains a comprehensive overview of systematically collected procedures and other relevant variables, which would be too labour-intensive and sensitive to collect through surveys. Lastly, our quality indicator set was face-validated for the data at hand by various care professionals from the studied care settings and regions.

Our study also has some limitations. Our data does not include non-reimbursed healthcare variables such as comorbidities or psychologist visits. Innovative procedures such as experimental trials, frequent in children's cancer care, are not included in sickness fund data. Actual use of medication and treatments is not measured, only reimbursements of prescriptions. Some care, such as follow-up visits in a hospital, may not be reimbursed due to acts of goodwill by providers, and therefore are not registered within administrative databases. Data was not collected with research questions in mind, and could therefore cause issues with

construct validity: verification of validity, sensitivity, specificity of variables and indicators is not possible for conceptualization and operationalization of indicators. Indicators may thus over- or under-measure the concept, or variables may not measure the concept in actuality. However, certain validity and reliability analyses were performed to address possible bias.

While our quality evaluation provides a starting point for further inspection and quality improvements, certain risks especially for interpretation need to be mentioned. We could not distinguish between children who had a foreseen end-of-life trajectory, where care could have been unjustified because the child was known to be at the end of life and probably would not benefit from curative treatment, and an unforeseen end-of-life trajectory, where care could have been justified in light of high chances for curation. Therefore, for instance, reducing diagnostics without knowing what percentage of diagnostics were justifiably delivered to children, could pose risk in that it could hamper the curation of some seriously ill children, even though another percentage of children would benefit from such decrease. Further prospective and retrospective studies with a measurement for duration of end-of-life care may first be performed to determine the specific characteristics of and indications for children who would benefit from treatment reduction.

Conclusion

Our measurement of the validated quality indicators for children who died with genetic and congenital conditions suggests that the quality for their end-of-life care can be improved in terms of palliative and comfort care provision, contact with care providers, and diagnostics. Further research is advised to study children's and families' perspectives on results, and gather reasonings behind healthcare use, in order to be able to provide family-centered solutions and care improvements. Additionally, care themes could be evaluated that were not addressed through the indicators, such as siblings and family bereavement care.

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Supplemental information 2: **Additional information on databases**

Institution	Database	Description
Intermutualistic Agency	Sociodemographic database	Sociodemographic information for all individuals with healthcare insurance,which is legally mandatory in Belgium (18)
	Healthcare database	Outpatient and hospital care providedin Belgium, except medication dispensed in pharmacies, with amongst others date, healthcare provider, setting. (18)
	Pharmaceutical database	Reimbursed medication dispensed inpharmacies in Belgium, with amongstothers date of prescription, date of delivery, information on prescriber, setting, for every reimbursed medication delivery (18)
StatBel	Death certificate database	Underlying cause of death, as well asassociated and intermediate causes of death on all deaths in Belgium, from Belgian death certificates [31]
	Population registry database	Citizens' household composition and highest attained level of education forevery Belgian citizen (18)
	Census database	Data from the last census in Belgiumin 2012, such as educational level and housing comfort characteristics. (18)

Supplemental information 4: Validation and reliability verifications for identification of bias

Database population
Validity
Our database population was compared to population numbers from Statistics Belgium. Statistics Belgium public documentation identified 6050 deaths for children between 1 and 25 years old. Our database includes5098 deaths for children between 1 and 25 years old, which is 84% of the number of deaths reported by Statistics Belgium. Differing selections for death, time and age by the governmental agencies providing the data may account for the differing number of deaths between databases.
Reliability
In order to verify the reliability of our ID selection, we compared the amount of children deaths in our differentdatabases. Between databases, there was around a 2% difference in children's deaths.
Indicators
Validity
To our knowledge, no publications are available to compare the percentages found to verify external validity.
Reliability
To evaluate reliability, measurements were repeated with a different method or by a different researcher for somequality indicators. For some quality indicators (physiotherapy, family physician contact, clinical care provision, involvement of specialist physicians, surgeries, care setting transfers), two different calculation methods were used to verify reliability. Categorical selection and selective selection were applied. Quality indicators were originally calculated with a selective method, meaning the researcher screened all nomenclature codes and hand-selected the relevant codes. The categorical selection method was used to validate the selective method, meaning the calculations were repeated while selecting categories, e.g. following the structure of the nomenclature codes orpractitioner categories. For example, for the quality indicator 'Physiotherapy', the selective method entailed selecting all individual nomenclature codes of which the description referred to physiotherapy. The categorical method entailed selecting all nomenclature codes that were categorized as prescribed by a physiotherapist by the healthcare funds. For most quality indicators, results of the two methods were similar, which suggests resultsare internally reliable. For the quality indicator care setting transfers, use of different variables gave differing results, which suggests results may not be reliable – however, conversations with the database providers indicatethat the more reliable variables were used for final analysis. Some quality indicators (palliative status, starting dialysis), were repeated by another researcher. Same resultswere found by the other researcher for these quality indicators, which suggests the calculations are reliable.

Supplemental information 5: Additional information and tables for scale construction and analyses of variance

Scale construction

Initial scale selection
We grouped variables per category of appropriateness and inappropriateness. We used thelast-30-days-version of the quality indicators where that time interval was relevant. When no30-day-version was available, a shorter time interval was used, for example surgeries was only validated for the last 2 days before death.

Scale optimalization
Per group of variables, we performed a principal component analysis with the number of factors limited to 1, on a correlation matrix of the variables, to see which variables were highly correlated with each other. We also performed Cronbach Alpha analysis. We deleted variables that did not load highly together with the other variables in the principal componentloadings.

Assumption tests
Prior to the PCA, a Kaiser–Meyer–Olkin (KMO) test was performed to verify whether there was sufficient Measure of Sampling Adequacy (MSA) . In order to obtain a sufficient matrix,some variables which consisted of full or near zeroes were deleted (e.g. starting dialysis, gastrostomy placement).

Final scales
The final scale for appropriateness of care included the variables: physiotherapy, specializedcomfort medication, family physician, continuous care relationships, palliative care, multidisciplinary care, palliative status, and involvement of specialist physicians.

The final scale for appropriateness of care included the variables: diagnostics and monitoring, starting dialysis, surgeries, late palliative care provision, new placement centralvenous catheter, drawing blood, hospital transfers, and care setting transfers.

Analyses of variance

General
We performed analyses of variance with post hoc tests with the SAS General Linear Model(GLM) procedure, with least squares to fit method, for each scale. Analyses were done for region (province and Flemish health care regions).

Initial variable selection
Estimated factor scores for each scale from the PCA (see above) were used as thedependent variable. Independent variables were provinces and Flemish health care regions (in separateanalyses).

Model construction
We included all independent variables.

Cut-off score
The alpha level of 0.05 defined statistical significance.

Supplemental Materials 6: Logistic regressions per separate quality indicator for province and Flemish healthcare region per quality indicator

	Physiotherapy a	Comfort medication[a]	Continuing anti-epileptic medication	Contact with family physician	Continuous care relationships	Palliative care	Multidisciplinary care	Palliative status	Specialist physicians	Diagnostics and monitoring
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Flemish healthcare region (separate logistic regressions from province) (n=108)										
Ostend (vs Antwerp)	0.26 (0.02-3.40)	0.15 (0.01-2.76)	0.15 (0.01-2.01)	0.27 (0.02-4.05)	0.67 (0.05-8.37)	0.15 (0.01-2.76)	1.69 (0.05-63.35)	0.64 (0.01-29.30)	1.06 (0.08-13.44)	2.33 (0.06-84.83)
Sint-Niklaas (vs Antwerp)	1.03 (0.10-11.03)	0.82 (0.02-2.82)	0.56 (0.05-6.54)	1.45 (0.04-50.23)	2.61 (0.25-27.10)	0.21 (0.01-3.30)	2.17 (0.07-70.41)	0.21 (0.01-3.30)	1.77 (0.20-15.90)	3.00 (0.10-94.13)
Brussels (vs Antwerp)	0.44 (0.09-2.21)	1.91 (0.06-59.35)	5.07 (0.21-125.5)	3.39 (0.13-89.80)	0.33 (0.06-1.91)	1.91 (0.06-59.35)	1.53 (0.18-13.37)	1.91 (0.06-59.35)	0.28 (0.04-2.19)	0.23 (0.04-1.23)
Genk (vs Antwerp)	0.73 (0.06-9.44)	0.15 (0.01-2.76)	0.40 (0.03-5.57)	0.27 (0.02-4.05)	0.67 (0.05-8.37)	0.15 (0.01-2.76)	1.69 (0.05-63.35)	0.15 (0.01-2.76)	0.25 (0.01-8.90)	0.20 (0.02-2.65)
Kortrijk (vs Antwerp)	0.44 (0.05-4.03)	0.82 (0.02-32.82)	2.17 (0.07-70.54)	1.45 (0.04-50.23)	1.12 (0.13-9.88)	0.82 (0.02-32.82)	0.56 (0.05-6.54)	0.82 (0.02-32.82)	0.76 (0.07-8.00)	0.78 (0.07-8.61)
Brugge (vs Antwerp)	0.14 (0.00-15.35)	0.26 (0.00-32.31)	0.08 (0.00-8.78)	0.46 (0.00-49.74)	0.36 (0.00-38.14)	0.26 (0.00-30.38)	0.63 (0.01-58.70)	0.25 (0.00-29.42)	0.56 (0.01-61.05)	0.10 (0.00-11.8)
Aalst (vs Antwerp)	1.61 (0.18-14.65)	1.18 (0.03-41.19)	0.89 (0.09-8.74)	0.29 (0.03-2.53)	0.62 (0.09-4.25)	0.16 (0.02-1.80)	3.14 (0.11-87.61)	0.16 (0.02-1.80)	0.48 (0.05-4.30)	0.60 (0.08-4.43)
Roeselare (vs Antwerp)	1.32 (0.14-12.80)	0.27 (0.02-3.88)	0.72 (0.07-7.62)	0.23 (0.02-2.14)	0.80 (0.11-6.00)	0.27 (0.02-3.88)	2.65 (0.09-78.7)	0.27 (0.02-3.88)	1.26 (0.17-9.67)	3.67 (0.13-105.14)
Mechelen (vs Antwerp)	0.97 (0.14-6.49)	1.36 (0.04-45.64)	0.53 (0.07-3.92)	0.36 (0.04-2.92)	0.51 (0.08-3.27)	0.20 (0.02-2.10)	3.62 (0.14-96.80)	0.20 (0.02-2.09)	0.80 (0.12-5.27)	1.44 (0.16-12.94)
Turnhout (vs Antwerp)	0.62 (0.08-4.81)	1.00 (0.03-36.88)	0.72 (0.07-7.62)	0.48 (0.04-5.59)	0.48 (0.04-5.59)	0.27 (0.02-3.88)	2.65 (0.09-78.72)	0.27 (0.02-3.88)	0.59 (0.06-5.61)	1.00 (0.10-10.00)
Leuven (vs Antwerp)	8.36 (0.35-199.09)	1.73 (0.06-54.74)	1.37 (0.15-12.21)	0.48 (0.06-3.73)	3.35 (0.56-19.97)	0.52 (0.04-6.35)	4.58 (0.18-115.67)	0.52 (0.04-6.35)	0.95 (0.18-5.16)	1.89 (0.22-15.95)
Hasselt (vs Antwerp)	0.79 (0.20-3.15)	3.73 (0.13-106.2)	1.79 (0.29-10.91)	0.29 (0.06-1.51)	0.62 (0.17-2.33)	0.45 (0.06-3.65)	1.79 (0.29-10.90)	0.45 (0.06-3.65)	0.48 (0.11-2.07)	0.74 (0.17-3.17)
Gent (vs Antwerp)	1.03 (0.22-4.79)	0.30 (0.04-2.49)	1.21 (0.19-7.67)	0.81 (0.12-5.76)	1.12 (0.27-4.60)	0.30 (0.04-2.49)	7.00 (0.30-164.03)	0.30 (0.04-2.49)	0.54 (0.11-2.63)	0.58 (0.12-2.70)

[a] Penalized logistic regression was performed due to low counts in the contingency table, [b] Due to low total and cell counts for these indicators, no logistic regression was performed

	Starting dialysis	Surgeries	Late palliative care provision	New placement central venous catheter	Drawing blood	Hospital transfers	Care setting transfers
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Flemish healthcare region (separate logistic regressions from province) (n=108)							
Ostend (vs Antwerp)	0.64 (0.01-29.30)	0.20 (0.00-17.65)	0.20 (0.00-17.66)	0.64 (0.01-29.30)	0.73 (0.06-9.44)	0.05 (0.00-1.96)	0.27 (0.02-4.05)
Sint-Niklaas (vs Antwerp)	0.82 (0.02-32.82)	0.26 (0.00-20.19)	0.26 (0.00-20.19)	0.82 (0.02-32.82)	1.03 (0.10-11.03)	0.26 (0.00-20.19)	1.45 (0.04-50.23)
Brussels (vs Antwerp)	1.91 (0.06-59.35)	0.60 (0.01-38.05)	0.60 (0.01-38.05)	0.58 (0.05-6.97)	0.21 (0.04-1.11)	0.10 (0.00-2.50)	0.23 (0.04-1.50)
Genk (vs Antwerp)	0.64 (0.01-29.30)	0.05 (0.00-1.96)	0.05 (0.00-1.96)	0.64 (0.01-29.30)	0.26 (0.02-3.40)	0.05 (0.00-1.96)	0.10 (0.01-1.46)
Kortrijk (vs Antwerp)	0.82 (0.02-32.82)	0.26 (0.00-20.19)	0.26 (0.00-20.19)	0.21 (0.01-3.30)	0.44 (0.05-4.03)	0.26 (0.00-20.19)	0.16 (0.02-1.77)
Brugge (vs Antwerp)	0.27 (0.00-32.79)	0.08 (0.00-14.72)	0.08 (0.00-15.96)	0.27 (0.00-33.18)	0.14 (0.00-15.31)	0.08 (0.00 -16.81)	0.05 (0.00 -6.10)
Aalst (vs Antwerp)	1.18 (0.03-41.19)	0.37 (0.01-25.91)	0.37 (0.01-25.91)	0.33 (0.03-4.49)	0.44 (0.07-2.95)	0.37 (0.01-25.91)	0.29 (0.03-2.53)
Roeselare (vs Antwerp)	1.00 (0.03-36.88)	0.31 (0.01-22.99)	0.31 (0.00-22.99)	1.00 (0.03-36.88)	1.32 (0.14-12.80)	0.31 (0.00-22.99)	0.23 (0.02-2.14)
Mechelen (vs Antwerp)	1.36 (0.04-45.64)	0.43 (0.01-28.90)	0.43 (0.01-28.90)	1.36 (0.04-45.64)	0.34 (0.06-2.10)	0.43 (0.01-28.90)	0.13 (0.02-0.96)
Turnhout (vs Antwerp)	1.00 (0.03-36.88)	0.31 (0.01-22.99)	0.09 (0.00-2.93)	1.00 (0.03-36.88)	0.62 (0.08-4.81)	0.31 (0.00-22.99)	0.48(0.04-5.59)
Leuven (vs Antwerp)	1.73 (0.06-54.74)	0.54 (0.01-34.98)	0.54 (0.01-34.98)	0.52 (0.04-6.35)	1.32 (0.21-8.21)	0.54 (0.01-34.98)	0.48 (0.06-3.73)
Hasselt (vs Antwerp)	3.73 (0.13-106.2)	0.37 (0.01-10.65)	0.37 (0.01-10.65)	0.67 (0.08-6.00)	0.3 (0.08-1.17)	1.17 (0.02-69.16)	0.29 (0.06-1.51)
Gent (vs Antwerp)	0.82 (0.07-9.49)	0.82 (0.01-50.44)	0.26 (0.01-7.54)	2.64 (0.09-78.00)	0.34 (0.08-1.47)	0.14 (0.01-3.56)	0.16 (0.03-0.91)

[a] Penalized logistic regression was performed due to low counts in the contingency table, [b] Due to low total and cell counts for these indicators, no logistic regression was performed

	Physiotherapy a	Comfort medication[a]	Continuing anti- epileptic medication	Contact with family physician	Continuous care relationships	Palliative care	Multidisciplinary care	Palliative status	Specialist physicians	Diagnostics and monitoring
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Province (separate logistic regressions from Flemish healthcare regions) (n=198)										
Antwerp (vs. Namur)	1.02 (0.25-4.16)	2.28 (0.20-25.75)	0.43 (0.06-3.10)	0.17 (0.01-3.58)	0.34 (0.09-1.34)	2.68 (0.57-12.61)	0.28 (0.01-6.49)	2.68 (0.57-12.61)	1.39 (0.32-6.10)	2.34 (0.57-9.69)
Flemish Brabant (vs. Namur)	1.25 (0.27-5.82)	4.68 (0.16 -136.63)	1.48 (0.13-17.15)	0.26 (0.01-6.55)	0.43 (0.10-1.87)	5.843 (0.74-46.12)	0.46 (0.02-13.56)	5.84 (0.74-46.12)	0.87 (0.17-4.55)	1.08 (0.25-4.60)
Walloon Brabant (vs. Namur)	0.18 (0.03-1.26)	0.60 (0.05-7.75)	2.04 (0.06-67.50)	0.19 (0.01-5.95)	0.30 (0.05-1.89)	0.74 (0.12-4.67)	0.19 (0.01-5.95)	1.23 (0.18-8.54)	1.15 (0.16-8.46)	1.02 (0.17-6.18)
Brussels (vs. Namur)	0.29 (0.06-1.37)	1.24 (0.11-14.58)	0.33 (0.04-2.67)	1.22 (0.02-75.48)	0.29 (0.06-1.37)	4.90 (0.61-39.30)	0.38 (0.01-11.48)	4.90 (0.61-39.30)	0.78 (0.14-4.45)	1.80 (0.37-8.66)
East Flanders (vs. Namur)	0.55 (0.11-2.69)	0.55 (0.06-5.29)	0.25 (0.03-2.09)	0.11 (0.01-2.69)	0.31 (0.06-1.53)	2.18 (0.35-13.66)	0.31 (0.01-9.40)	3.95 (0.48-32.49)	1.42 (0.26-7.87)	2.98 (0.49-18.07)
West Flanders (vs. Namur)	1.35 (0.31-5.92)	0.74 (0.09-6.03)	0.55 (0.07-4.22)	0.17 (0.01-3.78)	0.47 (0.12-1.95)	1.35 (0.31-5.92)	1.81 (0.03-108.66)	1.35 (0.31-5.92)	1.05 (0.22-4.98)	1.51 (0.37-6.21)
Hainaut (vs. Namur)	0.84 (0.21-3.37)	6.84 (0.24-193.90)	1.27 (0.14-11.45)	0.16 (0.01-3.44)	0.41 (0.10-1.64)	2.58 (0.55-12.15)	0.68 (0.02-19.81)	3.45 (0.68-17.56)	0.55 (0.11-2.78)	2.24 (0.54-9.30)
Liège (vs. Namur)	0.77 (0.16-3.57)	0.70 (0.07-6.52)	0.46 (0.06-3.91)	0.10 (0.01-2.36)	0.12 (0.02-0.66)	1.32 (0.26-6.58)	1.22 (0.03-75.39)	1.32 (0.26-6.58)	0.09 (0.00-2.14)	1.05 (0.23-4.69)
Limburg (vs. Namur)	0.86 (0.20-3.66)	1.80 (0.16-20.59)	0.70 (0.09-5.77)	0.07 (0.00-1.43)	0.26 (0.06-1.10)	2.05 (0.43-9.82)	0.32 (0.01-7.97)	2.05 (0.43-9.82)	0.69 (0.14-3.55)	1.18 (0.29-4.80)
Luxemburg (vs.Namur)	0.74 (0.12-4.67)	2.04 (0.06-67.47)	2.04 (0.06-67.50)	0.19 (0.01-5.95)	0.74 (0.12-4.67)	8.05 (0.32-205.90)	0.63 (0.01-42.45)	8.05 (0.32-205.9)	1.15 (0.16-8.46)	0.65 (0.11-3.83)

[a] Penalized logistic regression was performed due to low counts in the contingency table, [b] Due to low total and cell counts for these indicators, no logistic regression was performed

	Starting dialysis	Surgeries [b]	Late palliative care provision	New placement central venous catheter	Drawing blood	Hospital transfers	Care setting transfers			
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)			
Province (separate logistic regressions from Flemish healthcare regions) (n=198)										
Antwerp (vs. Namur)	0.70 (0.02-20.50)		0.70 (0.02-20.51)	6.33 (0.78-51.16)	1.39 (0.37-5.23)	2.19 (0.04-129.56)	1.42 (0.34-5.97)			
Flemish Brabant (vs. Namur)	1.44 (0.02-87.85)		1.44 (0.02-87.99)	2.33 (0.37-14.85)	0.96 (0.23-3.94)	0.26 (0.01-6.55)	0.98 (0.22-4.45)			
Walloon Brabant (vs. Namur)	0.63 (0.01-42.45)		0.19 (0.01-5.95)	5.67 (0.21-149.89)	0.55 (0.09-3.31)	0.19 (0.01-5.95)	0.47 (0.08-2.89)			
Brussels (vs. Namur)	1.22 (0.02-75.39)		1.22 (0.02-75.51)	1.93 (0.30-12.52)	0.68 (0.16-2.98)	0.38 (0.01-11.48)	1.32 (0.26-6.58)			
East Flanders (vs. Namur)	1.00 (0.02-62.96)		1.00 (0.02-63.07)	2.78 (0.32-24.08)	1.34 (0.28-6.36)	0.31 (0.01-9.40)	0.55 (0.11-2.69)			
West Flanders (vs. Namur)	0.58 (0.02-17.03)		0.58 (0.02-17.03)	5.22 (0.64-42.68)	0.87 (0.22-3.35)	0.33 (0.01-8.33)	0.77 (0.19-3.22)			
Hainaut (vs. Namur)	2.11 (0.04-125.34)		0.40 (0.02-9.76)	0.96 (0.21-4.34)	1.00 (0.27-3.72)	0.27 (0.01-6.25)	0.97 (0.24-3.97)			
Liège (vs. Namur)	1.22 (0.02-75.39)		1.22 (0.02-75.51)	11.00 (0.47 - 259.31)	0.54 (0.12-2.37)	1.22 (0.02-75.42)	0.37 (0.08-1.72)			
Limburg (vs. Namur)	1.74 (0.03-104.50)		0.32 (0.01-7.98	2.87 (0.46-17.95	0.57 (0.14-2.24)	0.56 (0.02-16.33)	0.72 (0.17-3.03)			
Luxemburg (vs.Namur)	0.63 (0.01-42.45)		0.63 (0.01-42.53)	0.87 (0.12-6.36)	0.33 (0.05-2.21)	0.19 (0.01-5.95)	8.05 (0.32-205.89)			

[a] Penalized logistic regression was performed due to low counts in the contingency table, [b] Due to low total and cell counts for these indicators, no logistic regression was performed

General discussion

1. INTRODUCTION

The main aim of this dissertation was to evaluate the appropriateness of end-of-life care for children with cancer, neurological conditions, and genetic and congenital conditions on a population level in Belgium, using pediatric-specific quality indicators and big data. First, to identify potential indicators, we performed a systematic review (**Chapter 1**). Second, we performed expert interviews and expert panels with pediatric care professionals to develop and validate the pediatric-specific indicators for appropriateness of end-of-life care for each of the three disease groups. This resulted in three sets of indicators for appropriateness and inappropriateness of end-of-life care in children: one for children with cancer (21 indicators), one for children with neurological conditions (24 indicators), and one for children with genetic and congenital conditions (23 indicators) (**Chapter 2**). Third, we measured the indicators within routinely collected healthcare databases on a Belgian population level, for children with neurological conditions (**Chapter 3**), cancer (**Chapter 4)** and genetic and congenital conditions (**Chapter 5**).

In this general discussion part, I will first present the main findings, then present methodological considerations for the studies, then discuss the main findings of our studies in relation to the current state of the art. Lastly I will present the implications of this dissertation for policy, practice and education, and research.

2. MAIN FINDINGS

2.1 Identification of healthcare interventions improving and/or reducing quality of life in children at the end of life

In **Chapter 1**, we described the results of a systematic review which identified the healthcare interventions that are associated with improved and/or reduced quality of life for children at the end of life. A total of twenty healthcare interventions were identified with quantitative evidence for improved or reduced quality of life. Nine healthcare interventions showed statistically significant associations.

Palliative care, certain comfort and pain medications and treatments, and symptom monitoring

seem to improve children's symptoms and quality of life at the end of life. The palliative care interventions with the strongest evidence quality had in common a multidisciplinary nature and that they provided full-time support to the family. The two comfort medications dexmedetomidine and methadone mainly seemed to lower pain at the end of life. Pleurodesis and non-invasive mechanical ventilation, administered as comfort treatments, were associated with better breathing in the children. Electronical symptom monitoring, i.e. weekly symptom surveys via an app of which summaries were sent to care providers, increased emotional quality of life.

Curative therapies, such as chemotherapy and stem cell transplant, can seemingly decrease quality of life at the end of life for children. IV chemotherapy provided to children at the end of life was associated with increased dyspnea. Stem cell transplant was associated mainly with increased physical and emotional symptoms at the end of life in children, for example increased sadness and fatigue.

We found that the current evidence base is broad yet limited in quality, and that many studies showed bias for design and execution.

2.2 Development of sets of face-validated quality indicators for appropriateness of end-of-life care in children with neurological conditions, cancer and genetic and congenital conditions

In **Chapter 2**, we described the development of three pediatric-specific sets of indicators for appropriateness and inappropriateness of end-of-life care, measurable with administrative healthcare data.

The final sets include 21 quality indicators for cancer, 24 for neurologic conditions, and 23 for genetic and congenital conditions, as presented in **Chapter 2**. All quality indicator sets cover 4 similar themes, namely:

1. Treatment, medication and monitoring (containing quality indicators such as physiotherapy, comfort medication, and pain control according to guidelines from the World Health Organization),

2. Place of care and death (containing quality indicators such as home death),
3. Care services and providers (containing quality indicators such as contact with a family physician or having continuous care relationships), and
4. Administrative measures (containing quality indicators such as receiving palliative status (and therefore being administratively entitled to higher reimbursements)).

The consulted experts found most quality indicators valid only for the very last period of life, such as the last 30, 14, 7, and 2 days of life.

2.3 Population-level analysis of the appropriateness of end-of-life care in children with cancer, neurological conditions, and genetic and congenital conditions

In **Chapter 3**, we evaluated the appropriateness of end-of-life care for all children (n=139) who died with neurological conditions in Belgium between 2010 and 2017 using our validated quality indicator set. **Chapter 4** did the same for all children (n=228) who died with cancer in Belgium between 2010 and 2017. **Chapter 5** did so for children who died with genetic and congenital conditions in Belgium between 2010 and 2017 (n=200). In all analyses we examined differences between the appropriateness and inappropriateness of care of different clinical and socio-demographic groups.

2.3.1. Potential appropriateness of end-of-life care

Comfort treatments were often not provided to children at the end of life. Generally, more than one third of seriously ill children received (reimbursed) physiotherapy at the end of life (34% for children with neurological conditions, 36% for children with cancer, 37% for children with genetic and congenital conditions). Less than one tenth of seriously ill children received specialized comfort medication (6% for children with cancer and genetic and congenital conditions, 8% for children with neurological conditions). Palliative care was provided for less than one fifth of children (14% for children with neurological conditions and for children with cancer, 17% for children with genetic and congenital conditions). For the category of place of care and death, findings show that half of children with cancer died at home (47%). For the category of care services and providers, specialist physicians were frequently present yet other

care providers were not. Continuous care (having reimbursements from the same physician in the last month before death as in the eleven months before) was provided to over half of all seriously ill children at the end of life (53% of children with cancer, 55% of children with neurological conditions, and 57% of children with genetic and congenital conditions). Additionally, 75% of children with neurological conditions received reimbursements from specialist physicians in the last month before death. However, not even one fifth of seriously ill children at the end of life received reimbursements from a general physician in the last month before death (13% for children with cancer, 17% for children with neurological conditions and for genetic and congenital conditions). Multidisciplinary care in the last month before death was low (4% for children with cancer, 5% for children with genetic and congenital conditions, 7% for children with neurological conditions). Administrative measures were not provided oftenfor children across illness groups. Palliative status was provided to circa one fifth of children with serious illness at the end of life (11% for children with cancer, 13% for children with neurological conditions, 16% for children with genetic and congenital conditions), and 8% of children with neurological conditions received increased child benefits.

2.3.2. Potential inappropriateness of end-of-life care

Treatments and medications labeled as potentially inappropriate were usually not frequent in seriously ill children at the end of life. No or fewer than 5% of children received a new dialysis, surgeries or old-generation reimbursements for nausea within the last month before death for any of the illness groups. Some quality indicators of inappropriateness were more prevalent. Around one fourth to one third of children received diagnostics and monitoring (receiving at least 2 MRI's, X-rays or CT scans) in the last month before death (26% for children with neurological conditions, 29% for children with genetic and congenital conditions, 31% for children with cancer). Blood drawings were very frequent, considering that roughly half of children received blood drawings in the last week before death (45% of children with neurological conditions and for children with cancer, 51% for children with genetic and congenital conditions). There was up to one third of children that received admissions to the

Intensive Care Unit in the last two weeks before death (18% for children with cancer, 27% for children with neurological conditions).

2.3.3. Clinical and socio-demographic differences in appropriateness of end-of-life care

Appropriateness and inappropriateness of care differed for certain clinical and socio-demographic groups. For children with neurological conditions, there is a difference between different neurological disease categories: disorders of the central nervous system and movement diseases showed lower scores for appropriate care. For children with cancer, there were differences for region and nationality: One Flemish healthcare region (Limburg) showed higher appropriateness, and children with a non-Belgian background received more inappropriate care. For children with genetic and congenital conditions, appropriateness differed for region: Some regions (Brussels, Genk, and Ghent) received more appropriate care, while less inappropriate care was also present in Brussels, and more inappropriate care in Genk.

In conclusion, our study showed that improvements could be made for involvement of specialized care providers such as general physicians and physiotherapists, comfort care such as specialized comfort medications, administrative support for families, and diagnostics such as blood drawing. Appropriateness levels did differ for certain disease categories, region, and nationality background. Findings for appropriateness and inappropriateness were similar across illness groups, yet differences for clinical, sociodemographic and regional factors varied per illness group.

3. METHODOLOGICAL CONSIDERATIONS

Four study designs were used within this dissertation, namely: systematic literature review (**Chapter 1**), expert interviews (**Chapter 2**), RAND/UCLA consensus method (**Chapter 2**), and population-level decedent cohort studies using administrative databases (**Chapters 3-5**). Some methodological considerations regarding these study designs for the dissertation at

hand are discussed below.

3.1 Literature review

A clear view on the evidence base is a requisite for the construction of quality indicators, yet one that is often missing. Most quality indicators for end-of-life care in adults and children are based on expert opinion and/or non-empirical quality indicators previously suggested in literature (1–3). Furthermore, when literature review for quality indicators is performed, it is often not done or reported systematically (4). We chose to perform a systematic review (**Chapter 1**) as it provides a rigorous and objective approach to summarize the best available evidence on a population level for quality indicator construction (5–7). It summarizes the best available evidence on a population level for quality indicator construction. It summarizes findings from studies conducted on tens or hundreds of children, which greatly exceeds the number of dying children individual pediatric care experts have had experience with (8). A limit of the systematic review is that it only provides an overview of the healthcare interventions that have been studied currently. Literature may not have studied all available medications and treatments, especially for a relatively new and ethically challenging domain such as pediatric end-of-life care (8). Lastly, even though we aimed to obtain the best available evidence, the current available evidence base for the field of pediatric end-of-life care may be biased as evidenced by low GRADE scores. Although biased, systematic literature study provides a necessary empirical starting point for public health indication.

3.2 RAND/UCLA Appropriateness Method

The main strength of the RAND/UCLA Appropriateness Method (**Chapter 2**) lies in its combination of literature review, individual opinion of experts, and collective discussion to validate quality indicators. Joining the perspectives of literature with expert opinion is particularly necessary for this quality evaluation, as strong empirical evidence on children's end-of-life care is missing (**Chapter 1**).

The use of administrative healthcare data as a focus within the RAND/UCLA method to validate quality indicators warrants certain considerations. Certain aspects of children's end-of-life care cannot be measured with administrative healthcare data. Therefore, themes such as patient and family preferences, symptom and quality of life monitoring, psychosocial support, communication, treatment intention, family care, upkeep of routine, and advance care planning (2,9–12) could not be included in the RAND/UCLA expert panels. Furthermore, some healthcare variables cannot be measured as they are not present in the databases. For instance, the measurement of preference of place of death is increasingly preferred to the measurement of place of death for children's end-of-life care in studies (2,12). No variables are available in Belgian administrative databases for the preference of place of death. Lastly, the experts as selected by RAND/UCLA standards could not evaluate the aspect of administrative data within panels. Pediatric care professionals validated the quality indicators' denominators and numerators as well as time periods. However, pediatric care professionals had little knowledge about the structure of and rules applied to the big data that would be used to measure the quality indicators. For instance, certain variables are only entered into administrative records once a year, which makes counting the instances of that variable unreliable, and administrative measures that are registered only once during the illness trajectory could have been indicated before the two-year period encompassed in the database, such as palliative status. Data administrators from the Belgian Intermutualistic Agency were consulted for the purpose of variable verification prior to the panels, yet there was no formal process of evaluation for the reliability and validity of the operationalization of the quality indicators present within the utilized RAND/UCLA methodology. Having translated the identified evidence base into candidate quality indicators could also be limited by the focus on administrative data of this dissertation: Not all evidence from the systematic review could be translated into candidate quality indicators. Electronic patient-reported symptom monitoring, for example, does not have a nomenclature code within the Belgian administrative healthcare data. The RAND/UCLA Appropriateness method is a consensus method, which means group consensus opinion is sought. No room is present for a possibly correct outlier opinion. Our

sample was hospital- and snowballing-based, which might have led to sampling of professionals that stand for a similar opinion (5). No expert opinion or panel was included for the translation of candidate indicators to the initial indicator sets.

3.3 Administrative databases to study appropriateness of end-of-life care for children in Belgium

To conduct the decedent retrospective cohort studies to evaluate appropriateness of end-of-life care for children who died of cancer, neurological conditions and genetic and congenital conditions (**Chapter 3 to 5**), we used population-level, routinely collected administrative databases. Databases from the Belgian Intermutualistic Agency, Statistics Belgium, and Cancer Registry Belgium were used. Below we describe methodological considerations for the use of big data in quality evaluation of end-of-life care in children, for the decedent cohort study design, for obtaining, exploring and linking the databases, and for statistical methods.

3.3.1 Methodological considerations for the general use of big data for the evaluation of quality of end-of-life care in children

The use of routinely collected databases provides valuable opportunities for the evaluation of the quality of care in children's research. These databases provide access to subgroups of children that normally would be hard to reach and not be included in studies, for example families with a migration background, single parent households, or persons with lower levels of education or income (13). Use of databases furthermore eliminates recall bias, as parents may not remember correctly the names of medications and treatments their child received when surveyed directly. Similarities in structure for administrative data, allow to pool and compare hospital systems across region or different countries, which can be beneficial for this field with little cases per hospital system or country in order to infer generalizations or subgroup characteristics which is not possible based on a few cases.

The use of administrative database can also hinder children's end-of-life care quality evaluation. The adult-focused nature of the data can lead to an overemphasis on themes for

adults' care, and underestimations. For instance, no nomenclature codes are available for children's palliative care liaison teams. Adult nomenclature codes are therefore used instead for collection by the administrative agencies and measurement by researchers. Reimbursement for certain pediatric care is sometimes provided by private, philanthropic funding or provided at no cost based on goodwill of providers and therefore not registered in administrative databases, for which visibility of the medication or treatment relies on reimbursements from the government. Also, not all factors especially relevant for children that could differ for appropriateness are available (14), such as psychological family characteristics. Moreover, our disease group selections may show overlap due to comorbidities, for instance brain tumors may be included in both the group of children with cancer and with neurological conditions.

3.3.2 Methodological considerations for the decedent cohort study design

The decedent cohort study design applied to administrative databases is often used in end-of-life care research to pragmatically provide a group of deceased persons (15). However, an important consideration for this dissertation, is that it is not possible to make a distinction between the children who care providers knew would die, and the children who died unexpectedly. In the latter case, aggressive medications and treatment in the last month or even days before death might have been provided, but this was properly justified in the light of survival chances of the child and therefore cannot be labeled as inappropriate. There may be a higher chance for such cases difficult to label as inappropriate treatment at the end of life in children's care as opposed to adults' care, due to the high rate of innovative yet high- risk treatments developed for and applied to children's medicine. For instance, the use of stem cell transplants: in children with cancer this treatment with many possible downsides forthe child at the end of life (**Chapter 1**), might be justified even in case of death due to its highchances for curation in a child. Carefulness in interpretation was applied, however, by classifying care as being potentially appropriate or inappropriate. Moreover, population-level conclusions also likely slope towards the larger group of predictable deaths.

3.3.3 Methodological considerations for linking of databases

The linking of different healthcare databases provided many variables available for quality indicator measurement that are not feasible to collect through survey methods. Linking the healthcare databases with a sociodemographic database made sure analyses for subgroups could be done. However, our linking also showed that there were differences in the number of children that died between databases. This is likely due to differing methods of classification between administrative agencies, such as for age selection, and misclassification errors by mutualities. Impact of the differences in death selection is likely minimal: there is about a 2% difference in the number of children's deaths between databases, and systematic linking errors were excluded. Larger differences were observed between cohort selection based on death certificate and cohort selection based on diagnosis. However, only analysis based on death certificate was possible as not all healthcare data was available for cohort selection based on diagnosis, and death certificate data is generally seen as the preferred method for cause of death selection despite potential issues with its validity (16).

3.3.4 Methodological considerations of obtaining and exploring the databases

The data in administrative databases are routinely collected and stored by mutualities and governmental agencies, which makes that costs and efforts for data collection are eliminated. Data cleaning and verification is also already done by database administrators. However, this does not mean administrative data is readily available: other challenges are present before data can be accessed. Due to privacy regulations, permissions need to be obtained from both the institutions that manage the data, as well as relevant privacy commissions. Data need to be thoroughly explored for selection of variables, in close collaboration with the responsible agencies, as data was not collected by the researchers. Variables within the database could not always capture concepts as described by experts in the expert interviews (**Chapter 2**), for example blood drawings are not a variable in the databases, and therefore all biological tests that probably require blood drawings were selected. Procedures had to be set in place to make sure sensitive data cannot leak (17). There was a long waiting period to obtain the data for this

dissertation due to workload-related delays at the responsible agencies, and only data from minimally three years ago could be delivered.

3.3.5 Methodological considerations of small cells within analyses

Robustness of our analyses for differences in appropriateness was hindered by the relatively low rate of children dying. Many small cells were present within the analyses in **Chapter 3 to 5** and therefore p-values could have become unreliable, due to the lack of data in some cells not allowing for the creation of a stable enough distribution. This is different from the situation for adults, where rates of dying are generally so high that analyses provide extremely robust results as there are only cells with numbers in the thousands. However, we obtained the whole population of (insured) children for Belgium and could therefore argue that p-values are not necessary for interpretation of our analyses. P-values and confidence intervals could be interpreted with the Belgian population as a sample for the global population of children at the end of life.

4. DISCUSSION OF THE FINDINGS

Quality indicators for three illness groups: Half overlapping, half unique

The final validated quality indicator sets that were developed in **Chapter 2** (see Appendix 7, 8 and 9) share a core set of validated quality indicators for the three illness groups, but also include validated quality indicators that are unique for each illness group. In total, there were 33 unique validated quality indicators, and 15 quality indicators were validated for all illness groups (**See Table 1** below).

Table 1: Overlapping and unique face-validated quality indicators for the three illness groups[a]

Core set of general face-validated quality indicators validated for all three illness groups			
	Cancer	**Neurological conditions**	**Genetic and congenital conditions**
Physiotherapy (A)	36% [b]	34%[b]	37%[b]
(Off-label) Comfort medication (A)	6% [b]	8%[b]	6%[b]
Pain control according to World Health Organization steps (A)	50%[c]	55%[c]	65%[c]
Follow-up by hospital (A)	0%[d]	0%[d]	0%[d]
Contact with a family physician (A)	13% [b]	17%[b]	17%[b]
Continuous care relationships (A)	53% [b]	55%[b]	57%[b]
Professional care provision (A)	75% [b]	76%[b]	79%[b]
Palliative care (A)	14%[e]	14%[e]	17%[e]
Multidisciplinary care (A)	4% [b]	7%[b]	5%[b]
Palliative status (A)	11%[e]	13%[e]	16%[e]
Diagnostics and monitoring (I)	31% [b]	26%[b]	29%[b]
Starting dialysis (I)	<2% [f]	0%[b]	0%[b]
Surgeries (I)	4%[f]	<4%[g]	0%[g]
Drawing blood (I)	45%[h]	45%[h]	51%[h]
Excessive monitoring[i] (I)	<2% [b]	0%[b]	0%[b]
Disease-specific face-validated quality indicators validated for only cancer, neurological conditions, and/or genetic and congenital conditions			
Home death (A)	47%[e]	N/A	N/A
Multidisciplinary oncological consult (A)	2%[b]	N/A	N/A
Involvement of specialist physicians (A)	N/A	75% [b]	79% [b]
Continuing anti-epileptic medication (A)	N/A	N/A	88% [b]
Increased child benefits (A)	N/A	8% [e]	N/A
Reimbursed prescriptions (A)	N/A	N/M	N/A
Old-generation nausea prescriptions (I)	N/A	N/M	N/A
New antidepressants (I)	N/A	0% [f]	N/A
Late palliative care provision (I)	N/A	4% [f]	88% [b]
New placement central venous catheter (I)	N/A	N/A	11% [h]
Care setting transfers (I)	N/A	<4% [b]	0% [b]
Transfers from medical-pedagogical institute to intensive care (I)	N/A	N/M	N/M
Care stop after receiving palliative status (I)	N/A	N/A	<16% [d]
Pediatric Intensive Care Unit admissions (I)	N/A	27% [f]	N/A
Gastrostomy placement (I)	<2% [b]	N/A	N/A
Installing port-a-caths (I)	<2% [f]	N/A	N/A
Hospital transfers (I)	6% [b]	N/A	6% [b]
Emergency Room visits (I)	N/M	N/A	N/A

[a]N/A indicates the indicator was not validated for the specific illness group, A signifies the indicator indicates potential appropriateness, I signifies the indicator indicates potential inappropriateness; N/M indicates the indicator was not measurable; [b] For the last month before death, [c] For the last 3 months before death, [d] From receiving the palliative status onwards, [e] For the last 2 years before death, [f] For the last 2 weeks before death, [g] For the last 2 days before death, [h] For the last week before death, [i] For the cancer group, only magnetic resonance imaging scans were measured, for the two other groups also computerized tomography scans and x-ray scans were measured, per validation by the expert panels

The 15 general quality indicators focus on comfort measures, palliative care, variety of care providers, aggressive treatments, and intense diagnostics. These themes reflect priorities for children's end-of-life care identified by adolescents and young adults, parents of children with advanced cancer, bereaved parents, and healthcare professionals (11,12). The overarching themes are mainly connected to the need for appropriate symptom management. Comfort measures and palliative care teams likely surfaced as an important overall theme as such treatments can alleviate the high suffering at the end of life (19). A variety in care providers and multidisciplinary working can ensure the treatment of diverse symptoms at the end of life, for which various roles and specialized expertise are necessary (20-22). The avoidance of aggressive care treatments and diagnostics may maintain quality of life by preventing burdensome and potentially futile side effects.

Around half of the quality indicators differ between illness groups, and they mainly do so for place of death, disease-specific treatments and administrative measures (See **Table 1** above). This likely reflects key differences between illness groups in terms of symptom knowledge and illness trajectory. For instance, children with cancer are the only illness group with a quality indicator for home death. This contrast may result from the greater knowledge base for symptom treatment in children with cancer (23,24), which makes home death more feasible on a group level as symptom control is expected to be reasonably provided at home. The difference could also result from structural support that is present for the illness group. For instance, home care provision for children with cancer has been supported since 1989 by governmental decree (25). The group of neurological conditions was the only group with quality indicators for financial measures besides palliative status, which may represent the financial hardships especially families with a child with a neurological condition face, which according to previous studies may result from transportation costs to care facilities and daily care necessities (26).

There was frequent contact with physicians, but less with other care professionals

Chapter 3 to 5 in this dissertation showed that children with serious illness in Belgium had frequent and continuous contact with (specialist) physicians in the last month of life, but seemingly less so with other care professionals such as physiotherapists, family physicians, and paramedics. Care for children with serious illness is closely connected to hospital care, with the treating physician in a central role in care provision. For instance, most terminal children with neurological conditions are in need of moderate- or high-intensity healthcare services, among which frequent inpatient hospital care besides home care services (27). Continuity of children's end-of-life care (defined in this dissertation as having reimbursements from the same physician in the last month before death as in the eleven months before) is a pillar of care provision for Belgian pediatric liaison teams (25) and a priority for children's end-of-life care cited by families (28–30). **Chapter 3 to 5** showed that more than half of children with cancer (53%) and genetic and congenital conditions (57%) in Belgium received reimbursements for the same physician in the last month before death as in the eleven months before. Importantly, our measurements indicate that multidisciplinary care could be a greater priority for improvement, as only a few children with cancer (4%) and neurological conditions (7%) received multiple (5 or more) reimbursements from at least two care provider groups, such as from a physician and a physiotherapist, in the last month of life. Our systematic review (**Chapter 1**) suggested there is some evidence base for the benefits of multidisciplinary care within the context of palliative care teams to increase children's quality of life at the end of life (10). Our quality indicators showed that contact with the family physician (13% for children with cancer to 17% for neurological, genetic and congenital conditions) and physiotherapy (34% for children with neurological conditions to 36% for children with cancer to 37% for genetic and congenital conditions) was not frequent. Other studies showing numbers for care provider involvement in children's end-of-life care are lacking. Additionally, there was a certain group of children (about one fifth) in the population that seemed not to have received clinical care at the end of life within the last month of life. This could have resulted from errors within mutuality registration, from children receiving care solely from a pediatric liaison team (for which there is

no formal registration within the databases), from parents taking the child to a location outside Belgium or outside the traditional clinical care system, or from children not receiving any care. Possible problems with multidisciplinary care provision have been identified on a system as well as patient level: there could be coordination difficulties (31), poor system resources (e.g. lack of funding) or lack of team structure (e.g. there are no previously assigned team members) (31,32) or children and their families show nonadherence to multidisciplinary therapies (33). Coordination difficulties may lead to problems with multidisciplinary care, such as a lack of role assignment and proper leadership (32). General studies on multidisciplinary care attribute well-working multidisciplinary care to shared locations, the involvement of key workers, appreciation for other agencies, and information sharing (34). Little literature is available on possible barriers or facilitators specifically to provision of physiotherapy for children at the end of life. Lack of involvement of the family physician could occur due to lack of knowledge (35) or experience with children at the end of life, the relationship between family and physician (36), communication problems with hospital care providers (37). Sixty percent of UK family physicians found their knowledge on children's pediatric palliative and end-of-life care to be inadequate (35). Communication difficulties can arise with e.g. intramural physicians (37). Conflicts in the family-physician relationship could arise due to discussions on medical futility (36). Facilitators for family physician involvement could be collaboration with and communication with palliative care teams (37,38), or clarification of the role of the family physician (37). In Belgium, the current legislative structure of pediatric palliative care teams requires collaboration with a primary care team including a family physician and home care nurses (25) and lack of involvement of the family physician could be due to the lack of financial incentives provided for such involvement (39).

Little palliative care: opportunity to start a conversation

Our findings seem to indicate that access to palliative care for children at the end of life can be improved in Belgium. Only about one in ten children receives palliative care according to our measurements (cancer/neurological conditions: 14%, genetic and congenital conditions: 16%).

In Belgium, referral of children with serious illness was previously found to be low: only 1,7% of children admitted to a hospital, were referred to a pediatric liaison team (which typically provides pediatric end-of-life care) (40). Internationally, studies identify low to moderate numbers for palliative care provision in children with serious illness, with numbers averaging a quarter to one third of children (41,42).

There are many identified barriers for pediatric palliative care provision. Barriers could be present on the familial or children's level (e.g. financial barriers, eligibility problems), the level of care providers and teams (e.g. access problems, standard care practices) or the system level (e.g. care system structure, legal considerations), or even interactions between these levels (e.g. communication problems) (43–45). For the Belgian context, barriers to pediatric palliative care have previously been reported to be one of access to other care providers such as general physicians, and to be financial and structural in nature in that governmental billing codes for the field are lacking and can prevent reimbursement (25,39).

Our numbers probably underestimate Belgian palliative provision as pediatric palliative care provision is registered differently compared to adults' palliative care. The care is often provided by goodwill or private funding, and therefore some pediatric palliative care provision possibly is not indicated in the databases at all. However, the numbers do provide an addition to the little numerical knowledge on Belgian pediatric palliative care provision and they provide an opportunity to reflect on the possible need for improvements in terms of pediatric palliative care provision within children's end-of-life care in Belgium.

MRI's, X-rays, CT scans and blood drawings: a complex picture of diagnostics at the end of life

Potentially inappropriate care was generally low for children dying from serious illness in Belgium. For instance, no or almost no surgeries, new dialyses or new antidepressants were given in the last month of life across illness groups. Our findings also revealed that a substantial proportion of children still receives imaging (MRIs, X-rays, CT scans) and blood drawings at the end of life. Imaging occurred for nearly one third of children (26% of children with

neurological conditions received 2 or more MRIs, X-rays or CT scans in the last month before death, 31% of children with cancer). Blood drawings were performed for around half of all children per illness group (45% of children with cancer and neurological conditions received blood drawings in the last week before death, 51% of children with genetic and congenital conditions). International studies show a similar pattern of high imaging and blood drawing use, particularly for X-rays and blood drawings (41). In a cohort of US children at the end of life with an inpatient stay, 73,7% of children received X-rays, 20% received CT-scans or MRIs,and 81,6% received blood draws in the last 2 days of life (41). These numbers may be higherthan ours as they result from children with hospital stays only – inpatient stays give quicker access and probably more immediate reason for imaging and blood drawings.

Diagnostics and blood drawings are ambiguous within children's end-of-life care: On the one hand, they can be necessary as a means to provide adequate comfort care (69). For example, CT may be used to refer to palliative chemotherapy (46). On the other hand, they can also negatively impact the child's quality of life, as blood drawings might be painful to the child (47). Our systematic review (**Chapter 1**) also showed that curative therapies can significantly decrease quality of life at the end of life for children. Blood drawings and imaging then might provide unnecessary discomfort for the child at the end of life, resulting in overtreatment. According to interviews with parents, such overtreatment may also be caused by standardization, as standard treatment plans are followed in the hospital which subject the child to unnecessary procedures (48). The difficulties of diagnostic care provision are reflected in the models of pediatric end-of-life care that have been developed. For children with cystic fibrosis, for example, a transitional model has been proposed as a solution, which strives for a transition period to comfort care which constantly calibrates for likelihood of death and unacceptable quality of life (49).

Differences for region, disease group, and nationality may point to differences in evidence base, structural support and family preference

Chapter 3 to 5 showed that appropriateness in Belgium differs for region, disease categories and nationality: children with non-Belgian background significantly more often received inappropriate care compared to those with Belgian nationality for children with cancer, region differences surfaced for both the cancer and genetical group, and rarer neurological conditions were shown to receive less appropriate care.

Children with non-Belgian background received more inappropriate care for the cancer group. Disparities in end-of-life care for nationality have often been reported in previous literature. For example, racial disparities have been identified for psychosocial pediatric end-of-life care and intensity of care (50). Similar to our results, US children of color received higher intensity of end-of-life care than children not of color (51). For example, children of color receive more hospital and intensive care, active resuscitation, and in-hospital deaths (52–57). However, studies also indicate these differences might be in favor of the wishes of the parents: Patients of different racial backgrounds may prefer end-of-life hospital care (58). For instance, one study showed that families with children of color had requested their child died in the hospital more often (52).

There were differences in end-of-life care for region for both the cancer group and group of genetic and congenital conditions. For the cancer group, one Flemish care region (Limburg) showed significantly higher appropriateness of care compared to other regions. This is surprising, as the region is a rural region and does not have an anchored pediatric liaison team. Studies often refer to rural regions as a barrier for pediatric palliative care (45). However, other care networks and close care bonds may be present in the area. For genetic and congenital conditions, appropriateness and inappropriateness varied for various regions. Most of these regions were regions with an anchored pediatric liaison team and university hospitals. As genetic and congenital conditions often present a challenging and rare symptomatology, this population may receive better care in regions with highly specialized centers. Treatments and side effects may not be known sufficiently due to lack of empiric knowledge of the diseases,

and successful treatment may therefore rely on the knowledge of individual care providers. For example, papers are available on the treatment of regular end-of-life symptoms in children with cancer, such as nausea due to opioid use (10). However, less studies for treatment of regular end-of-life symptoms are present for children with genetic and congenital conditions, such as spasms (10). This can be linked to another finding, namely that patients with certain neurological conditions receiving less appropriate care: disorders of the central nervous system and movement diseases showed lower appropriate care scores. These conditions display a more unknown and irregular disease progression within the group of neurological conditions (9,59). Therefore, symptoms again may be hard to predict or relieve. More well-known conditions, such as cerebral palsy, may have a greater knowledge base and may therefore receive more appropriate end-of-life care.

Reasons for differences such as the above likely surface due to multiple factors. A model was developed by Linton et al. (60) to summarize the mechanisms behind disparities in pediatric end-of-life care, which includes three levels: broader contextual influences (e.g. access to care or poverty), patient-clinician engagements (e.g. clinician bias or prejudice), and patient-specific features (e.g. perceptions of control and religion and spirituality). For instance, differences in pediatric end-of-life care for nationality could occur on a family level (language differences) as well as different cultural expectations (60,61).

Other indicator sets and countries: Do indicator results compare?

Two other quality measure sets for end-of-life care in children have been developed (2,4), yet these sets do not focus solely on administrative data, and are based on expert panels and interviews with care providers and families from within the United States (2,4). The sets both included quality indicators for healthcare use, but also provide quality indicators for other themes such as advance care planning. Many healthcare use quality indicators differ between the three sets. For example, receiving hemodialysis was rejected as a quality indicator for the set constructed by Johnston (4), but starting a new dialysis was accepted as a quality indicator within our set. Some findings regarding healthcare use indicators are similar: palliative care is

consistently recognized as an indicator for appropriate end-of-life care, and chemotherapy has been consistently rejected as an indicator for inappropriate end-of-life care. The indicator of palliative care provision may therefore be high in external validity and can be seen as an important indicator, and measurement of chemotherapy may not provide a valid indication of inappropriate end-of-life care for children. This finding contrasts with previous studies, who have largely focused on intense treatments as an evaluation of the quality of children's end-of-life care, e.g. showing that more than half of children with cancer in Taiwan at the end of life received chemotherapy or underwent intubation in the last month of life as an implied indication of inappropriate care (62). All current sets imply that most aggressive treatments are not relevant for children's end-of-life care as quality indicators. Indicators such as dialysis were outright rejected in panels for the set of Ananth and Johnston, and provided very low measurements (<5%) for our sets. Aggressive treatments may not be prevalent enough to provide an indication of quality (4). For future measurement, the indicators with low measurements, such as surgeries or installing a port-a-cath, could be deleted from our set. Our indicator measurements align with population-level numbers from other countries. Many of our quality indicators have not yet been measured on a population level for other countriesfor seriously ill children, yet some quality indicators have been, such as receiving dialysis, home death, and ICU admissions. Studies from the US show equally low occurrence of dialysisas Belgium (below one tenth of children) and a similar proportion of children at the end of life that receives ICU admissions (around one third of children) (51). Half of Belgian children withcancer dying at home seems to be relatively high compared to other countries, with home deaths for children with cancer varying from 7% to 45% for other countries (63).

5. IMPLICATIONS OF THIS DISSERTATION

5.1 Recommendations for policy

Policy recommendations include to support palliative care provision with measures on an administrative and legal level, and to provide systematic care performance evaluation through feedback learning and flexible benchmarks.

Supporting pediatric palliative care provision with administrative and legal measures

This dissertation indicated the importance of palliative care for children's end-of-life care: Our systematic review found that multidisciplinary palliative care teams may increase quality of lifeat the end of life in children (64–71). Expert interviews and expert panels revealed the importance of comfort medication and treatment as well as the provision of palliative care and visits by pediatric liaison teams. In Belgium, palliative and end-of-life care is mainly coordinatedby the pediatric liaison teams, as determined by royal decree (61,88). Administrative efforts bythe RIZIV/UNAMI could support pediatric palliative and end-of-life care services, such as the pediatric liaison teams and pediatric home care services (24,36). Such efforts have been requested in a 2017 policy document by the Belgian federal cell of palliative care evaluation and the pediatric liaison teams. Pediatric-specific nomenclature codes could provide adequate financial compensation for pediatric palliative care provision (39), which would also allow for more accurate administrative registration. For example, nurses who provide pediatric end-of-life care at home currently struggle to receive appropriate financial compensation from the government as there are no billing codes for such care provision. Such administrative codes for pediatric care could be created along with certain requirements within the legal texts, for instance doing a yearly internship at a pediatric liaison team, in order to avoid antisocial misuse of the national social budget and make the measure goal-effective. Certain legal aspects are missing from the framework for children's palliative care: A pediatric-specific palliative statute could be thought out to add to the existing legal texts. For instance, within such statute the well-thought-out digital registration of pediatric palliative patients and pediatric liaison teams could be set up by e.g. agencies suchas eHealth or the Agency of Care and Health (39). In this regard, it is important to maintain the balance between providing necessary safeguards, such as privacy protection of the data for the child and explicitly given consent to medical or scientific experimentation, while still creating a systemic, prosocial workflow that can generate and summarize evidence generation to further sustain care betterment for children at the end of life. It is advised that such legal change is first tested for impact within one care region or other relevant system, and only after careful investigation put down into official legal texts, in order to

optimally engineer social change taking into account the whole system with all the prosocial as well as antisocial impact of the measure, in line with complex system thinking, instead of only taking into account part of the system (75).

Systematic care performance evaluation through quality indicator measurement: The case for flexible benchmarks and double-loop learning

Traditionally, quality indicators are used to evaluate the performance of healthcare systems (7). Quality indicators are often translated to performance standards, which means certain ideal percentages for the quality indicators are set, which regions then should strive for (73). However, it is argued following results from this dissertation that the complexity of children's end-of-life care complicates the use of fixed performance standards, and instead requires a flexible learning approach (74,75). Fixed standards could lead to inappropriate care provision, and lead to the masking of underlying systemic problems (75). For example, prescriptions of comfort medications particular to specialized pediatric palliative care were very low for all illness groups (below 10%), and a relative performance standard could be set of prescribing specialized comfort medication to a minimum 10% of children at the end of life for each hospital. However, due to the likely heterogenous sample of pathologies per hospital, certain subgroups of children could now receive overtreatment or even undertreatment as their ideal benchmark of off-label comfort medication lies lower or higher, and the possibly underlying systemic problem of a lack of knowledge on specialized comfort medication for children at the end of life in physicians is not adjusted. Instead of fixed performance standards, 'double-loop learning' (75) is advised, as part of a learning and improvement strategy, with quality indicator measurements functioning as flexible benchmarks. In such case, interventions could be developed by researchers (see recommendations for research) based on low-scoring quality indicators, and then be evaluated by increases or decreases in subsequent indicator measurements. After the intervention, as a second learning loop and evaluation (74,75), forums and panels could be set up by researchers, quality-of-care cells in hospitals and/or governmental agencies such as the Agency for Care and Health or the Flemish Institute for Quality of Care. In such forums, the results of the quality indicators before and after

interventions can then be discussed and analyzed with relevant stakeholders such as pediatric care providers and families and children (see recommendations for family and children's involvement). Such feedback discussions would also provide room for the emergence of qualitative yet important themes that are currently not measurable with quality indicators, such as symptom monitoring and communication. Forums for feedback could also stimulate multidisciplinary care (75), which was signaled to be low in this dissertation. Feedback rounds have also been suggested in other system improvement approaches, such as the Bowen Family Systems Theory applied to healthcare, with possibly beneficials outcomes for team members (76). Preconditions for effectively maintaining such learning and improvement systems, such as middle manager effort (75) or self-differentiation of team members (76), may be monitored in ongoing efforts, stimulating self-correction. To illustrate, starting from the low numbers of specialized comfort medication provision found in our measurements, a pediatric palliative care curriculum segment could be implemented in an existing palliative care course, and be evaluated through quality indicator measurement, after which feedback forums can be organized for evaluation and further discussion and improvement of the curriculum. The double-loop approach could also be used to reconcile certain seemingly paradoxical quality indicators within our sets, for instance the quality indicators for home care and professional provision. These indicator measurements, which are relatively high for both quality indicators, could be discussed within forums as to whether these results are goal-concordant for children and families on a group level, and to define the preferable conditions for home care and professional care, hereby providing specification and complex development starting from the generalized measurements. Feedback from forums could be shared, and discussed internationally, with measurement of quality indicators for each country functioning as the starting point for ongoing discussion. Double-loop learning and continuous self-correction of the system can also be implemented through digital self-learning networks, set up by hospitals, researchers and agencies such as eHealth, by linking quality indicator measurement to patient-reported outcome measures. For instance, the increase and decrease in quality indicators could be compared to the general quality of life and symptoms reported by children.

5.2 Recommendations for practice and education

Practice and education are recommended to provide pediatric palliative care education, and adjust multidisciplinary care based on systemic adjustments and mapping.

Providing education and updating the current knowledge base to improve palliative and comfort care

This dissertation indicated that there may be little administration of comfort treatments for seriously ill children at the end of life. Better preparation of pediatricians and other care providers may lead to a deeper understanding and therefore more routine application of comfort treatment and pediatric palliative care provision in practice (21). No education on pediatric palliative or end-of-life care is provided in the standard medicine training curriculum nor in specialized palliative care trainings in Belgium (39). A set of competences for children's end-of-life care may be identified by higher education facilities in collaboration with educators and researchers (77), and added to the current standard medicine curriculum or specialized palliative care trainings provided in Belgium. Competences are best based on the current and continually updated evidence base (**Chapter 1**) (10). Knowledge of comfort medication may be included, such as known benefits and downsides, and expert-backed (**Chapter 2**) tools such as the stepwise approach to analgesia in children (cfr. NICE guideline 1.3.27 (21)) may be included.

Setting up multidisciplinary care structures

Our measurements indicated that there was little reimbursed multidisciplinary care provided to children with serious illness at the end of life, and that there were not many reimbursements for certain care providers, such as general physicians and physiotherapists. Predefined structures for multidisciplinary care may be implemented in the Belgian context, after mapping of the current structures. Previous research for instance reports the benefits of predefined roles within multidisciplinary networks (32) or standardized templates for multidisciplinary communication, such as verbal handoff templates (78). Various internationally recognized

guidelines and reports for children's end-of-life care (21,79) recommend the appointment of a medical specialist who coordinates the multidisciplinary team to care for children with serious illness (21). Studies and reviews on solutions for general multidisciplinary care furthermore suggest including time to prepare for multidisciplinary care into job plans, team and leadership training, and systematic input from nursing personnel, and improving working relationships to improve multidisciplinary care (34,80). In order to determine which specific alterations are most beneficial to the Belgian context and to avoid waste of resources (75), a systemic map of the existing multidisciplinary working relationships may be constructed first, for example using health system genograms (81,82). For instance, the different care elements for children's end-of-life care could be charted on a legal (relevant law), structural (organizations), professional (care providers), interpersonal (family dynamics) as well as intrapersonal level (feelings involved in care provision for family and care givers). This could allow to determine possible solutions for interventions. For instance, for palliative status, given that the provision of this financial incentive is low, one possible solution may lie in the legal assignment of care: legal texts assign the responsibility for palliative status to the general physician, but our results show children mostly are in contact with physicians in hospitals and not with general physicians. From understanding these dynamics onwards, solutions may be tested to better the care system. For example, the legal responsibility of the palliative status could be changed to the hospital for one region, and system dynamics may be tested for the subsequent results for care setting.

5.3 Recommendations for research

Further research is recommended to increase efforts for empirical knowledge on pain and comfort treatment for non-cancer and cancer conditions, to incorporate the perspective of children and families within indicator development and evaluation, to develop complex subspecialty interventions based on our results, to compare indicators internationally and for interventions, and to construct tools for the appropriate timing of diagnostics in children's end-of-life care.

Increasing empirical pain and comfort research for non-cancer and cancer conditions

Our systematic review and other studies (83) illustrate that insufficient evidence may be present for the appropriateness of end-of-life care for children with neurological, genetic and congenital conditions: most studies in the current evidence base are conducted for children with cancer. While children with cancer represent a large group of deaths in children (n=228), combined the other conditions represent a larger group of children that succumb to their disease (n=200 + n=139 = n=339). Similar patterns of a larger non-cancer population surface in international studies (84–86). Research might be set up to generate empirical knowledge on pain and symptom control for these conditions, besides similar research for children with cancer. Our systematic review (**Chapter 1**) and authoritative textbooks (8) mention that also in general, empirical knowledge is lacking for the impact of medication and treatment on the quality of life in children with serious illness, which might also be stimulated through grant provision, e.g. through the King Baudouin Foundation, and gained knowledge can then be disseminated through curricular segments (see education recommendations).

Studying the perspective of children and families

A limitation to our expert panels was that no children or parents were included. To ensure patient- and family-centered care, further studies are advised to incorporate the perspective of children and their families into the development and application of the quality indicators. Families feel excluded from authorities' decisions on children's end-of-life care- (79). NICE and Together for Short Lives guidelines indicate as a first general principle for children's end-of-life care that children and parents or caregivers have a central role with) in their end-of-life care (21,79). Input can be asked from children and families on the reasons for their healthcare use. For instance, families' reasoning for the use of diagnostics might clarify whether diagnostics were administered in concordance with the families' wishes, and whether children maintained a reasonable quality of life at the end of life. A large enough number of children and families is best included in such designs, as population-level results are required for quality indicators. To shed light on possible disparities in preferences for end-of -life care, study samples could

represent the socioeconomic, cultural and ethnic diversity within society, due to the possible disparities in end-of-life care discussed in this dissertation. Designs that survey or interview children at the end of life are often considered too burdensome and non-ethical. However, our systematic review and other studies have indicated that electronic surveys can benefit the quality of life at the end of life of the child, and can provide valuable research data via patient-reported measures (2,87,88). Efforts can therefore be taken to incorporate the voice of the child into research designs using such eHealth designs, in collaboration with pediatric liaison teams or agencies such as eHealth Belgium.

Comparing quality indicators for other countries and for interventions

Our quality indicator sets can be used to evaluate children's end-of-life care in other countries, as well as within interventional designs. The measuring of the quality indicator sets can be complicated because of the different structures of administrative datasets available by country, as well as the different political and health care systems, and should be evaluated. For instance, Belgium does not provide child hospice care while this is an existing structure in other countries, such as in the UK (90). Additionally, not all countries have a coordinating data collection structure, or population-level health insurance, such as the Belgian Intermutualistic Agency, which would not allow for the (effective) collection of population-level data. Furthermore, solely focusing on the indicators measurable with data in Belgium would pose the risk of reducing care quality evaluation to themes only measurable with certain administrative, Belgian data. Some of the potential indicators that were suggested by experts in our study (see p.72-79 of this thesis), were not measurable with Belgian data, but could possibly be measured within other countries, providing a larger and more comprehensive overview of the quality of care. For example, the rate of unemployment of parents, by linking parent data with child data, could be measured. For the reasons above, validation may be needed before measuring the indicator sets in another country, for instance through an expert meeting, ideally with a varied range of experts having knowledge on the data structure of the country as well as pediatric-specific knowledge. Benefits of measuring the quality indicators for various countries are that they can provide a starting point for ongoing discussion and knowledge dissemination between countries. In comparing countries, it is important

that this leads to reflective comparison between systems with different characteristics, rather than drawing hard conclusions about quality of care issues from benchmarking results. Such approach would confuse the measure with the solution, and ignore that healthcare is a complex multi-factorial system (75). The international sharing of indicator results can best be done with a focus on initiating a process of further understanding of the reasons behind the differences and learning from each other about different approaches, taking into account a variety of opinions. For the indicator of multidisciplinary care, for example, the European Association for Palliative Care could provide a financial incentive for organizing an international panel on the provision of pediatric multidisciplinary care at the World Congress, best with an additional group incentive for obtaining a wide range of expert voices, the latter best judged by an external panel.

Administrative data is collected ongoingly, and coding for the quality indicators was written so that measurement can be automated. Quality indicator measurements could therefore be repeated every year for multiple years in the future, by researchers or agencies such as eHealth and the Agency for Care and Health, in a cost- effective manner. Likewise, intervention designs could use the developed quality indicators as flexible benchmarks to evaluate the effectiveness of interventions (see also recommendations for policy) (5,15).

Differentiated intervention development guided by quality indicators

Our study indicated that the quality of end-of-life care for seriously children could differ for disease category, nationality and region. In recent years, studies increasingly advocate a more specialized approach to assessment of children's end-of-life care quality due to its complex nature (2). Some scholars have stated the "bottom line is that one size does not fit all" within children's end-of-life care and urge to avoid blanket statements (58). However, a middle road can be found in the combination of generalization and specification: specialized interventions can be developed by researchers based on the signposts provided by quality indicators. This way, generalized statements do not hamper care improvement but allow for further evidence-guided specification, by providing validated direction. For example, interventions could be set

up to increase palliative care provision for children with neurological conditions at the end of life. To accommodate for the complexity of children's end-of-life care, interventions are advised to be different in content for subgroups, as shown to differ within this dissertation. For example, interventions could differentiate for different types of neurological conditions: known versus unknown disease trajectories. Complex system theory may be used to aid such differentiation, such as the SHIFT-Evidence framework (Successful Healthcare Improvements From Translating Evidence in complex systems), as they allow for complexity, and emphasize feedback learning strategies as suggested for implementation above (75).

Developing tools for estimation of appropriate timing for diagnostics

Our study found that one third to half of seriously ill children at the end of life still receives blood drawings and imaging, such as MRIs, X-rays or CT scans. Decreasing diagnostics such as X-rays and blood drawing can prove difficult for physicians due to the unpredictability of the disease trajectory in seriously ill children, estimation of short-term versus long-term quality of life, and requests for diagnostics by parents. Research may aid by developing tools to better indicate the optimal point of decreasing diagnostics. For instance, survey tools could be developed that more specifically indicate the point of disease trajectory the child is at, and its short-term versus long-term quality of life. For the latter part, more short- as well as long-term evidence for treatments and medications would be needed as well (see recommendations above). Indications for palliative care needs in children may be identified and validated for use in a discriminatory survey tool (25). Such tools would also allow families to be realistic in hope for cure, and allow them to better prepare for death of the child (21). Exception clauses for children at the end of life might be added to standardized procedures for diagnostics, as parents indicated strict adherence to standardized protocols as a possible cause for futile diagnostics (48).

The (perceived) duration of the end-of-life period is necessary to know whether overtreatment was present in children at the end of life

The amount of unjustified diagnostics and other potentially inappropriate treatments remains

unclear: no information is present within administrative databases on the duration of the end-of-life period. This means that it is unknown whether, for instance, the percentage for diagnostics in the last month of life for children with cancer (31%), would be equally high if only children with an actual full-month end-of-life trajectory were included – it could be possible that children with only a two-day end-of-life period raised the diagnostics rates with justifiable diagnostics in their curative period that also fell within their last month of life. A decrease of diagnostics and treatment should therefore be approached very carefully and through further study. Simply decreasing diagnostics for the group of children with serious illness as a whole could hamper the chances of curation of seriously ill children who do still have a high chance of survival, and can benefit from and survive due to sufficient diagnostics. Children with acute lymphoblastic leukemia, for instance, have a current estimated survival rate of 90% in high-income countries, that is estimated to grow towards a 100% survival rate (91), and death of the child can be acute and occur in a matter of days. Should our percentages be used as percentages to strive for within a non-specific public health effort to decrease diagnostics for children with cancer, which is heavily discouraged, an enforced decrease of treatments could negatively impact the care of children with acute lymphoblastic leukemia who are often still curable. Instead, subgroup-specific recommendations could be provided, with various safeguards for potential misuse, e.g. in case of Münchhausen by proxy. Guidelines could be made with suggestions for curative care decrease for children with a specific disorder who would specifically benefit from lesser diagnostics, based on further research such as prospective cohort and case studies, with the necessary specific variables measured to gain a good perspective. To gather more evidence for such guidelines, characteristics of various disorders could be obtained through studies that also keep record of the duration of the end-of-life care period. To minimize burden of research for care providers, children and parents, such designs could be connected with big data (see recommendations for policy).

Risks of financial incentivization tied to the measurement of quality indicators:

Avoiding the budget approach and focusing on long-term social and economic returns (89), maintaining expertise as well as overview, and structure over content

Lastly, it is emphasized that quality indicators are not to be incentivized directly financially, as there is risk they will be used as a short-cut to decrease hospital costs, when our study explicitly excluded cost as a motivator from the RAND/UCLA methodology. One financial strategy that could occur is when indicator outcomes are purposefully misreported to 'game' the system and receive more compensation (92). A "budget approach" (89) is also sometimes used by administrators through indicator use, where care is decreased for the sole purpose of cost reduction while ignoring long-term effects, e.g. to provide short-term debt relief for a hospital. Economic theorists have previously discouraged a "budget approach" to children's poverty as it diminishes value and advancement overall for children as well as society, and ignores the capitalist system's mechanics (89). Instead, such theorists vouch for "achieving [a] good 'double bottom line' return on investments" (89), meaning "investments that produce both good social returns and good economic returns" (89). In terms of children's serious illness, we can similarly best focus on overall return of investments in terms of the provision of expertise care, for the long-term support for families and society as a whole. An example is the funding of studies into intolerable pain medication or provision of practical help in the last days of the child, which also look at the impact on emotion regulation and lack of employment in guardians and other family members following the death of a child. Within such approach, a balance is best maintained between expertise and overview from a structural level, through indicators: for instance, research grants could be provided to projects that looks into the theme of an indicator deeply, or grants could incentivize variety within designs by selecting projects with inherent sufficient variety for indicators, which signify various themes. The structural quality, in short, is best incentivized instead if the content quality of the indicators.

6. CONCLUSION

This dissertations' overall aim was to evaluate children's end-of-life care in Belgium. In order

to do so, quality indicators were developed and validated to measure potentially appropriate and potentially inappropriate end-of-life care for children with cancer, neurological conditions, and genetic and congenital conditions within routinely collected databases for healthcare reimbursements. For potentially appropriate end-of-life care, reimbursements for palliative care and comfort measures, such as physiotherapy and specialized comfort medications, were generally low. Care provision from physicians was continuous, yet multidisciplinary care reimbursement wasprovided infrequently across all disease groups. Administrative measures, such as palliative status and heightened child benefits, were seemingly not provided often. Potentially inappropriate treatments were not provided frequently, except for diagnostics and monitoring (MRI's, X-rays and CT scans) and blood drawings. There were differences in appropriatenessand inappropriateness for disease category, region, and nationality.

Further quality improvement efforts could focus on the increase of comfort measures and palliative care, the stimulation of multidisciplinary care, and the decrease of diagnostics and blood drawings. Administrative and legal measures for the support of palliative care provision and pediatric liaison teams are encouraged. The development of interventions with attention for different subgroups, such as disease trajectories, is also advised. Learning and improvement strategies could be implemented using the quality indicators as flexible benchmarks. Competences for children's end-of-life care are best added to the current standard medicine curriculum or specialized palliative care trainings provided in Belgium. Further empirical research on pain and symptom management is best carried out for both non-cancer and cancer conditions. It is paramount to include the perspectives of child and family in further research efforts.

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ENGLISH SUMMARY

INTRODUCTION

A quality evaluation of children's end-of-life care is needed. Evaluations have already been performed for adult's end-of-life care, using routinely collected administrative healthcare data for the whole population. Some international evaluations with routinely collected administrative data have been performed for children, yet these studies use quality measures constructed for adult end-of-life care for measurement. The adult-focused measures likely do not properly reflect the issues relevant for children's end-of-life care. There are currently no pediatric-specific quality indicators for administrative healthcare data. **Quality indicators tailored specifically to the child at the end of life are requested nationally as well as internationally**.

The healthcare use in children's end-of-life has gained interest in recent decades. There is significant evidence that part of the children with serious illness, such as cancer and neurological conditions, suffer from heavy symptom burden in the last days of life. **Concerns are present for overly aggressive and futile healthcare provision, while comfort measures are shown to be available to relieve child and family yet possibly not provided sufficiently.** Current studies on the topic indicate that the quality of children's end-of-life care may vary widely for clinical and sociodemographic characteristics of children and families. Differences in healthcare provision at the end of life have been identified previously, for example for age and nationality.

An evaluation of the quality of care with quality measures tailored to children can guide future steps in practice, research and policy for children's end-of-life care: **administrative data can provide a bird's-eye-view, that cannot be obtained from individual practice**, as children's deaths from serious illness are relatively rare and most healthcare providers only ever experience a handful of cases. Administrative data is well-positioned to analyze disparities, as the full population is included and subgroups that normally are hard to reach are included in the cohort, such as families with a lower income or migrant background.

RESEARCH AIMS

This dissertation had the overall goal to **evaluate end-of-life care for children with a serious illness**, such as cancer, neurological conditions, and genetic and congenital conditions, using quality indicators and administrative healthcare data.

The specific goals of this dissertation were:
1. To **develop population-level pediatric-specific quality indicators** for appropriateness of end-of-life care for children dying with cancer, neurological conditions, and genetic and congenital conditions,
2. To **measure these indicators** within Belgian administrative databases; and to look into **possible sociodemographic, clinical, and regional differences** for appropriateness and inappropriateness of end-of-life care.

Due to the use of administrative databases, the focus was limited to medication, treatments, and care providers, as only these aspects are measurable within the data.

METHODS

For research aim 1, **development of the pediatric-specific quality indicators**, we performed a systematic literature review and a RAND/UCLA panel. The RAND/UCLA consensus method consisted of expert interviews, an electronic survey, a group discussion round, and a second electronic survey. Interviews and panels included pediatricians, nurses, psychologists, physiotherapists, pharmacologists, care coordinators, general practitioners, social workers from hospitals, care teams, and general practice. Three indicator sets were developed: one for children with cancer, one for children with neurological conditions, and one for children with genetic and congenital conditions.

For research aim 2, **measurement of the pediatric quality indicators within population-level administrative databases**, we first linked several Belgian databases. Then, we calculated and described the quality indicator results. For the **sociodemographic, clinical, and regional differences in appropriateness of children's end-of-life care**, we performed analyses of variance as well as logistic regressions.

MAIN FINDINGS

In **Chapter 1,** we presented the results of a systematic review, which identified the healthcare interventions that are associated with improved and/or reduced quality of life for children at the end of life. We found that the current evidence base is broad (20 interventions were studied), yet studies were limited in quality, and many showed bias for design and execution. Palliative care, certain comfort and pain medications and treatments, and symptom monitoring were

associated with improved children's symptoms and quality of life at the end of life. Curative therapies, such as chemotherapy and stem cell transplant, were associated with decreased quality of life at the end of life for children.

In **Chapter 2**, we described a RAND/UCLA consensus method to develop the pediatric-specific indicators. Across all illness groups, the quality indicators fell into four themes: 1. Treatment, medication and monitoring (with quality indicators such as physiotherapy and specialized comfort medication), 2. Place of care and death (containing quality indicators such as home death), 3. Care services and providers (containing quality indicators such as contact with a family physician or having continuous care relationships), and 4. Administrative measures (containing quality indicators such as receiving palliative status (and therefore being administratively entitled to higher reimbursements)).

Chapter 3 to 5 described the measurements of the pediatric-specific quality indicators for each of the three illness groups.

For **potentially appropriate care**, we found that reimbursements for comfort treatments were often not provided to children at the end of life. For instance, palliative care reimbursements were provided to less than one fifth of children. Half of children with cancer died at home (47%). Continuous care was provided to over half of all seriously ill children at the end of life. Over two thirds of children with neurological conditions received reimbursements from specialist physicians in the last month before death. However, less than one fifth of seriously ill children at the end of life received reimbursements from a general physician in the last month before death. Multidisciplinary care in the last month before death was low. Administrative measures were not provided often for children across illness groups. Palliative status was provided to circa one fifth of children with serious illness at the end of life.

Potentially inappropriate care were usually not frequent in seriously ill children at the end of life. No or fewer than 5% of children received a new dialysis, surgeries or old-generation reimbursements for nausea within the last month before death for any of the illness groups. Around one fourth to one third of children received 2 MRI's, X-rays or CT scans at the end of life, and blood drawings were very frequent, that is they were present for half of children across illness groups. Admissions to the Intensive Care Unit were provided to up to one third of children.

For **clinical, sociodemographic and regional differences**, children with neurological conditions, showed differences for appropriateness for disease categories: disorders of the central nervous system and movement diseases showed lower scores for appropriate care. For children with cancer, there were differences for region and nationality: One rural healthcare region showed higher appropriateness, and children with a non-Belgian background received more inappropriate care. For children with genetic and congenital conditions, appropriateness

differed for various regions.

DISCUSSION OF MAIN FINDINGS

Our discussion pointed out **that there was frequent and continuous contact with physicians, but less with other care professionals, and little palliative care provision**. We indicated that while the numbers may underestimate the actual care provision due to the partly philanthropic nature of children's end-of-life care, these numbers may provide a starting point for further inquiry into the palliative care provision and involvement of other care providers.

Additionally, we discussed that **findings for inappropriate care paint a complex picture of intense care at the end of life in children.** Treatments such as chemotherapy, commonly seen as futile treatment and a staple quality indicator for inappropriate care in adult indicator sets, were not seen as a proper indicator for inappropriate care in three recently developed quality indicators for children at the end of life. The treatments may not be provided, such as dialysis, as our numbers as well as international measurements show, or the treatments may be used to provide long-term comfort, such as chemotherapy. Diagnostics and blood drawings were an exception to the rule and could possibly be decreased at the end of life due to futility. However, we stressed the limitation that our study does distinguish between children who died with a foreseen end of life and those without.

Lastly, we pointed out that **differences for region, disease group, and nationality may point to differences in evidence base, structural support and family preference.** It was hypothesized that a difference in knowledge on symptomatology and treatment may underlie these differences, especially region and disease group. Differences for children with a non-Belgian background may be goal-concordant and require further insight.

CONCLUSION

This dissertation found that children with serious illness at the end of life **may require amongst others more comfort care provision, increased care provider support and follow-up, decreased imaging and blood drawings, and increased administrative support** for families as well as care providers. Differences in appropriateness and inappropriateness for

disease category, region, and nationality are present and may be caused by underlying knowledge gaps.

IMPLICATIONS

Administrative and legal measures for the support of palliative care provision and pediatric liaison teams are encouraged. The **development of interventions** with attention for different subgroups, such as disease trajectories, is also advised. **Learning and improvement strategies** could be implemented using the quality indicators as flexible benchmarks. **Competences for children's end-of-life care** are best added to the current standard medicine curriculum or specialized palliative care trainings provided in Belgium. Further **empirical research on pain and symptom management** is best carried out for both non-cancer and cancer conditions. It is paramount to include the **perspectives of child and family** in further studies.

NEDERLANDSE SAMENVATTING

INLEIDING

Een evaluatie van de kwaliteit van levenseindezorg bij kinderen is nodig. Kwaliteitsevaluaties werden al uitgevoerd voor volwassen levenseindezorg, met behulp van administratieve gezondheidszorgdata, die toegang geven tot de gehele populatie in België. Enkele internationale studies met administratieve data werden reeds uitgevoerd voor kinderen aan het levenseinde, maar deze studies gebruikten steeds meetwaarden (kwaliteitsindicatoren) die voor volwassenen aan het einde van het leven werden gevalideerd. Dergelijke indicatoren gaan waarschijnlijk voorbij aan de thema's die relevant zijn voor levenseindezorg bij kinderen.**Er zijn momenteel nog geen kwaliteitsindicatoren specifiek ontwikkeld voor kinderen aan het einde van het leven ter gebruik op administratieve data**. Kwaliteitsindicatoren gevalideerd voor kinderen aan het einde van het leven worden nationaal en internationaal aangevraagd.

Medicatie en behandeling bij kinderen aan het einde van het leven wekte de laatste decennia steeds meer interesse op. Er is evidentie dat een deel van de kinderen met ernstige aandoeningen, zoals kanker en neurologische aandoeningen, zware symptoomlast ondervinden in de laatste dagen van het leven. **Bezorgdheden zijn er omdat mogelijk te agressieve behandelingen worden toegediend, terwijl comfortzorg, die kwaliteit voor kind en gezin kan verbeteren, mogelijk te weinig wordt voorzien.** Studies tonen ook dat de kwaliteit van levenseindezorg bij kinderen beïnvloed kan worden door klinische, socio-demografische en regionale factoren.

Een evaluatie van de kwaliteit van zorg met kwaliteitsindicatoren specifiek gevalideerd voor kinderen kan verdere stappen voor het veld uitklaren: **administratieve data voorzien een overzicht, dat niet kan achterhaald worden binnen de individuele praktijk**, aangezien kindersterfte door ernstige aandoeningen relatief zeldzaam is in de moderne context en zorgverleners waarschijnlijk slechts enkele cases ervaren. Administratieve data geven ook de kans om verschillen in subgroepen te onderzoeken, omdat de volledige populatie groepen bevat die anders moeilijk te includeren zijn binnen een cohort, zoals families met lager inkomen.

ONDERZOEKSDOELEN

Deze studie had als overkoepelend doel om de **levenseindezorg voor kinderen met een ernstige aandoening te evalueren**, bij de ziektegroepen van kinderen met kanker, neurologische aandoeningen, en genetische of congenitale aandoeningen, aan de hand van kwaliteitsindicatoren en administratieve data.

De onderzoeksdoelen hieraan gekoppeld zijn:
1. Het **ontwikkelen van kwaliteitsindicatoren specifiek voor kinderen**, voor het evalueren van de gepastheid van levenseindezorg bij kinderen met kanker, kinderen met neurologische aandoeningen, en kinderen met genetische of congenitale aandoeningen
2. Het **meten van deze kwaliteitsindicatoren met Belgische administratieve gezondheidszorgdata** en het bekijken van **mogelijke socio-demografische, klinische, en regionale verschillen** in gepastheid en ongepastheid van levenseindezorg

Door het gebruik van administratieve databases, lag onze focus op medicatie, behandeling, en zorgverleners, aangezien deze aspecten meetbaar zijn binnen de data.

METHODEN

Voor onderzoeksdoel 1, de ontwikkeling van **kwaliteitsindicatoren specifiek voor kinderen**, voerden we een systematische literatuurstudie en RAND/UCLA-panel uit. De RAND/UCLA-methode bestaat uit experteninterviews, een elektronische survey, een groepsdiscussie, en een tweede survey. Interviews en panels werden gedaan met pediaters, verpleegkundigen, psychologen, kinesisten, apothekers, zorgcoördinatoren, huisartsen, en sociale werkers uit ziekenhuizen, zorgteams, en de huisartsenpraktijk. Drie indicatorensets werden ontwikkeld: één voor kinderen met kanker, één voor kinderen met neurologische aandoeningen, en één voor kinderen met genetische of congenitale aandoeningen

Voor onderzoeksdoel 2, het **meten van deze kwaliteitsindicatoren met Belgische administratieve gezondheidszorgdata**, linkten we eerst verschillende Belgische populatiedatabases. Hierna berekenden en beschreven we de indicatorenresultaten. Voor het bekijken van **mogelijke socio-demografische, klinische, en regionale verschillen**, voerden we variantie-analyses en logistische regressies uit.

BELANGRIJKSTE BEVINDINGEN

In **Hoofdstuk 1** presenteerden we de resultaten van een systematische literatuurstudie, die gezondheidsinterventies identificeerde die geassocieerd waren met verhoogde en/ofverlaagde kwaliteit van leven bij kinderen aan het einde van het leven. We vonden dat de huidige kennisbasis relatief breed is (20 gezondheidsinterventies werden bestudeerd), maar de studies waren van beperkte kwaliteit en vele studies toonden een groot potentieel voor vertekening door design. Palliatieve zorgteams, bepaalde comfort- en pijnmedicaties, en symptoommonitoring waren geassocieerd met verbeterde symptomen en kwaliteit van leven bij kinderen aan het einde van het leven. Behandelingen zoals chemotherapie en stamceltransplantatie waren geassocieerd met een vermindering van kwaliteit van leven.

In **Hoofdstuk 2**, beschreven we een RAND/UCLA-panel voor het ontwikkelen van indicatoren voor het meten van mogelijke gepaste en ongepaste levenseindezorg bij kinderen. Overheen alle ziektegroepen vielen de gevalideerde indicatoren uiteen in 4 groepen:: 1. Behandeling, medicatie en monitoring (met kwaliteitsindicatoren zoals kinesitherapie en gespecialiseerde comfortmedicatie), 2. Plaats van zorg en sterven (met kwaliteitsindicatoren zoals thuissterfte), 3. Zorgverleners en -services (met kwaliteitsindicatoren zoals huisartsencontact en continue zorgrelaties hebben), en 4. Administratieve maatregelen (met kwaliteitsindicatoren zoals palliatieve status, en hierdoor recht hebben op een vergoeding).

Hoofdstuk 3 tot 5 beschreven de metingen van de indicatoren voor alle ziektegroepen.
Voor **mogelijk gepaste zorg**, vonden we dat terugbetalingen voor comfortzorg laag was voor alle kinderen aan het einde van het leven. Bijvoorbeeld, terugbetalingen voor palliatieve zorg werden voorzien voor minder dan een vijfde van de kinderen. De helft van de kinderen met kanker stierf thuis. Langdurige zorg werd voorzien voor de helft van de kinderen. De meerderheid van de kinderen met neurologische aandoeningen kreeg terugbetalingen van een specialistisch arts. Echter, minder dan een vijfde van ernstig zieke kinderen kreeg terugbetalingen van een huisarts in de laatste maand voor het sterven en multidisciplinaire zorg was laag van frequentie. De uitgifte van administratieve maatregelen was laag voor alle ziektegroepen. Palliatieve status werd voor een vijfde van de kinderen geregistreerd in de laatste 2 jaar voor het sterven.
Mogelijk ongepaste zorg was algemeen niet veelvoorkomend in ernstig zieke kinderen aan het einde van het leven. Bijna geen kinderen ontvingen terugbetalingen voor een nieuwe dialyse of operaties. Wel kreeg een substantieel aandeel van de kinderen nog beeldvorming (MRI, X-ray, CT-scan), en was het trekken van bloed frequent: dit kwam voor bij de helft van de kinderen in alle ziektegroepen.
Voor de **klinische, socio-demografische en regionale verschillen**, toonden kinderen met neurologische aandoeningen verschillen voor gepastheid van levenseindezorg voor

ziektecategorieën: aandoeningen van het centraal zenuwstelsel of bewegingsstoornissen toonden lagere scores voor gepastheid van zorg. Voor kinderen met kanker waren er verschillen voor regio en nationaliteit: Eén regio toonde meer gepastheid van zorg en kinderen met een allochtone achtergrond kregen meer ongepaste zorg. Voor kinderen met genetische en congenitale aandoeningen waren er vele verschillen voor verschillende regio's.

BESPREKING VAN DE BELANGRIJKSTE BEVINDINGEN

Onze discussie besprak dat er frequente en **continue zorg was van artsen, maar minder van andere zorgverleners, en bovendien weinig palliatieve zorgverlening**. We duidden aan dat onze cijfers waarschijnlijk een onderschatting zijn van de reële zorgvoorziening, door de private en filantropische structuur voor funding van levenseindezorg bij kinderen. Echter, deze cijfers kunnen een startpunt zijn voor verdere inzichten in palliatieve zorgvoorziening en de inclusie van andere zorgverleners.

Ook haalden we aan dat onze bevindingen **een complex beeld schetsen van ongepaste en intense zorg aan het levenseinde bij kinderen**. Behandelingen zoals chemotherapie, vaak gezien als onnodige behandeling en een typische indicator voor ongepaste levenseindezorg bij volwassenen, werden niet gevalideerd als indicator van ongepaste zorg, in alle recente studies over indicatoren bij levenseindezorg bij kinderen. De behandelingen worden ofwel niet veel gegeven, zoals dialyse, of de behandeling kan mogelijk nog comfort geven, zoals palliatieve chemotherapie. Beeldvorming en het afnemen van bloed zijn een uitzondering op de regel en werden frequent terugbetaald, en zouden dus mogelijk verminderd kunnen worden aan het einde van het leven. Echter, we benadrukken dat onze studie geen onderscheid kan maken tussen een verwacht en onverwacht levenseindetraject.

Uiteindelijk toonden we ook dat verschillen voor regio, ziektegroep, en nationaliteit zouden kunnen duiden op **verschillen in kennisbasis, structurele ondersteuning, en voorkeur van het gezin**.

CONCLUSIE

Dit proefschrift toont dat kinderen aan het einde van het leven met een ernstige aandoening mogelijk **meer comfortzorg zouden kunnen ontvangen, meer opvolging van multidisciplinaire zorg kunnen krijgen, minder beeldvorming en bloedafnames, en meer**

administratieve ondersteuning. Er werd ook aangegeven dat er mogelijk verschillen zijn voor gepastheid en ongepastheid van levenseindezorg **op gebied van ziektegroep, regio, en nationaliteit.**

IMPLICATIES

Administratieve en legale maatregelen zouden extra ondersteuning kunnen voorzien voor de voorziening van palliatieve zorg en de liaisonteams voor kinderen. Het **ontwikkelen van interventies** met aandacht voor mogelijke verschillen naar klinische, socio-demografische en regionale factoren is aangeraden. **Leer-en-verbeter-strategieën** kunnen geïmplementeerd worden met indicatoren als startpunt en flexibele benchmarks. **Leerdoelen voor levenseindezorg bij kinderen** worden best toegevoegd aan de inhoud van cursussen zoals bijscholingen in palliatieve zorg. Verder **empirisch onderzoek naar pijn- en comfortcontrole** wordt best uitgevoerd voor zowel de groep van niet-kanker-patiënten, als de groep van kankerpatiënten. Het is sterk aangeraden **kinderen en gezinnen te includeren in vervolgonderzoek.**

CURRICULUM VITAE

Veerle Piette (°1992) holds a Master's degree in Language Psychology and Pathology as well as a Bachelor's in Biological Psychology from the Vrije Universiteit Brussel. During her studies, she has worked as a care teacher and care coordinator in kindergarten and middle school, and has done clinical internship for pediatric neuropsychological practice. After her studies, Veerle joined the End-of-Life Care Research Group as a PhD researcher in 2017, working on an FWO-funded project for the development of quality indicators for children with serious illness at the end of life, and various other research projects centering on the improvement of children's care. Veerle was supervised by Prof. Dr. Luc Deliens, Prof. Dr. Joachim Cohen, and Prof. Dr. Kim Beernaert. The findings reported and discussed in her dissertation were published in international high-impact pediatric journals, and were presented at various national and international conferences.

LIST OF RELEVANT PUBLICATIONS, PRESENTATIONS, AND GRANTS

RELEVANT PUBLICATIONS IN INTERNATIONAL PEER-REVIEWED JOURNALS

Piette V, Dombrecht L, Deliens L, Cools F, Chambaere K, …, Chambaere K. Barriers and facilitators for parents in end-of-life decision-making for neonates at the Neonatal Intensive Care Unit: A qualitative study. Palliative Medicine, 2022. (2021 JCR IF 5,713, ranking 14/109, Q1 in category Healthcare sciences and services)

Piette V, Deliens, L., van der Werff ten Bosch, J., Beernaert, K., & Cohen, J. Face-Validated Quality Indicators for Appropriateness Of End-Of-Life Care in Children With Serious Illness: A Study Using the RAND/UCLA Appropriateness Method. The Journal of Pediatrics, 2021. (2021 JCR IF 6,314, ranking 9/130, D1 in category Pediatrics)

*Piette V***,** Beernaert K, Cohen J, Pauwels, NS, Scherrens A, van der Werff ten Bosch J & Deliens L. Healthcare Interventions Improving and Reducing Quality of Life in Children at the End of Life: A Systematic Review. Pediatric Research, 2020. (2020 JCR IF 3,756, ranking 26/130, Q1 in category Pediatrics)

Dombrecht L, *Piette V*, Deliens L, Cools F, Chambaere K, Goossens L, Naulaers G, Cornette L, Beernaert K, Cohen J, Laroche S. Barriers to and facilitators of end-of-life decision making by neonatologists and neonatal nurses in neonates: a qualitative study. Journal of pain and symptom management. 2020 Mar 1;59(3):599-608. (2020 JCR IF 3,612; ranking 33/107, Q2 in category Healthcare sciences and services)

Dombrecht L, Deliens L, Chambaere K, Baes S, Cools F, Goossens L, Naulaers G, Roets E, *Piette V*, Cohen J, Beernaert K. Neonatologists and neonatal nurses have positive attitudes towards perinatal end-of-life decisions, a nationwide survey. Acta paediatrica. 2020 Mar;109(3):494-504. (2020 JCR IF 2,299; ranking 60/129, Q2 in category Pediatrics)

Piette V, Cohen J, Deliens L, Pauwels N, van der Werff ten Bosch J, Beernaert K. Influence of health interventions on quality of life in seriously ill children at the end of life: a systematic review protocol. Systematic reviews. 2019 Dec;8(1):1-8. (No JCR IF)

RELEVANT PRESENTATIONS AT INTERNATIONAL CONFERENCES

Quality of end-of-life care in children with neurological conditions in Belgium: A population-level evaluation using face-validated quality indicators, World Research Congress of the European Association for Palliative Care, oral presentation, 2022

Developing Quality Indicators for Potentially (in)Appropriate End-of-Life Care in Children with Cancer, Neurological Conditions or Genetic and Congenital Conditions: A RAND/UCLA Appropriateness Study, World Congress of the European Association for Palliative Care, poster presentation, 2021

Effects of healthcare interventions on quality-of-life outcomes in children at the end of life: a systematic review, World Congress of the European Association for Palliative Care, poster presentation, 2020

Modifiable Factors for Improving End-of-Life Decision-Making for Neonatologists, Nurses, and Parents in the Neonatal Intensive Care Unit: A Qualitative Study, World Congress of the European Association for Palliative Care, poster presentation, 2019

GRANTS RECEIVED FOR THIS THESIS

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