The moral landscape of pediatric oncology

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THE MORAL LANDSCAPE OF PEDIATRIC ONCOLOGY

AN EMPIRICAL STUDY ON BEST INTERESTS, PARENTAL AUTHORITY AND CHILD PARTICIPATION IN DECISION MAKING

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Virtue then is a settled disposition of the mind determining the choice of actions and emotions, consisting essentially in the observance of the mean relative to us, this thing being determined by principle, that is, as the prudent man would determine it.
Aristoteles, Ethica Nicomachea, II. vi.15

Voor mijn ouders

CONTENTS

Chapter 1

GENERAL INTRODUCTION

Dennis is a 15-year old boy. He was diagnosed with Ewing sarcoma in his left femur 6 months ago. He has been treated with chemotherapy and subsequently an operation. Since the tumor did not respond well to the chemotherapy, the next step is treatment with high dose chemotherapy followed by autologous stem cell infusion.

During the courses of chemotherapy, Dennis has gained 'experience' in feeling sick, nausea and vomiting. Up to his admission for the high dose chemotherapy he never needed nasal tube feeding. He always recovered in time and had enough intake to not lose weight. Dennis is very motivated to prevent the need for nasal tube feeding.

Just before admission an informational meeting is planned with one of the treating pediatric oncologists and Dennis' parents. The physician explains the procedure and informs the parents that almost no children can undergo the treatment without the need for nasal tube feeding. The high dose chemotherapy gives so many side-effects, like mucositis, that most children are not able to eat enough themselves. To prevent a daily battle over eating, nasal tube feeding is started early. Dennis' parents again express their child's opinion: Dennis definitively does not want nasal tube feeding, except when there is no other option.

During treatment Dennis develops severe mucositis and his intake deteriorates. Weight loss cannot be measured reliably due to hyperhydration and changing splints. The dietician calculates that his caloric intake is only 25% of his daily needs. Her conclusion is that Dennis needs nasal tube feeding. The matter is discussed with Dennis, his parents, the treating physicians and the dietician. Although in the first instance Dennis and his parents respond negatively, eventually they agree with the nasal tube feeding. The nasal tube feeding is continued up to the day of discharge, and has good results.

At the day of discharge Dennis throws up and the nasal tube is dislocated. He refuses to have a new one brought in. The treating physician and the nurses, however, share the opinion that it is in the interest of Dennis that the tube feeding is continued at home. An alternative would be that Dennis stays admitted and shows that he can eat enough himself. A new meeting takes place with Dennis and parents, in which again emphasis is placed on the importance of enough caloric intake.

Nonetheless, Dennis and his parents decide to go home without the nasal tube. They state that the family has gained enough experience with Dennis' eating habits after chemotherapy. Especially the father calls himself an expert in cooking things that Dennis likes, and that because of that he will eat enough when he is at home.

The parents and the medical team do not reach an agreement. Eventually, the medical team wants the family to sign a statement that they leave the hospital against medical advice. Dennis and his parents however leave the hospital without saying good bye and without signing the statement.
(Case published in De Vries et al 2005)

Few medical specialties encounter so many ethical challenges as pediatrics does. It is a specialty that inherently has features that are morally charged. The above case shows in a concise matter the ethical issues which play a role when caring for severely ill children: what is in the best interest of a severely ill child, what influence does the child itself have on its treatment, what is the role of parents in decision making, and what is the role of the pediatrician and other health care professionals? In this thesis we will study these issues in the setting of pediatric oncology. Furthermore, insights gained in this particular setting will be translated, where possible and appropriate, to pediatrics in general.

THE PHILOSOPHICAL QUINTESSENCE OF PEDIATRICS

Pediatrics is the discipline concerned with the well-being of infants, children, and adolescents, focusing on their health; their physical, mental, and psychological growth and development; and their opportunity to achieve full potential as adults (Kliegman *et al* 2011, p1). Although this description is short, it encompasses several important features that are philosophical in nature. The fact that pediatrics is a medical specialty, separate from adult medicine, reflects that children are considered as a special group in medicine, and that they cannot be treated as just small adults. But what is a child? How can we define childhood separate from adulthood? The description of pediatrics gives us some direction: it has to do with growth, development and hope to become a (healthy) adult. Growth relates to a dynamic process in which children develop from fully dependent infants to independent adults. This raises questions of (in)competence: at what stage in their development should children be allowed to make their own decisions and have them respected? The opportunity to achieve a full potential relates to the question what a full potential might be, and who decides in what direction a child should develop. The fact that pediatrics is concerned with these issues inevitably means that the medical profession takes a responsibility in facilitating and supporting the developmental process that a child undergoes to become an adult who can reach his full potential. But to what extent? And what is the responsibility of parents as protectors of and investors in the upbringing of their children? The responsibilities of parents and physicians intersect but do not necessarily coincide. What is then the scope of parental choice and authority and what are the responsibilities of physicians in medical decisions influencing the health and future opportunities of children?

According to Nelson Textbook of pediatrics, for many the world's most trusted resource for best approaches to pediatric care, pediatricians should serve as advocates for all chil-

dren, because 'children cannot advocate for themselves' (Stanton and Behrman 2011, p1). The statement that children cannot advocate for themselves means that someone else has to take care of them. In medical, but also daily practice, parents or legal guardians[1] are the obvious and (most of the times) appropriate caretakers for children. When surrogate decision making is at hand, as is often the case in pediatrics, questions arise about what the best interests of the child are, and how parental authority can be reconciled with medical judgment on the best interests**.** These questions, that are ethical by nature, define pediatric practice. In general terms, the autonomy driven framework of adult medical ethics is replaced by a beneficent paternalism (or parentalism) in pediatrics with an independent role for the pediatrician to protect and promote the health-related interests of children (McCullough 2010, p11).

As pediatrics deals with growing and developing children, ultimately the patient population at some point reaches a developmental level at which they *can* decide for themselves (or at least we hope that they will). The issues of (in)competence of children, assent and informed consent are also central in pediatrics.

In conclusion, pediatric ethics examines the broad issues of (1) the concept of the child's best interest; (2) parental responsibility and authority in decision-making about the life and health of a child; (3) the emerging desire and capacity for self-determination of an older child, and (4) the professional obligation of a pediatrician to act in the best interests of the child.

BACKGROUND AND AIMS OF THE PRESENT STUDY

Much is written about the concepts best interests, child participation and parental authority. Most literature on these topics is either theoretical in nature (see for example: Elliston 2007; Diekema 2004; Kopelman 1997 and 2010; Miller 2003; Schapiro 1999), or casuistic (De Beaufort *et al* 2008). It remains difficult to utilize these concepts in the reality of pediatric practice. Our goal was to further reflect on the question how these concepts can and should be translated and made operational in the everyday encounter between parents, physicians and children. We therefore combined theoretical conceptions of the best interest standard, child participation and parental authority with a close look on how these concepts actually function in pediatric practice, and how they are conceived by actors in the pediatric field. The alliance with practice is a prerequisite for practicing ethics well-informed and pro-actively and for avoiding armchair philosophy

[1] In the remainder of the text, whenever there is mention of 'parents' one can also read 'parents or legal guardians'.

(Bredenoord 2010, Borry *et al* 2005). Attention to the lived reality of pediatric practice however raises the question how to integrate experiences from clinical practice in ethical theory and analysis. Although intuitions and experiences are highly valuable as moral markers, it is generally stated that in ethics they need to be subjected to systematic, rational analysis in order to prevent violation of the so-called 'fact-value distinction' (De Vries and Gordijn 2009). In other words, if one wants to use information from practice, one needs to reflect on the methodology applied to integrate this information in normative-ethical analysis and decision making.

Aims and scope of this thesis

The aim of the study presented in this thesis is threefold. Our first concern is to find a method to integrate ethical theory ('norms') and information from practice ('facts', intuitions, experiences). Ethical theory is often used to give structure to the interpretation of moral experiences in a practice. It clarifies, in a deductive manner, the conditions under which theoretical ethical concepts can function in that practice (Gillon 1985). However, practical insights into a lived moral reality may also be a starting point for theory development and change, sometimes even using inductive reasoning (Kon 2009). Taking the view that people's actual moral beliefs, intuitions, experiences and reasoning in a (medical) practice yields information which is meaningful for the operationalization of ethical concepts, we will refine an existing methodology that successfully combines empirical research and ethical reflection, namely Reflective Equilibrium.

Subsequently, we will use this methodology to study one specific pediatric medical practice, namely pediatric oncology (for reasons specified below). Our goal is to describe in detail the forms that the concepts of best interests, child participation and parental authority take in the studied pediatric oncology practice. In order to gather the empirical data for our ethical reflection, we use qualitative methods: observations and semi-structured interviews with all actors involved.

Finally, we will reflect on the question whether the insights gained in our particular research setting can be translated to pediatric oncology in general and, where possible and appropriate, even to pediatrics in general.

Central research questions

1. Which method should we use to give voice to people's actual moral beliefs, intuitions and reasoning in a (medical) practice? How can this method truly integrate ethical theory ('norms') and information from practice ('facts'). In other words: how can we

use experiences of parents, children and doctors to develop our understanding of ethical concepts?
2. Using this method in a specific medical practice, namely pediatric oncology, can we further develop our understanding of the concepts of best interests of children, child participation and parental authority?

In order to answer the central research questions the following subquestions will be addressed:

1. What methodology is needed to address the problems of best interests, child participation and parental authority in a specific setting like pediatric oncology, especially when we want to incorporate the views of the relevant actors in the field? (Chapter 2)
2. What makes the pediatric oncology setting special from an ethical point of view? (Chapter 4)
3. What interpretations of best interests are found in pediatric oncology? (Chapters 4 and 5)
4. What is the role of parents in decision making in pediatric oncology? (Chapters 4, 5, 6 and 7)
5. What is the role of physicians in decision making in pediatric oncology? (Chapters 4, 5,6 and 7)
6. What is the view of the different actors on child participation in decision making in pediatric oncology? (Chapters 6 and 7)

METHODS

Reflective Equilibrium

In the last decades, it has become increasingly clear that the study of people's actual moral beliefs, intuitions, behavior and reasoning in (medical) practice yields information that is meaningful for ethics (Borry *et al* 2004; Hope 1999; Solomon 2005). Adding intuitions and experiences from parties involved in ethically sensitive situations offers an important supplementation and enrichment of the scientific and scholarly debates, literature and theory. In ethics, the use of empirical data therefore has become more and more popular, even leading to a distinct form of applied ethics, namely empirical ethics. Especially in bioethics, this 'empirical turn' is visible (Borry *et al* 2005). Empirical ethics is a broad category, grasping different interpretations of integrating ethics and empirical

research. There is, however, one basic assumption in all sorts of empirical ethics: it denies the structural incompatibility of empirical and normative approaches, and believes in their fundamental complementarity. It is an answer to the critique of bioethics for being too abstract, too general, too dogmatic, too top-down as well as too far removed from clinical reality, insensitive to the peculiarities of specific situations.

There are various ways of combining empirical research and ethical reflection (Solomon 2005). In chapter 2 we will discuss the use of empirical data in Reflective Equilibrium (RE). Although inclusion of moral experiences in this specific model of RE can be well defended, their use in the application of the model still raises important questions. What precisely are moral experiences? How to determine relevance of experiences, in other words: should there be a selection of the moral experiences that are eventually used in the RE? How much weight should the empirical data have in the RE? And the key question: can the use of RE by empirical ethicists really produce answers to practical moral questions? In this thesis we start to answer the above questions by using the method to reflect on the data gained in our interview study and observations.

The study object: pediatric oncology

Until now, most studies using empirical data to discuss interpretations of best interests, parental authority, child participation and the physician's fiduciary obligations have focused on neonatal care and end-of-life decision making (Kopelman 2010; Leuthner 2001; Placencia and McCullough 2011; Spence 2000). However, also outside these realms these ethical concepts have a role in daily practice. For our study's purposes there was no absolute need for a specific medical diagnosis of the children studied. For principal reasons (relatively high density of decisions to be made, day-to-day, as well as high impact decisions), as well as practical reasons (easy accessible study group due to prior pilot study), our study field became pediatric oncology. Although a first reflex could be to again study end-of-life (EoL) decision making in this group, we focused on day-to-day decision making. First, because EoL decision making has been described before (for example: Kars *et al* 2011). Second, because we anticipated that day-to-day decision making could tell us more about how the ethical concepts function in everyday pediatric practice, i.e. also outside pediatric oncology.

Pediatric oncology: a short introduction

Cancer in patients below the age of 19 years is uncommon, with an age-adjusted annual incidence rate of 16.6/100.000, representing only about 1% of all new cancer cases in a year in the USA (Kliegman *et al* 2011). In the Netherlands, every year about 400 children

between 0-15 years of age are diagnosed with cancer (Integraal KankerCentrum Nederland 2011). Although relative 5-year survival rates have improved over the past 30 years from less than 20% to about 75% ((Ries *et al* 2007; Jemal *et al* 2003), malignant neoplasms remain the leading cause of disease-related (noninjury) mortality, namely 12.8%, among persons between 1-14 years of age (Kliegman *et al* 2011).

Pediatric cancers differ markedly form adult malignancies in both prognosis and type of cancer. Lymphohematopoietic cancers (i.e. acute lymphoblastic leukaemia, lymphoma) account for 40%, nervous system cancers for 30%, and embryonal tumors and sarcomas for 10% of the broad categories of childhood cancers (Kliegman *et al* 2011). Epithelial tumors of organs such as lung, colon, breast and prostate, which are commonly seen in adults, are rare malignancies in children. The fact that childhood cancer is a rarity and that evidence from research with adults cannot be generalized to children (due to the different cancer types) makes it inevitable that pediatric oncology has a strong research culture. If long delays in making evidence-based treatments available to children with cancer are to be avoided, it is important that trials in pediatric oncology recruit a much greater proportion of the patient population than adult cancer trials. As a consequence, most pediatric oncologists are investigators involved in both clinical care and research. Multi-institutional cooperative clinical trials investigate novel therapies and ways to improve survival rates through supportive care. In the Netherlands treatment and research are coordinated by the Stichting Kinderoncologie Nederland (SKION, Dutch Childhood Oncology Group). As a result of these research efforts, a remarkable proportion of children with cancer - up to 70% of children in the developed world - enrolls in a study during their cancer treatment, as compared to only 1-4% of adult patients (Ablett and Pinkerton 2003; Bleyer 1997; Ablett *et al* 2004). Because increasingly more patients survive their disease, research is also focussing on the quality of life among survivors and the late outcomes of therapies experienced by pediatric and adult survivors of childhood cancer. In the Netherlands, every 1 out of 250 people aged 18-45 years is a survivor of childhood cancer (SKION Later 2010). Potential adverse late effects include subsequent second malignancy, early mortality, infertility, cardiomyopathy, osteoporosis, neuro-cognitive impairment and altered social functioning.

In the setting of pediatric oncology most treatments are given according to national or international protocols which describe in detail the treatment plan for each type of cancer. The treatment period varies depending on the cancer type, but stretches from months to years of invasive and intensive treatment. Clearly, childhood cancer has an enormous impact on the family. Whilst survival rates have improved dramatically, it is still a devastating, potentially life-threatening diagnosis for child and family members and an illness which severely disrupts the lifestyle of the family. Poder *et al* (2008) for

example showed that at commencement of treatment 33% of parents exhibit post-traumatic stress symptoms. Children show high levels of psychosocial and emotional stress at the start of treatment (Tsai *et al* 2012). Survivors of childhood cancer are at increased risk of various psychological and behavioral problems (Marcoux *et al* 2012).

Gaining empirical data: observations and semi-structured interviews

In order to gather the empirical data we were going to use for the ethical reflection, we performed a qualitative multicenter project in which we explored patients', parents', and physicians' experiences, roles, and considerations in treatment decisions in pediatric oncology. In this project we invited patients (aged 8-18 years) attending the pediatric oncology units of two Dutch university hospitals, their parents, and their physicians to participate in one-to-one, semi-structured in-depth interviews. Interviews were conducted 8-10 weeks after initial diagnosis or diagnosis of relapse. The project was approved by the Institutional Review Boards at both study sites (Leiden University Medical Center and VU Medical Center). Informed consent was obtained from all participants.

All physicians, parents, and children were interviewed by the author of this thesis. Initial interview topics were formulated after examination of the relevant literature and a preliminary observational study, during which the interviewer spent three months in the children's oncology ward of one of the university hospitals and observed the daily routine and the discussions between parents, children, and physicians. Consistent with standard qualitative research techniques, the interview topics evolved as the interviews progressed through an iterative process to ensure that the questions captured all relevant emerging themes (Britten 1995; Guest, Brunce, and Johnson 2006). The interviews contained general topics and no closed-ended questions. Examples of interview questions are given in the following chapters, where the interview data are presented.

The physician interviews lasted between 30 and 60 minutes. The in-depth interview topics covered work experience; general goals of pediatric oncology; the physician–patient-parent relationship, especially concerning decision making during treatment; considerations deemed important in treatment decision making; patient and parent autonomy; and physician's ideas on what is in the best interest of a child.

The child interviews lasted between 30 and 45 minutes. The parent interviews lasted between 60 and 90 minutes. Both were conducted at the hospital. The interview topics covered general characteristics of the patient; the history of the disease; discussions with physicians about the recommended treatment; parents' and child's attitudes to these discussions; considerations deemed important in treatment decision making; and the perceived role of parents and children in decision making during treatment.

All interviews were audio-taped and transcribed verbatim. Data analysis was based on the constant comparative method (Malterud 2001; Strauss and Corbin 1998).We used an iterative process wherein we continually went back to the field and interviewed new participants to collect more data. The following process of data gathering and analysis was used: (1) interviews; (2) transcribing the interview data; (3) open coding, which involved identifying relevant concepts in the text; (4) constantly comparing open codes, looking for conceptual similarities and differences; (5) identifying emerging themes and a theoretical framework; (6) continued sampling and interviewing as theoretical categories emerged and novel questions arose; and (7) continued coding and comparison of codes until nothing new was added to the theoretical categories. The author of this thesis coded the full transcripts. An independent researcher coded five transcripts to check for consistency and adequacy of the framework. The author and the independent researcher engaged in a discussion on the themes each of them had identified from the transcripts. No inconsistencies were found. When no new thematic content was found in the interviews, subject enrollment was stopped. This process, called thematic saturation, is a well-described qualitative method to avoid unnecessarily large and repetitive data sets (Denzin and Lincoln 2000; Guest, Brunce and Johnson 2006).

We used qualitative software (Kwalitan 5.0) for multiple text management, including coding, locating, and retrieving key phrases (Peters 2000). Finally, representative quotations were chosen to illustrate the themes identified. These quotations are included in the text of the various chapters.

Age of child participants

The age of the children we wanted to study played an important role in shaping our research project. We specifically wanted to look at the role of the child in the decision making process. For this purpose it was necessary that the child could express its own views. Several studies have assessed and reviewed children's capacity to participate in medical decision making (Dorn *et al* 1995, Mårtenson and Fägerskiöld 2008, Ondrusek *et al* 1998). The data on this topic have been ambiguous. All that these studies suggest is that the major period of rapid change and individual variability in children's capacities occurs between age 9 and 14 years. Some have concluded that relatively young children can participate meaningfully in the assent process (Committee on Bioethics 1995), whereas others have raised doubts about what children can understand (Wendler and Shah 2003). When interpreting these studies, it is important to realize that the way in which researchers define assent drives their conclusions. It greatly depends on the capacities one requires for children to be deemed capable of providing assent (Miller and Nelson 2006). The closer the definition of these capacities comes to the capacities

needed to be an ideal adult, the older the child will be before it can meet the criteria. The ambiguity of the above mentioned studies shows that it is not so straightforward to select a specific age group for our study. Of course it was easy to exclude Neonatology, but every other age limit remains the object of debate. We decided to include children from the age of eight.

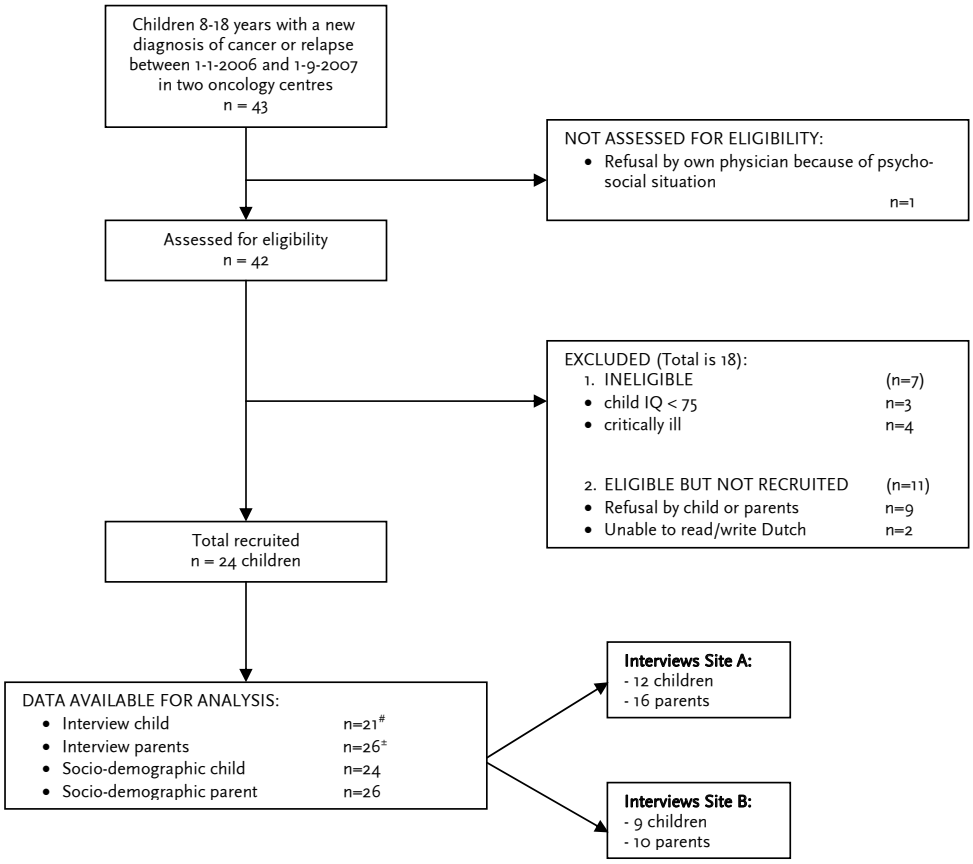


Figure 1: *Enrollment, eligibility and recruitment of children and parents*

In three families the child refused an interview, but one of the parents did participate (with the agreement of the child). ± In two families both parents were interviewed.

Characteristics of the study sample

The sample consisted of 15 physicians, 24 children, and 26 parents of these children. Figure 1 shows eligibility criteria and the recruitment process for children and parents. Parents had a mean age of 40 years (range 32-50 years). Their children had a mean age of 13.4 years (range 8-18 years). The parents' occupations varied, indicating social diversity. All families were of Dutch origin. Demographic and clinical characteristics of the parents and their children are given in Tables 1 and 2.

The group of physicians comprised the entire medical staff of both pediatric oncology units (9 and 6 physicians, respectively). They were the primary providers of care for the children who participated in the study. Physicians had a mean age of 42.1 years (range 32-52 years) and worked in pediatric oncology for a mean of 7.6 years (range 1.5-20 years); 7 (46.7%) were male. Characteristics of the physicians are shown in Table 3.

Table 1 *Demographic and clinical characteristics of the children included in the present study (n = 24). Values are n (%)*

Sex	
Male	13 (54)
Female	11 (46)
Age	
8-11 years	5 (21)
12-14 years	10 (42)
15-18 years	9 (37)
Cancer diagnosis	
ALL	5 (21)
AML	3 (12.5)
MDS	2 (8.5)
Non Hodgkin Lymphoma	4 (17)
Hodgkin	2 (8)
Ewing Sarcoma	3 (12,5)
Osteosarcoma	2 (8)
Brain tumour	3 (12,5)
Treatment phase	
Initial cancer diagnosis	18 (75)
Relapse	6 (25)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

Table 2 *Demographic characteristics of the parents included in the present study (n = 26). Values are n (%)*

Sex	
Male	10 (38)
Female	16 (62)
Marital status (n = 24 families)	
Single / divorced	6 (25)
Married / registered partnership	18 (75)
Education	
Primary school / lower level high school	4 (15)
Middle level high school	12 (46)
Advanced vocational / university	9 (35)
Unknown	1 (4)

Table 3 *Physician Characteristics*

Physician number*	Profession	Age (years)	Sex	Working experience in pediatric oncology (years)
A1	consultant pediatric oncology	47	M	8
A2	consultant pediatric oncology	51	F	20
A3	consultant pediatric oncology	45	F	9
A4	consultant pediatric oncology	52	M	15
A5	consultant pediatric oncology	43	M	8
A6	consultant pediatric oncology	51	M	18
A7	consultant pediatric oncology	42	M	7
A8	clinical fellow	32	F	3
A9	consultant pediatric oncology	38	M	3
B1	clinical fellow	37	F	2
B2	consultant pediatric oncology	39	F	4
B3	consultant pediatric oncology	39	F	5
B4	consultant pediatric oncology	38	F	4
B5	consultant pediatric oncology	44	M	10
B6	clinical fellow	33	F	2

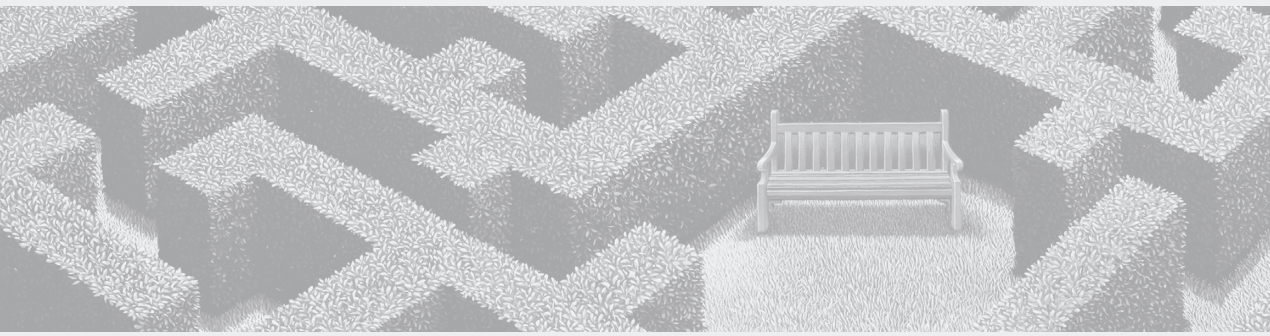
* A and B denote the two treatment centers.

OUTLINE OF THE THESIS

This thesis consists of four parts. **Part A** (*Chapter 2)* deals with the empirical ethical methodology used throughout the book. In chapter 2 we progress from the use of empirical data only to clarify a morally laden situation, to the possible use of these data to justify action and even formulate policy. **Part B** sets the scene of pediatric oncology. We focus on the fact that pediatric oncology has a strong research culture. As stated above, most pediatric oncologists are investigators involved in clinical care as well as research. Consequently, various concepts studied in research ethics are relevant for our investigation. *Chapter 3* is a theoretical introduction to the ethical concepts studied empirically in chapter 4. We describe the criteria for valid informed consent, and the concepts of equipoise and therapeutic misconception. In *Chapter 4* we discuss the ethical consequences of the unprecedented integration of research and care in pediatric oncology from the perspective of parents and physicians. We use an empirical ethical approach to answer the question whether this characteristic of pediatric oncology interferes with the parental task to promote the best interest of the child. **Part C** (*Chapter 5)* describes different interpretations by parents, children and physicians of the best interest of the child in pediatric oncology. Again, an empirical ethical approach is used to weigh these interpretations and formulate recommendations for communication. **Part D** deals with the role of children in medical decision making. *Chapter 6* discusses child participation in decision making concerning research participation. We focus on pediatric oncologists' attitudes towards involving adolescents in this decision making. In *Chapter 7* we present the problem of fertility discussions as an example of involving children in decision making. Both chapter 6 and 7 combine empirical data with ethical theory and principles to formulate a reflective approach to child participation in the pediatric oncology practice. Finally, in *Chapter 8* the principal results of this thesis are put into perspective. We focus on two issues: first, we give methodological considerations: does our methodology prove valuable for answering ethical questions in practice, and what are the limitations?; and second, what are the implications of our study for our thinking about child participation, the use of a best interests standard and parental authority in pediatric oncology and in pediatrics in general?

PART A

Methodology in Empirical Ethics



Chapter 2

REFLECTIVE EQUILIBRIUM AND EMPIRICAL DATA: THIRD PERSON MORAL EXPERIENCES IN EMPIRICAL MEDICAL ETHICS

De Vries MC, Van Leeuwen E.
Bioethics 2010;24(9):490-498

ABSTRACT

In ethics, the use of empirical data has become more and more popular, leading to a distinct form of applied ethics, namely empirical ethics. This 'empirical turn' is especially visible in bioethics. There are various ways of combining empirical research and ethical reflection. In this chapter we discuss the use of empirical data in a special form of Reflective Equilibrium (RE), namely the Network Model with Third Person Moral Experiences. In this model, the empirical data consist of the moral experiences of people in a practice. Although inclusion of these moral experiences in this specific model of RE can be well defended, their use in the application of the model still raises important questions. What precisely are moral experiences? How to determine relevance of experiences, in other words: should there be a selection of the moral experiences that are eventually used in the RE? How much weight should the empirical data have in the RE? And the key question: can the use of RE by empirical ethicists really produce answers to practical moral questions?

In this chapter we start to answer the above questions by giving examples taken from our research project on understanding the norm of informed consent in the field of pediatric oncology. We especially emphasize that incorporation of empirical data in a network model can reduce the risk of self-justification and bias and can increase the credibility of the RE reached.

INTRODUCTION: BIOETHICS, EMPIRICAL RESEARCH, REFLECTIVE EQUILIBRIUM

In ethics, the use of empirical data has become more and more popular, leading to a distinct form of applied ethics, namely empirical ethics. Especially in bioethics, this 'empirical turn' is visible (Borry *et al* 2005).[1] Empirical ethics is a broad category, grasping different interpretations of integrating ethics and empirical research. There is, however, one basic assumption in all sorts of empirical ethics: the study of people's actual moral beliefs, intuitions, behaviour and reasoning in a practice yields information that is meaningful for ethics (Borry *et al* 2004). It denies the structural incompatibility of empirical and normative approaches, and believes in their fundamental complementarity. It is an answer to the critique of bioethics for being too abstract, too general, too dogmatic, as well as too far removed from clinical reality, insensitive to the peculiarities of specific situations.

In this chapter, we wish to discuss the use of empirical data in a method of ethical reflection in which coherence is central: Reflective Equilibrium.

Reflective Equilibrium (RE) was first (thoroughly) defined in the works of John Rawls (Rawls 1971). In contrast to other approaches in ethics on evaluating and justifying moral judgments, the RE approach allows an *a priori* equal status or weight to the various data used, like (background) theories, principles and considered moral judgments (and, in our form of the RE, empirical data; we'll come to that). The RE approach liberates us in this way from the idea that we have to approach a moral question *either* 'from theory' *or* 'from practice'. It tries to facilitate a real dialogue between theory and practice by not assigning a preferential status to either of them. Considerations on different levels of abstraction have an equal status at the start of the reflection. Rawls himself wrote: '(...) its justification is a matter of mutual support of many considerations, of everything fitting together into one coherent view' (Rawls 1971, p21). Stated otherwise:

> *'A reflective equilibrium process pays attention to our moral and non-moral beliefs at various reflective levels (particular intuitions, moral principles, abstract theories), and 'tests' various parts of our belief system by revising and refining beliefs at all levels. In a process of mutual adjustment, we seek coherence among the widest possible sets of beliefs (...)'* (Van der Burg and Van Willigenburg 1998, p1)

Coherence is achieved by interaction between the different elements in RE. This interaction can have an effect on all these elements. Thus, some elements need to be altered or

[1] Because our research field is bioethics, we will mainly talk about this field.

removed, others kept. The equilibrium reached is also a dynamic one; it can change due to new elements in the reasoning process. In RE the reasoning is normally done by one individual, whom we will call: 'the thinker'.

VARIETIES OF RE-METHODS – THE NETWORK MODEL WITH THIRD PERSON EXPERIENCES

There are various versions of the RE approach, each differing in the nature and amount of the elements used.[2] Certain types of consideration are deliberately included or excluded, depending on the goal of the reasoning process.[3] This pragmatic (and of course reasoned) selectivity in the light of specific purposes is also a response to the danger of all-inclusiveness, which could make a RE method unworkable.

We will not discuss all RE versions here. We will only talk about the version we use in our research project on understanding the norm of informed consent in the field of pediatric oncology. In the remainder of this chapter, we will give examples taken from this research project to illustrate how we use RE to give answers to our research questions. The RE version we use is an adjusted form of the 'Network Model', first introduced by Van Willigenburg and Heeger (1989). They formulated an equilibrium which consists of considered moral judgments (they called it 'intuitions'), applicable moral principles and the morally relevant facts of a case. Considered moral judgments are defined here as judgments containing specific ideas and particular situations. This form of RE is particularly useful if one uses RE for justifying a specific course of action in an individual case, as, in order to judge a situation, we must distinguish between the morally salient features of that situation. It is important to notice that in this model facts are not regarded as merely passive objects to which moral judgments or principles have to be applied, but as factors in the equilibrium process itself. There is a genuine interplay between facts, principles and moral judgments (intuitions).

We used The Network Model, but with two adjustments. First, we added background theories (on the moral status of a child and on developmental psychology) to the RE.[4] This was done because these theories provide the normative background of the principles used. Without background theories, the focus would be exclusively on the individual case (as in the Network Model), instead of on developing a (modest) theory which is

[2] For an overview of the various versions, see: Van der Burg and Van Willigenburg 1998, p12-17.

[3] This goal can be establishing a (modest) moral theory, selecting moral principles or deciding a specific moral problem

[4] Van der Burg called this Network Model, supplemented with background theories, the wide or extended Network Model. See: Van der Burg 1991.

applicable in a concrete field of ethical considerations and judgments, like Pediatrics.[5] Furthermore, their prescriptive or performative nature makes background theories particularly fit to correct for the tendency towards moral conservatism, as Norman Daniels (1979) suggests. Second and the topic of this chapter, the moral experiences[6] of others than 'the thinker' were integrated in the Network Model. This means that the experiences with a case or practice in the relevant moral community – collected by empirical research – are brought into the RE process. A basic assumption of this suggestion is the idea that the experiences people have in a practice[7] are potentially morally relevant. The judgments and behaviors of these people give us unique insights in the practice at hand and should be taken into account in ethical reflection (Van Delden 1993, 1999[8]). The experiences are used in order to enrich the deliberation of 'the thinker' with the norms and practical wisdom of the field. The deliberation process remains that of the 'thinker', not necessarily of all the individual people in the practice. But because of the resemblance of the justification process in RE to the day-to-day moral reasoning within the moral community, the judgment reached will be more readily accepted and acted upon in practice (Van Willigenburg and Heeger 1989, p61).

To sum up our approach: the dialogue between theory and practice will consist of going back and forth between information stemming from practice (morally relevant facts and moral experiences of people in the practice) and from theory (principles and background theories). Figure 2 shows the different elements of our 'Network Model with Third Person Moral Experiences' in a model.

The idea that empirical research on moral views is relevant to reflective equilibrium methods has been suggested by various authors (Van der Burg and Van WIlligenburg 1998, p15). But applying RE this way in empirical bioethics also raises questions and criticism. What precisely are moral experiences? How to select the moral experiences that are eventually used in the RE? How much weight should the empirical data be given in the RE? And the key question: can the use of RE by empirical ethicists really produce answers to practical moral questions?

In this chapter we will address the reasons for including empirical data, and we will try to give an answer to the above questions and to criticism. As mentioned earlier, we

[5] Although we aim at a modest theory, we still talk about concrete cases. With 'concrete' we mean that we do elaborate on real persons in real situations. We do not hold a theoretical debate, but we deal with specific situations in which decisions have to be made that affect real people.

[6] When elaborating on the input of persons other than the 'thinker', we talk about experiences rather than intuitions or considered moral judgments. This is to distinguish them from the judgments of the 'thinker'. In the paragraph on moral experiences we will come back to this preference.

[7] We use MacIntyre's definition of 'practice': 'a practice is a coherent and complex form of socially established cooperative human activity' (MacIntyre 1984, p187)

[8] Van Delden used the considered judgments of practitioners in the medical field in RE to construct a set of guidelines on do-not-resuscitate decisions.

will illustrate this by giving examples taken from our research project on understanding the norm of informed consent in the field of pediatric oncology. The examples are to be found throughout the text, but in separate textboxes. Our aim is to show how empirical information can practically be incorporated in a network model.

Let us also mention what we are not going to do. Our focus will be entirely on the use of empirical data in the RE process. We will not discuss other (also fundamental) elements of the RE, like principles or background theories. Neither will we discuss criticism on these elements or on coherentism as justifying principle. This has been done elsewhere and falls beyond the scope of this chapter.[9]

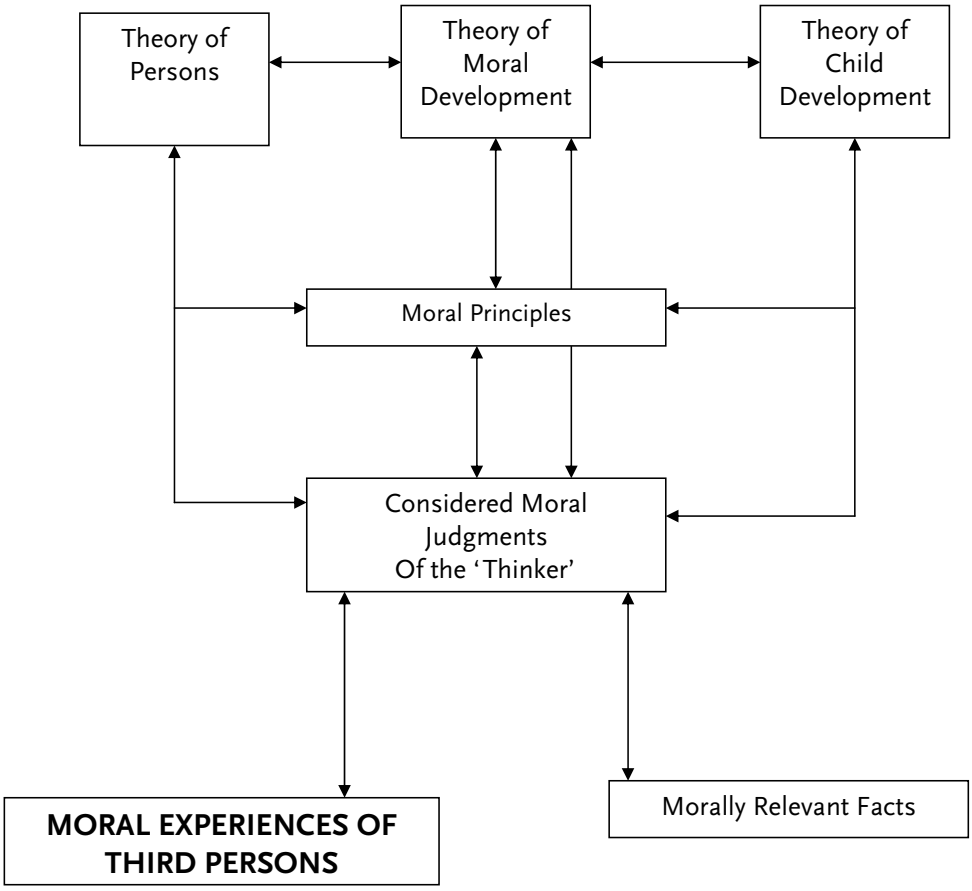


Figure 2: *The different elements of the 'Network Model with Third Person Moral Experiences'. (Adapted from: Daniels 1996, p51)*

[9] On coherentism: Daniels 1979. For a summary of the different elements: Van der Burg and Van Willigenburg 1998. See also: Van Delden *et al* 2005.

MORAL EXPERIENCES

In Rawls' RE the considered judgments are only those of the 'thinker'. In our use of RE we also include the judgments of people acting in the studied practice, namely the pediatric oncology ward. For this purpose, we have added some notions from the empirical ethical approach used in phenomenology to the standard use of RE. Instead of using concepts like considered judgment or intuitions concerning the people in the field, we use the term *moral experience*. This is to emphasize the importance of the conscious events that make up an individual life and the events that make up the conscious past of a community.[10] Phenomenologically speaking, moral experiences show the normative structure of the historical social reality in which they take place. In this, we follow Richard Zaner and his interest in 'narratives' (Zaner 1988). With the use of moral experiences, we want to emphasize the notion that moral life is rooted in the context in which it is lived. Every encounter is interpreted in terms of acquired understandings, shaped by previous experiences and the prevailing cultural system.

In epistemology, the central role of perceptual experience in grounding knowledge and justification is widely recognized. In ethical theory literature, there is not much attention given to the moral counterpart of this perceptual experience. Robert Audi attempts to fill the gap. According to him, moral experiences are the basis of knowledge or justified belief regarding one's moral obligations. He attributes a significant epistemic (evidential) role to moral experience in grounding knowledge and justified belief of both singular moral judgments and general moral principles. On the difference between intuitions and moral experience he says:

> '*(...) far from reducing to a keen awareness of intuited propositions, moral experience may be a ground of such intuitions in the first place. We may intuitively judge that a deed is wrong because our experience of it is one of moral revulsion; the intuition may be a product, not a cause, of the revulsion.*' (Audi 1998, p360)

And on considered moral judgments as formulated by John Rawls:

> '*(...) one kind of intuitive moral judgment – a kind that for intuitionists and other moral theorists plays an epistemically basic role in ethics – is often not only a cognitive appraisal but also a response to a moral experience.*' (p362)

[10] With this view we commit ourselves to a social basis for morality, instead of a psychological one.

Audi moreover states that the practice of moral judgment epistemically depends on moral experience (p362).

Moral experience is also connected with another concept of pre-logical knowing: 'tacit knowledge'. This concept, introduced by Michael Polanyi (1967), comprises a range of conceptual and sensory information and images that can be brought to bear into an attempt to make sense of something. Tacit knowledge can be understood to be culturally embedded knowledge (including regional culture, organizational culture or social culture) and is difficult to share with people not embedded in that culture. It involves learning and skills in a way that cannot solely be prescribed or written down. The knowledge of how to ride a bike is an example: one cannot learn to ride a bike by reading a textbook; it takes personal experimentation and practice to gain the necessary skills, as well as a valuation of cultural norms. Much experience of a personal and normative character in medical practice resembles forms of tacit knowledge.

Acquiring the moral experiences of people in a practice

In our study we try to grasp the moral experiences of children, parents and physicians on treatment and research decisions in a pediatric oncology practice and the role of informed consent. We based our study on a qualitative design with in-depth semi-structured interviews with patients (age 8-18 years), their parents and physicians. As our study aimed to explore views, motives and practices, a qualitative interview design seemed most appropriate. The interview topics that structured the interviews were formulated after examining the relevant literature and after preliminary observational studies had been performed. All the families and physicians were interviewed by MdV, who kept a reflexive diary to record contextual details of the interviews and her reflections on the research process. The moral experiences thus obtained expressed the internal norms of the physicians on decision making and gained insight in the problems children and parents faced during the decision making process.

WHY USE EMPIRICAL DATA TO FIND ANSWERS TO PRACTICAL MORAL QUESTIONS?

One cannot answer a practical moral question unless one knows the facts. Therefore, the need for 'fact-finding' by empirical research seems evident. As indicated earlier, in our model, the data about the practice (the moral experiences of third persons involved in a practice) have a special position. They are not merely the object about which statements are formulated, but they themselves can have an input into the process of formulating arguments.

There are good reasons for including empirical data in RE, and thus using them as independent input.[11] First, it acknowledges the fact that every practice (in our case the medical practice) contains in itself special characteristics that should be involved in ethical reasoning. It brings ethics closer to beliefs that play a role in daily life. Second, it enriches moral reasoning because it illuminates relevant aspects of the case or solutions that one wouldn't have thought of when starting from theory. Moreover, moral experiences reflect the internal norms, the practical wisdom and the subtle, context-driven paths that practitioners follow when specifying abstract principles in concrete cases; and therefore they constitute a good deal of the internal norms and wisdom included in moral reasoning. Empirical research opens large sources of relevant expertise and thus generates potentially important information on the normative structure of reasoning and acting. Outside a practice it is difficult, if not impossible, to grasp these sources. Third, the chance of implementing the outcome of moral reasoning is increased when it is better applicable to the particularities of a practice. Fourth, it enhances moral thinking by taking into account the difficulties and problems that a certain moral dilemma poses in practice. Hereby we want to stress the importance of elaborating on the difficulties and problems encountered by patients, not only by medical workers. The target groups of patients and their relatives have been neglected for a long time in the professionally oriented ethics discussions in health care. Patients and their relatives have at best been considered as topics of theoretical or problem-oriented medical ethics, but not real partners in ethical discourse. Focus on patients broadens the scope and therefore the credibility of the equilibrium reached. Reiter-Theil calls this: 'Interest Groups-Related Medical Ethics' (Reiter-Theil 2004). Related to this fourth reason is the final reason to include empirical data in the RE (especially third-person experiences): one reduces the risk of self-justification and bias by the 'thinker'. The risk of self-justification is one of the main weaknesses of the RE model: coherence is not a sufficient guarantee for credibility or moral truth. As in legal practice and theory, facts and norms need to be combined in a search for truth. By including third-person experiences, one reduces the risk of self-justification in two ways: since the experiences of many are brought into the RE process, there is a good chance of getting a pluralistic view on the matter at hand. Furthermore, minority positions can also gain attention in the process of reasoning.

When addressing the problem of credibility and self-justification, we will have to explore more specifically the considered moral judgments of the 'thinker'.

[11] For these reasons, see also: Van Delden JJM and Van Thiel GJMW 1998; Van Delden *et al* 2005, p45.

CONSIDERED MORAL JUDGMENTS AND CREDIBILITY

In every form of RE, considered moral judgments of the 'thinker' (sometimes called: intuitions)[12] play an important role. They are the foundation stones of the equilibrium.

Rawls (1971) takes considered judgments to be judgments in which our 'moral capacities are most likely to be displayed without distortion because they are given under conditions favorable for deliberation and judgment in general.' The judgments are moral convictions that the 'thinker' has and that tells him which goods, situations and acts are (*prima facie*) good or bad. The judgments are well considered in the sense that they are not the result of an impulse or emotional reaction. They are made under conditions conducive to avoiding errors of judgment and therefore the holder of the judgment is relatively confident.

In our study, the considered moral judgments of the 'thinker' are the judgments of the primary researcher (MdV). For us, these judgments function as a basic assumption, a practical (in the sense that it refers to a specific practice, namely pediatric oncology) hypothesis. The practical hypothesis originates from (initial) theoretical deliberation about known facts of the practice, applicable principles and known norms within the practice. After the deliberation, the 'thinker' reaches some sort of 'hypothetical equilibrium'. In our research, the data used to formulate the hypothetical equilibrium were obtained by a literature search and observations in the (outward) pediatric oncology clinic. From these data we formed a theoretical framework, from which eventually an empirical study could be developed into decision-making in pediatrics, the various moral experiences of the actors involved and the weight of parental authority and child assent.

One of the hypotheses of our research was formulated as follows:

Considering that:

- *The ethical ideal of respect for all persons supports respect for the developing autonomy of children and adolescents in decisions about their participation in research.*
- *In pediatric oncology, almost every treatment is combined with research, ranging from evaluations of the current treatment protocols to randomized clinical trials; and*
- *For this research, Dutch law requires the informed consent of children above the age of 12, as well as parental permission.*

[12] In most literature on RE, the terms considered judgments and moral intuitions are used synonymously. Some authors want to separate the two terms. See for instance: Van Willigenburg 1991.

The hypothetical equilibrium could be:

'Children aged 12 years and older should always be fully informed about research and give independent consent before entering a trial'

This hypothetical equilibrium is the starting point for reaching a new, reflective, equilibrium, which is based on the dialogue between information stemming from practice (morally relevant facts and moral experiences of people in a practice) and from theory (principles and background theories).

In our study, facts about the pediatric oncology practice are for example that discussions regarding diagnosis and treatment almost always include dialogue about participation in research, ranging from evaluations of the current treatment protocols to randomized clinical trials. This makes it difficult for physicians, parents and children, to determine whether research or clinical issues are at hand (for example when talking about goals and risks) and makes obtaining informed consent for the research a difficult task. Moreover, in pediatric oncology, the complex treatment- and research-related decisions arise against a background of acute, serious medical illness and extraordinary psychological and emotional strain. Then, treatment and research protocols, because of their complex scientific structure, are difficult for laymen to understand. And finally, decisions about research participation often need to be made within hours or days. Still, a remarkable proportion of children with cancer – about 70% - participate in a trial during their illness.

Important principles in pediatric research include: respect for autonomy (obtaining both parental permission and the child's assent for research purposes is promoted, beneficence (can research be good for the child / in its best interests?) and non-maleficence (do we harm a child by letting it participate in research, or do we harm it when it cannot participate?).

We want to emphasize the 'deliberative' starting point of the RE process, because no 'thinker' enters an equilibrium process with a *tabula rasa*. His judgments are based on certain premises. Often, especially in bioethics, there is a great deal of activism in this starting point, in the sense that bioethical research presupposes that there exists some kind of moral wrongdoing in practice, and one accordingly strives to change the practice into something one believes to be good. To improve the transparency of the process of RE and to prevent self-justification, it is important to show one's premises. The con-

sidered judgment, or: hypothetical equilibrium of the researcher is formed out of these premises and the known facts and norms of the practice. As has been said, it's the starting point for the subsequent RE process.

The subjective character and therefore the credibility of considered judgments are often questioned.[13] Many authors note that nothing prevents one's considered judgments from expressing only the arbitrary commitments and sentiments of a prejudiced viewpoint (Van der Burg and Van Willigenburg 1998, p8). With our interpretation of a judgment as a hypothetical equilibrium we at least try to be transparent about what elements or premises constitute this first judgment. Furthermore, judgments can alter during the RE process. In this way, the RE process itself can function as a filter, which can separate reliable from unreliable judgments. The process of weighing and balancing judgments, principles and background theories can let us identify judgments that are apparently wrong or prejudiced. Reasoning in RE means precisely this: the consideration of judgments in the light of principles and theories (Van Delden *et al* 2005, p44).

Michael DePaul proposed a similar solution. He called it: a *radical conception of RE* (DePaul 1993,p40). In DePaul's view, the considered moral judgments at the beginning of the reasoning process can differ substantially from the judgements which eventually end up in equilibrium with principles and theories. Initial beliefs or judgments may start the process of reflection, but they will in no sense determine the direction of the reflective process. His method may lead to 'a very great shift in moral view' of the researcher, which he called 'conversion' (p40-42). Typically, a person can acquire the ability to make relevant discriminations in judging and arguing only after a considerable amount of experience and training. Philosophical deliberations along the lines of the RE method should not only be thought of as affecting our beliefs and arguments, but should also be expected to cause 'changes in a person's judgmental faculties, so that these faculties no longer function in the same way, yielding the same beliefs and theories, as they previously did' (p211). The radical conception of RE may therefore demand the expansion of one's range of experiences, for example 'real-life' experiences through submersion in a certain practice, or by listening to voices in the practice. Of course: selecting the experiences and the views that people express in this practice, remains difficult. There is a significant risk that (in order to 'prove' the hypothesis of the 'thinker') certain experiences are left out and others are emphasized. It is therefore very important that the 'thinker' describes the reasons for including and excluding experiences. Of course, reflection on background and tenability of moral experiences is always necessary, before we can use it

[13] The question of how to reconcile the perspective of a particular person on a subject with an objective view on the same subject is a fundamental issue in ethics, knowledge theory and theories on the relation of mind to the physical world. For an introduction, see: Nagel 1986.

as an insight in practice. But eventually, the process of reasoning towards an equilibrium should culminate in that reflection. As soon as experiences are further examined, the RE process has started. This means that in the RE process itself, experiences are selected as tenable or not. This selection should be transparent and documented in a descriptive qualitative approach.[14]

When philosophical deliberations that lead to an equilibrium can guarantee that some (seemingly wrong) judgments are abandoned by the researcher during the process, then the problem of restricted credibility of moral judgments at the start of the process is reduced. As long as radical changes in someone's judgments (and, according to DePaul, judgmental faculties) are possible, there is less danger of systematically wrong judgments in an equilibrium. It is remarkable, that in bioethics, various researchers describe a 'conversion', especially when confronted with empirical data (e.g. The 1999a, 1999b).

Using moral experiences to reach RE

The moral experiences relevant to the above mentioned hypothetical equilibrium were as follows: almost every physician stated that full informed consent from adolescents ≥ 12 years, although required by Dutch Law, is difficult to achieve. In discussing treatment as well as research, physicians relied on proxy consent and their ideas on how to protect the best interests of the child. They acted in this way because in their opinion a child (even aged 12 or older) is not capable of deciding, especially in a stressful situation. Furthermore, they themselves conformed to the research protocol. And, since they had proxy consent from parents, a positive IRB-review[15] and their own investigator integrity, they felt confident that the research project protected the children from harm. Parents and children found it difficult to distinguish research from treatment and were preoccupied with survival, not with research participation. Children often felt comfortable that their parents made the decisions about research issues. Parents found it difficult to refuse research participation because they were afraid to offend the physician that had to save their child.

These internal norms, problems and views were subsequently included in moral reasoning using RE. We asked ourselves whether the internal norms of the physicians were compatible with the 'theoretical' norms expressed in the hypothetical equilibrium. Furthermore, we deliberated on the views of parents and children and on how to integrate them in a coherent way. In other words: we readjusted the hypothetical equilibrium into

[14] For the reader of empirical ethical research it can sometimes be easy to see trough a biased selection. Certain respondents would be mentioned often, others never.

[15] An Institutional Review Board (IRB) is a group that has been formally designated to approve, monitor, and review biomedical and behavioral research involving humans with the alleged aim to protect the rights and welfare of the subjects.

an empirical reflective equilibrium. To reach a new equilibrium, we compared the data on the moral experiences of the different actors with the existing interpretations of the principle of respect for autonomy (on which informed consent is based) and with the theories and ideals lying behind these interpretations. This can be described as follows: At first sight, it seems quite safe to rely on proxy consent and physicians' ideas on how to protect the best interests of the child. But discussion should focus on the appropriateness, in the research setting, of this substitute for the adolescent's consent. This model needs to be balanced in a RE with the moral weight of the principle of autonomy. We have to be aware that there is a difference between the treatment relationship and the research relationship, and that this difference remains valid in pediatric oncology. In the research relationship, the researcher seeks to advance knowledge to improve the care of future children. Any therapeutic benefit to the individual is in principle secondary to the overriding goal of obtaining new knowledge. Because of the fundamental differences between the research- and treatment-relationships, we claim that, although this is sometimes acceptable for treatment decisions, informed consent by adolescents (and their parents) in the research setting can never be ignored. Adolescents deserve a reasonable opportunity to make decisions about what happens to them within a research setting. To do so, both clinicians and researchers need to do more in explaining to adolescents the differences between experimental research and standard care. This can turn out to be a laborious task, especially in pediatric oncology, as much research is intertwined with clinical care and it may therefore be difficult to define clearly what portion of a given protocol is research rather than clinical care. But the mere fact that this intertwinement is an important feature of pediatric oncology, and that treatment centres conform to research protocols, is not an excuse to omit the effort. Furthermore, one of the background theories, developmental psychology (e.g. Piaget 1965), shows that a firm lower age limit of 11 years can be set, at which children achieve the capacity for abstract thought and gain the ability to understand the risks and benefits of research. Well-crafted information materials could aid investigators in explaining to potential child research participants and their parents exactly which elements of their care are research, and therefore optional (for example additional blood samples or spinal taps). If we take informed consent (and therefore respect for patient autonomy) seriously, we have to develop an understanding of this norm that takes into account the complex setting of pediatric oncology and the limits herein of autonomous decision-making by child patients and their parents.

CONCLUSION

Different aspects can strengthen the credibility of the moral judgments of the 'thinker' and can make the resulting RE free of bias. All these aspects have to do with using empirical data. We think that the best answer to the question of how to identify non-biased moral judgments is that there needs to be space for a moral conversion, a radical shift in judgments, just as DePaul described. It is the duty of the 'thinker' to stay susceptible to various moral experiences. In our opinion, this means three things for the methodology of an empirical study.[16] First, the 'thinker' needs to have gained relevant experiences in the field studied and with this experience a relevant moral sensitivity on the subject. Second, when entering a practice, the thinker should investigate the norms and facts of the studied field, and the moral experiences of the people in the practice, until a state of saturation is reached. The search and subsequent analysis of data should be transparent and documented in a descriptive qualitative approach.[17] Moreover, the search should be described in such a way that it is repeatable. Third, we should strive for intersubjectivity. This can be done by discussing the steps taken in RE, openly and with the utmost transparency, with other researchers and by making explicit the arguments used to reach RE. It does not mean that a consensus has to be reached on the facts and judgments that will eventually be used in RE. The intersubjectivity should be based on reasonableness (Van Delden *et al* 2005). Other researchers should be able to understand why the 'thinker' selected certain judgments and facts, although they perhaps would have selected other judgments.

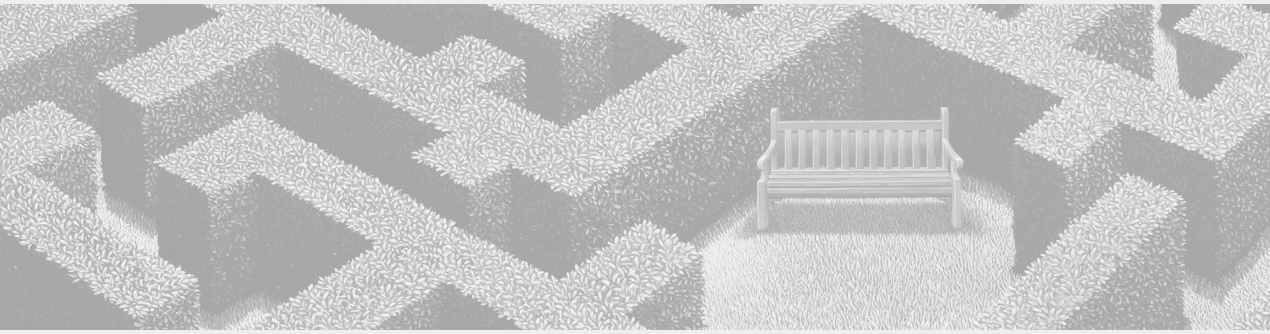
The RE model we embrace, The Network Model with Third Persons Experiences, gives us many opportunities to involve the context of a moral problem and therefore empirical data in ethical thinking. As long as the 'thinker' stays susceptible to a wide range of experiences and facts, and accepts that his own judgments can change due to the RE process (the 'conversion'), we expect this model to work very well for problem solving in specific cases.

[16] We can learn a lot from the social sciences and their experience with the methodology of qualitative research. There is extensive literature on validity, reliability and generalizability. For an overview, see: Denzin and Lincoln 2000.

[17] During our analysis, we used computer software (Kwalitan 5.0; see: Peters 2000) for multiple text management, including coding, locating, and retrieving key materials, phrases, and words.

PART B

Setting the scene



Chapter 3

THE ETHICS OF MEDICAL RESEARCH: INFORMED CONSENT AND THE THERAPEUTIC MISCONCEPTION

Parts of this chapter have been published in Dutch:
De Vries MC, Van Leeuwen E. Ethiek van medisch-wetenschappelijk onderzoek. Informed consent en de therapeutische misconceptie. *Ned Tijdschr Geneesk. 2008; 152(12): 679-683.*
De Vries MC, Zwaan CM. Mogelijkheden tot uitbreiden van geneesmiddelenonderzoek bij kinderen. Afweging van risico's en belasting en de informed consent-procedure in de kinderoncologie. *Tijdschr Kindergeneeskd. 2009;77(2): 59-66.*

ABSTRACT

Pediatric oncology has a strong research culture. Most pediatric oncologists are involved in clinical care as well as research. Consequently, various concepts analyzed in research ethics are also relevant when studying the pediatric oncology practice. This chapter offers a theoretical introduction to the ethical concepts studied empirically in chapter 4.

Medical-ethical approval of research involving human beings is based on two pillars:
(1) 'assessment' by an institutional review board (IRB) or by a Central Committee of the scientific merit of the research and the risks and burdens for the research subject, and
(2) 'informed consent' by the research subject or his legal representatives.
Discussions on the ethical acceptability of research generally focus on the 1st pillar, assessment by an IRB or Central Committee. Much less frequently there is concern about the 2nd pillar, obtaining informed consent from the research subject. In this chapter we analyze some ethical concepts which play a role when asking informed consent. We describe the criteria for valid informed consent: knowledge, competence and voluntariness. We especially focus on the concept of 'therapeutic misconception': the misconception that participating in research is the same as receiving individualized treatment from a physician. We assess this concept in the light of the fundamental difference between the research relationship (between investigator and subject) and the treatment relationship (between physician and patient). We argue that understanding the concept of 'therapeutic misconception' is essential to explaining why it is often difficult to obtain valid informed consent from patients or parents for medical research.

INTRODUCTION

Pediatric oncology has a strong research culture. Most pediatric oncologists are involved in clinical care as well as research. Consequently, various concepts analyzed in research ethics are also relevant when studying the pediatric oncology practice. This chapter offers a theoretical introduction to the ethical concepts studied empirically in chapter 4. We describe the criteria for valid informed consent: knowledge, competence and voluntariness. We pay extra attention to the concept of therapeutic misconception, i.e. the tendency to mistake the scientific aim of the trial for the therapeutic aim of a treatment.

RESEARCH ETHICS IN THE MEDIA

On the 23rd of January 2008, the medical center of the University of Utrecht (UMC Utrecht) announced that during a randomized study on the effects of probiotics on patients with acute pancreatitis an unusually high mortality rate occurred among the group of patients who received treatment with probiotics (UMC Utrecht 2008). In total, twenty-four patients (16%) from the study group died, as compared to only nine patients (6%) from the control group (Besselink *et a*l 2008a; 2008b).
There were various responses to the press release. Some people wondered whether there had been a stratification problem in the inclusion phase. Others raised doubts about how the research was performed. Still others expressed worries about the way in which the participants were informed about the trial. The media openly asked the question whether this outcome could have been prevented and whether the research had been performed in the proper way. The government health care inspectorate announced an investigation into the execution of the research. At the talk show *Pauw en Witteman* a patient who had participated in the trial stated that he had not been sufficiently informed during the informed consent procedure (show of January the 24th 2008; http://pauwenwitteman.vara.nl). In his perception, he had not been told about the possible risks involved in participating in the trial. He claimed that the doctors had told him that the medication was ´as safe as one of those probiotic drinks from the supermarket´. Moreover, he ´might as well have been buying a house´ when he signed the informed consent form, indicating that he did not know what he was signing for.

The responses to the news from the UMC Utrecht reflected the two pillars on which the ethical acceptability of medical research involving human subjects is based, namely:
(1) the assessment of the scientific soundness of the trial and the risks and burdens for

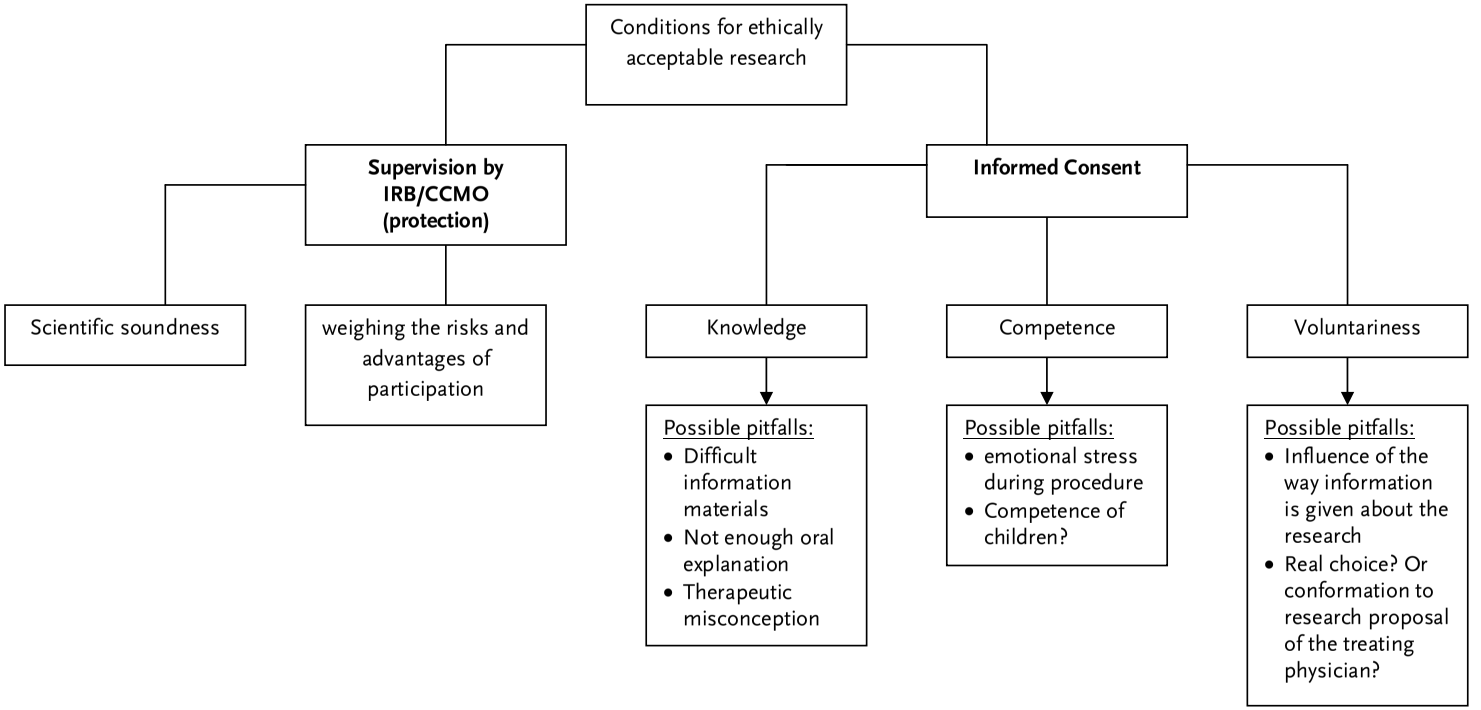


Figure 3: *The two pillars of ethical acceptability of research. In the Netherlands, there is supervision by a local review board (IRB) or by the Dutch Central Committee for Research involving Human Subjects (CCMO). 'Informed consent' is achieved through the relationship between the physician-researcher and the patient and/or his legal representatives. Pitfalls during the informed consent procedure are indicated underneath the three criteria for informed consent.*

the subjects by an institutional review board (IRB) or by a Central Committee, and (2) the obtainment of informed consent from the subject or from his or her legal representative (see figure 3). In the Netherlands, these 2 pillars have been laid down in the Medical Research with Human Subjects Act (WMO, Wet Medisch-wetenschappelijk Onderzoek met Mensen).

This chapter will examine some of the ethical concepts involved in the pillar of informed consent. As mentioned above, the focus will be on the concept of 'therapeutic misconception'. This concept is crucial to understanding why it is so difficult to obtain valid consent for medical research from subjects.

INFORMED CONSENT AS PILLAR OF ETHICAL ACCEPTABILITY OF RESEARCH

In discussions on the ethical acceptability of research, the focus is generally on the first pillar: supervision by a review board. The second pillar, the obtainment of informed consent for research approved by an IRB, rarely gets questioned. But this second pillar requires discussion as well. For example: do subjects actually understand what the research entails? Are they able to weigh the risks and burdens themselves? Is it at all possible to obtain valid consent in emergency situations?
According to the researchers from the UMC Utrecht, their research was conducted in compliance with the prevailing regulations and with the law. They point at the methodological soundness of the research and at the approval obtained from the local review board of every participating hospital. This means they mainly base their claim on the first pillar. They are supported by peer reviewers of the scientific article on the research results (Van Santen 2008). But what about the second pillar? Was informed consent obtained in a valid way as well?

CRITERIA FOR INFORMED CONSENT

The principle of informed consent does justice to the ethical ideal of respecting a patient's autonomy, and his right to self-determination. A valid informed consent meets 3 criteria (see figure 3): knowledge, competence, and voluntariness.

Knowledge requires that the subject is supplied with sufficient information to be able to make a deliberate choice. Knowledge transfer, however, may be problematic. For instance, research shows that a large number of patients find the written information they

receive hard to read and to understand (Paasche-Orlow *et al* 2003; Grossman *et al* 1994; Tarnowski *et al* 1990). Even after explanation by the physician, many of the patients who agree to take part in a trial still have misconceptions about the research procedures (Greenley 2006; Wendler 2004). In many cases, they do not have sufficient insight in necessary elements of informed consent, such as risks, burdens, possibility of alternative treatments, duration of the trial, the right to withdraw, and the voluntariness of participation.

Competence means that the subject is able to understand the information he receives and that he realizes the consequences of his choice to either participate in the trial or decline participation. When the decision whether or not to participate in research occurs at the onset of treatment for a severe illness, patients may be under extreme psychological and emotional pressure. One may question their competence under such circumstances. The subjects in the UMC Utrecht trial all came in with an acute pancreatitis which was predicted to take a serious course - not an ideal situation to be in when one needs to weigh information and make a deliberate choice. In hindsight, patients may start to doubt their apparent competence at the time, as did the patient in the talk show *Pauw en Witteman*.

Voluntariness means that the subject is able to give his or her consent without being coerced or influenced. However, it is easy to influence a patient. By the way in which the information is given or by not mentioning some of the information, physicians even unconsciously manipulate the choice of the patients or their representatives. The emotional circumstances surrounding a serious disease foster reliance on the doctor who brings up the treatment and the trial (Ong *et al* 1995). In pediatric trials, parents indicate that they find it difficult to oppose the physician's proposal because they are afraid this will have an adverse effect on their child's treatment (Heneghan *et al* 2004). Moreover, they may be under the pressure of having to decide on participation in the trial within a few hours or days.

THERAPEUTIC MISCONCEPTION

One aspect of the informed consent procedure which merits separate attention is the so-called 'therapeutic misconception': the tendency to mistake the scientific aim of the trial for the therapeutic aim of a treatment. This therapeutic misconception was first described in 1982 as the misunderstanding that taking part in a trial is the same as receiving individualized treatment (Appelbaum *et al* 1982; Appelbaum *et al* 1987). Subjects may have difficulty to recognize that the aim of a trial is to obtain scientific information

(even if this will contribute to enabling better care in the future); they may not understand that potential benefits for the subjects themselves are formally a mere by-product of gaining such information, and that research participation may involve the sacrifice of some degree of personal care.

Research shows that 40-80% of study participants express inaccurate beliefs regarding the degree of individualization of their treatment, or regarding the likelihood of benefit, given the methods of the study (Appelbaum *et al* 2004). Current medical practice, in which research and treatment may be closely interrelated, leaves much room for such misunderstandings. For instance, participants in a randomized trial may think that they can decide for themselves which arm they will be assigned to, or that a physician will decide on the basis of what seems best for them. It may not always be clear that the assignment will actually be random.

Physicians, too, may suffer from the therapeutic misconception. They may, for example, experience tension between their role as a clinician and as a researcher. Two studies show that oncologists, even those with plenty of research experience, mostly adopt the perspective of clinician instead of that of researcher when they discuss participation in a trial (Joffe *et al* 2002; Taylor 1992). They often sincerely think that clinical trials provide a perfect harmony between the aims of patient care on the one hand and scientific advancement on the other. The best possible treatment then seems to be offered in the strict set-up of a research protocol (Joffe *et al* 2002).

TREATMENT RELATIONSHIP AND RESEARCH RELATIONSHIP

A fundamental point of departure in medical ethics, however, is the important distinction between the treatment relationship which exists between clinician and patient, and the research relationship which exists between researcher and subject (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979). In the treatment relationship, the individual well-being of the patient prevails. The ethical principles of beneficence and non-maleficence are important here. Incidentally obtained new information is secondary to the overriding goal of the medical activity, i.e. treating the patient. The treatment is often conducted without explicit consent from the patient. This is called implicit or presumed consent and is exemplified in a patient's stretching of an arm for a vena puncture. Concerning children, pediatricians routinely carry out medically indicated procedures on children without obtaining consent or assent. Indeed, many procedures are even performed over the child's vigorous objections. This is acceptable because it is the interest of the child which is the sole motivation prompting the intervention (Lee *et al* 2006).

In a research relationship, by contrast, the aim of the researcher is to obtain new knowledge and thus enable the improvement of future treatments. Potential therapeutic advantages are secondary to the prevailing aim of obtaining information. Therefore, every act of research requires explicit consent.

It is sometimes claimed that in randomized trials the basic requirement of therapeutic benefit is met because of the so-called 'clinical equipoise'; the researcher sincerely does not know which of the trial arms will turn out to be the best for the group of patients as a whole at completion of the trial. However, the fundamental difference between a treatment and a research relationship is that the experienced clinician selects and conducts the treatment – in accordance with individual, patient-specific considerations – while the researcher refrains from patient-specific considerations and opts for randomized assignment in order to obtain general results for the group of patients as a whole, with no importance given to individual traits or preferences. And even though the benefits and risks of participating in a trial may seem to be at least as favorable as those of undergoing a standard treatment, a characteristic of randomized trials remains precisely that researchers may never positively know in advance what the actual benefits and risks will turn out to be – as the UMC Utrecht study clearly shows. If one, in spite of this, communicates the absolute equality of the arms of a trial to potential subjects, this will increase the chance that they will fall prey to the therapeutic misconception (Miller and Brody 2003).

DISCUSSION

Obtaining valid consent is not an easy task. The informed consent procedure should start with a clarification of the situation: subjects who think they will receive individualized treatment, while in reality they will be treated according to the research protocol, cannot give their valid consent. Subjects have the right to a fair opportunity to make a deliberate decision on whether or not to participate in a trial. Therefore, clinicians and researchers should clearly explain the difference between the standard treatment and the treatment administered in the trial (Appelbaum 2002). This may take a fair amount of time, especially in a setting where research and treatment are closely interrelated. When the research pertains to an acute disorder and when the intervention involves taking a nutritional supplement, as was the case in the UMC Utrecht study, it seems natural to rely on the argument of clinical equipoise. However, approval by an IRB and the reasonable expectation of clinical equipoise may never replace the consent procedure.

Well-formulated written information may help researchers in explaining which elements of a treatment protocol are in fact part of research and therefore optional (Ungar *et al* 2006). In a study in pediatric oncology, parents themselves were asked for advice on how to improve the informed consent procedure (Eder *et al* 2007). They stated that the information should be based on the individual situation of the subjects and not on legal requirements – the latter often leading to long and complicated patient information forms. Parents also wanted a clearer distinction, in time and/or in spokesperson, between consultations regarding the treatment on the one hand and the trial on the other. Finally, they desired more time to decide. It is precisely this last point which is hard to realize if the trial has to start immediately after the diagnosis and the patients are critically ill, as in the probiotics study.

A first step towards solving this problem might be to always have a close relative of the patient present, who listens in on the informed consent procedure. Moreover, the informed consent procedure should be seen more as a process than as one decisive moment. During the course of a trial, there should be multiple moments in which patient-participants are again informed of what the trial entails, what the risks are, and what the difference is with regular treatment. This will prevent them from afterwards feeling that they have not been sufficiently informed.

Notably, most researchers indicate hardly having received any training in conducting consent consultations or in the requirements that such consultations should meet. And IRBs are confined to assessing the written information, and do not monitor the actual informed consent procedure with patients.

CONCLUSION

The above proves that the informed consent procedure is full of pitfalls, and that it is difficult to obtain consent that is actually valid, especially when it comes to trials involving acute disorders. It therefore seems necessary to provide physicians involved in such trials with additional training in this area. The focus should then be at perceiving the informed consent procedure as a process in which the subject gains more insight throughout the study into what the trial actually entails.

Chapter 4

ETHICAL ISSUES AT THE INTERFACE OF CLINICAL CARE AND RESEARCH PRACTICE IN PEDIATRIC ONCOLOGY: A NARRATIVE REVIEW OF PARENTS' AND PHYSICIANS' EXPERIENCES

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ABSTRACT

Background. Pediatric oncology has a strong research culture. Most pediatric oncologists are investigators, involved in clinical care as well as research. As a result, a remarkable proportion of children with cancer enrolls in a trial during treatment. This chapter discusses the ethical consequences of the unprecedented integration of research and care in pediatric oncology from the perspective of parents and physicians.

Methodology. An empirical ethical approach, combining (1) a narrative review of (primarily) qualitative studies on parents' and physicians' experiences of the pediatric oncology research practice, and (2) comparison of these experiences with existing theoretical ethical concepts about (pediatric) research. The use of empirical evidence enriches these concepts by taking into account the peculiarities that ethical challenges pose in practice.

Results. Analysis of the 22 studies reviewed revealed that the integration of research and care has consequences for the informed consent process, the promotion of the child's best interests, and the role of the physician (doctor vs. scientist). True consent to research is difficult to achieve due to the complexity of research protocols, emotional stress and parents' dependency on their child's physician. Parents' role is to promote their child's best interests, also when they are asked to consider enrolling their child in a trial. Parents are almost never in equipoise on trial participation, which leaves them with the agonizing situation of wanting to do what is best for their child, while being fearful of making the wrong decision. Furthermore, a therapeutic misconception endangers correct assessment of participation, making parents inaccurately attribute therapeutic intent to research procedures. Physicians prefer the perspective of a therapist over a researcher. Consequently they may truly believe that in the research setting they promote the child's best interests, which maintains the existence of a therapeutic misconception between them and parents.

Conclusion. Due to the integration of research and care, their different ethical perspectives become intertwined in the daily practice of pediatric oncology. Increasing awareness of what this means for the communication between parents and physicians is essential. Future research should focus on efforts that overcome the problems that the synchronicity of research and care evokes.

BACKGROUND

Children treated for cancer are increasingly likely to survive. For all childhood cancers combined, 5-year overall survival has improved over the past 30 years from less than 20% to about 75%, due to improved treatment and supportive care (Ries *et al* 2007; Jemal *et al* 2003). A major factor contributing to these advances is the systematic research effort in pediatric oncology. Pediatric oncology has a strong research culture. This is instigated by two circumstances: evidence from research with adults with cancer cannot be generalized to children and childhood cancer is a rarity. If long delays in making evidence-based treatments available to children with cancer are to be avoided, it is important that trials in pediatric oncology recruit a much greater proportion of the patient population than adult cancer trials. As a consequence, most pediatric oncologists are investigators involved in both clinical care and research.

In the setting of pediatric oncology most treatments are given according to national or international protocols which describe in detail the treatment plan for each type of cancer. Protocols represent the best available treatment at a given moment according to the published medical literature, but may also include research components which contain potential improvements of the treatment. Table 4 shows different types of research which are often performed during treatment. As a result of these research efforts, a remarkable proportion of children with cancer – up to 70% of children in the developed world - enrolls in a study during their cancer treatment, as compared to only 1-4% of adult patients (Ablett and Pinkerton 2003; Bleyer 1997; Ablett *et al* 2004). Due to the integration of research and care the pediatric oncology practice always faces ethical challenges inherent to research participation.

The aim of this chapter is to describe the ethical consequences of the fading boundary between research and care from the perspective of parents and physicians. We present an empirical ethical approach using a narrative review of existing empirical research evidence on parents' and physicians' experiences of the integration of research and care. The use of empirical evidence enhances moral thinking by taking into account the peculiarities and difficulties that ethical challenges pose in practice. The results therefore remain much closer to the particular reality of the ethical consequences than a theoretical analysis would permit (De Vries and Van Leeuwen 2010).

Table 4: *description of different types of research in pediatric oncology*

Type of research	Description
Randomized Controlled Trials (RCT)	The random allocation of different treatments to patient-subjects. The best available treatment is compared to one or more regimens that are expected to either improve overall survival or lessen toxicity with equivalence of outcome. Most 'front-line' pediatric cancer studies are phase III randomized controlled trials.
Clinical Controlled Trial (CCT)	Evaluation of singe-arm treatment protocols by clinical and epidemiological data collection and systematic analysis of disease characteristics, actual treatment, treatment results and side-effects. Current treatment results are compared to historical results and to results obtained by other research groups.
Laboratory research using tissue from patients	Unraveling the pathogenesis of childhood cancers, characterization of tumor biology, detection of new treatment targets and identification of novel prognostic factors. For this purpose left over blood, bone marrow or cerebrospinal fluid is used, or additional biological specimens are taken at defined moments during treatment. In fact, permission is often asked for storage of biological materials in a cell bank for future, as yet not specified research.

METHODOLOGY

A narrative review within empirical ethics

In ethics, the use of empirical evidence has become more and more popular, leading to a distinct form of applied ethics, namely empirical ethics. Especially in bioethics, this 'empirical turn' is visible (Borry *et al* 2005). Empirical ethics is a broad category, grasping different interpretations of integrating ethics and empirical research. There is, however, one basic assumption in all sorts of empirical ethics: the study of people's actual moral beliefs, intuitions, behavior and reasoning in a practice yields information that is meaningful for ethics (Borry *et al* 2004). It denies the structural incompatibility of empirical and normative approaches, and believes in their fundamental complementarity. It is an answer to the critique of bioethics for being too abstract, too general, too dogmatic, as well as too far removed from clinical reality, insensitive to the peculiarities of specific situations.

To gain empirical information, we conducted a narrative review of (primarily) qualitative studies on experiences of parents and physicians in the pediatric oncology research practice. We subsequently confronted these experiences with existing theoretical ethical concepts about (pediatric) research, namely goals of research, informed consent, best interests, equipoise and therapeutic misconception. In other words, the theoretical ethical concepts were the starting point and were subsequently enriched by the emergent themes from the narrative review. The experiences of parents and physicians give us unique insights in the research practice and the way ethical concepts function in this practice. Because we use empirical findings we come much closer to the reality of the ethical challenges faced than a theoretical essay could (De Vries and Van Leeuwen 2010; Denzin and Lincoln 2000).

Literature search

An initial work-up established that the literature was too heterogeneous to permit a systematic review of qualitative studies along the lines proposed by Dixon-Woods (Dixon-Woods *et al* 2001). Furthermore, a systematic review would not permit a wide and comprehensive scope and the opportunity to cover a wide range of issues (concepts) within the topic of pediatric oncology research ethics (Collins and Fauser 2005). For these reasons, a narrative review was undertaken.

Studies included in the review were identified by keyword searches of Web of Science, Picarta, Pubmed, Cochrane and EMBASE. Keywords searched included 'oncology', 'clini-

Table 5: *Summary of study characteristics*

Author & Date	Setting	Methodology	Sample characteristics
Vries e.a. 2010	Pediatric oncology clinical research	- Retrospective interviews	Physicians n = 15
Kodish e.a. 2004	Pediatric oncology clinical research	- Observations - Retrospective interviews	Parents n = 137
Wiley e.a. 1999	Pediatric oncology clinical research	- Questionnaire (retrospective)	Parents n = 192
Stevens e.a. 2002	Pediatric oncology clinical research	- Retrospective interviews	Parents n = 12
Chappuy e.a. 2010	Pediatric oncology clinical research	- Retrospective interviews	Parents n = 43
Dermatis e.a. 1990	Pediatric oncology clinical research	- Questionnaire (retrospective)	Parents n = 61
Levi e.a. 2000	Pediatric oncology clinical research	- Focus group interviews (retrospective)	Parents n = 22
Van Stuijvenberg e.a. 1998	Pediatric general practice clinical research	- Questionnaire (retrospective)	Parents n = 181
Tait e.a. 1998	Pediatric anesthesia clinical research	- Questionnaire (retrospective)	Parents n = 246
Singhal e.a. 2002	Neonatology clinical research	- Questionnaire (retrospective)	Parents n = 231
Reynolds e.a. 2007	Pediatric endocrinology clinical research	- Interviews (hypothetical decisions about research)	Parents n = 31
Kupst e.a. 2003	Pediatric oncology clinical research	- Retrospective interviews	Parents n = 20
Snowdon e.a. 1997	Neonatology clinical research	- Questionnaire (retrospective) - Retrospective interviews	Parents n = 71
Eiser e.a. 2005	Pediatric oncology clinical research	- Retrospective interviews	Parents n = 50
Heneghan e.a. 2004	Pediatric general practice No research	- Focus group interviews	Parents n = 44
McKenna e.a. 2010	Pediatric oncology clinical research	- Questionnaire (retrospective) - Retrospective interviews	Parents n = 66
Appelbaum e.a. 1982	Adult psychiatry clinical research	- Observations - Retrospective interviews	Adult patients n = 31
Joffe e.a. 2001	Adult oncology clinical research	- Questionnaire (retrospective)	Adult patients n = 207
Taylor 1992]	Adult oncology clinical research	- Questionnaire (retrospective) - Retrospective interviews	Physicians n = 101
Taylor e.a. 1994	Adult & pediatric oncology clinical research	- Questionnaire (retrospective – quantitative study) - Retrospective interviews (n = 43)	Physicians n = 1485
Joffe e.a. 2002	Adult & pediatric oncology clinical research	- Questionnaire (retrospective) (quantitative study)	Physicians n = 547
Instone e.a. 2008	Adult gastroenterology clinical research	- Observations - Retrospective interviews	Physicians + nurses, n = 19

cal trials', 'pediatric*', 'decision making', 'informed consent', 'parents', randomized controlled trials' in combination with 'qualitative study', 'semi-structured', 'ethnograph*' and 'experiences'. Manual searches of other relevant journals (JCO, Pediatric Blood and Cancer, Journal of Pediatric Hematology and Oncology, Pediatrics) and reference lists of primary articles found from initial searches were also conducted.

The focus of the review was on the research types described in Table 4. Other types of research, especially phase I and II studies, are also performed in the pediatric oncology setting. However, the described three types of research have typically become integrated into pediatric oncology practice in such a way that, in contrast with phase I and II studies, almost all patients and their parents are confronted with them at the start of initial treatment. The ethical challenges of phase I and II studies fall beyond the scope of this chapter, because these studies are usually applied in second line treatment and are not part of initial treatment protocols.

The median age of children diagnosed with cancer is below 6. Therefore it is assumed in this chapter that the child is not competent, and that parental authority and the physician's care are the main factors in determining the best interest of the child. We discuss the difficulties of obtaining assent and consent for research from older children elsewhere (Chapter 6). Studies focusing on children's experiences were excluded. In common with other narrative reviews, evaluations of methodological quality were not used to exclude papers.

The search revealed 20 qualitative studies, 1 quantitative study, and 1 combination of a quantitative questionnaire and qualitative interviews. Not all studies focus (only) on the pediatric oncology research context, but (also) on adult and clinical context. These studies were still included because they provided important information on especially physicians' attitudes towards research and their conflicting professional roles of physician and investigator. For this topic, it was not necessary to have a pediatric setting. Table 5 summarizes the 22 study characteristics, including setting (pediatric vs. adult, research vs. clinical context), methodology applied (interviews, observations, questionnaire) and perspective (parents, physician).

The existing (theoretical) ethical concepts about research were studied using ETHX on the web, Philosopher's Index and Bioethics Line. We focused on 'research goals', 'informed consent', 'best interests', 'equipoise' and 'therapeutic misconception'.
Articles and books were included up to January 2011.

RESULTS AND DISCUSSION

Analysis of the 22 studies reviewed revealed four main themes: intertwinement of research and treatment goals, problems with informed consent, promoting best interests in a research setting and therapeutic misconceptions.

Goals of research and care: who's best interest?

One of the consequences of the fading boundary between research and clinical care is that the goals of research and treatment become intertwined. From an ethical point of view, the goals of treatment and research are fundamentally different (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979; Miller and Brody 2003). In the treatment relationship, the best interests of the individual child prevail when treatment options are discussed. Generation of new knowledge is incidental compared to the overriding goal of providing optimal therapy. In the context of research, the researcher seeks to advance knowledge about what could be the best care of children, as well as to serve other interests like academic merit. Therapeutic benefits to the individual child are, in the research perspective, secondary to the overriding goal of obtaining robust data and new knowledge. Children therefore may have to undergo procedures that are not determined by the goals of treatment, like additional blood samples, spinal taps and (PET-) scans.

The different ethical perspectives of treatment and research can also be illustrated by the different types of ethical principles governing the two activities (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979; Miller and Rosenstein 2003; Council of Europe 1997). In the context of pediatric treatment the principles of beneficence and non-maleficence dictate the practice, translated in the statement that treatment should be in the best interest of the individual child. Usually parents and physicians share the same ideas on what constitutes the child's best interest, making it possible to use the concept of implicit consent.

In the context of research, however, beneficence also involves benefits to others. The prevailing principle therefore is respect for autonomy. Respect for autonomy incorporates two ethical convictions: firstly, that individuals should be treated as autonomous subjects, and secondly, that persons with diminished autonomy are entitled to protection (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979). Respect for autonomy demands that subjects voluntarily participate in research, with adequate information and only after explicit consent. In the case of incompetent subjects, like young children, there should be vigorous protection against abuse, and substitute permission should be sought.

Due to the integration of research and care, their different ethical perspectives must simultaneously be applied in the daily practice of pediatric oncology. This has consequences for the informed consent process, the promotion of the best interest of the child by parents, and the role of the physician (doctor vs. scientist).

Informed consent in the pediatric oncology research setting

Joffe and all have shown that the context of pediatric oncology contains many obstacles to a good informed consent process (Joffe *et al* 2006), especially when discussions regarding diagnosis and treatment include dialogue about participation in research. Parents have the difficult task to differentiate between research and clinical issues, for example when talking about goals and risks. Informed participation in decision making requires adequate understanding of treatment options, but simultaneously the understanding of the distinction between research and therapeutic intent and of difficult research-related concepts, such as randomization, voluntariness and the risk–benefit ratio. The consent forms involved, explaining concepts and methods, are complex by nature and difficult to understand (Berger *et al* 2009; Paasche-Orlow *et al* 2003; Tarnowski *et al* 1990; Grossman *et al* 1994). Studies show that parents frequently have an incomplete understanding of the necessary elements of informed consent in research, especially of the risks, the procedures, the possibility of alternative treatments, the duration of participation, their right to withdraw, and the voluntariness of participation (Kodish *et al* 2004; Wiley *et al* 1999; Stevens and Pletsch 2002). A reason for this incomplete understanding might be that the standard treatment protocols often include research interventions, like extra blood draws, or a randomization, as if these research elements were an integral part of the treatment. For example, the Dutch protocol for acute lymphoblastic leukemia (ALL) states in the parent information form:

> *'Almost all children with ALL are treated according to a national protocol of the Dutch Childhood Oncology Group or according to an international protocol. A protocol contains guidelines for research and the mode of treatment'.* (Dutch Childhood Oncology Group 2007, p61)

This can make parents think that when they consent to the protocol, they consent to the treatment as well as to the research elements, and that it is not an option only to accept the treatment and to decline research participation (Chappuy *et al* 2010).

The literature also shows that physicians find it difficult to obtain truly informed consent for complex treatment and research proposals from parents who are emotionally

distressed because their child has a life threatening condition (Joffe *et al* 2006; Dermatis and Lesko 1990). The extraordinary psychological strain influences physician-parent communication and limits its potential effectiveness, especially when decisions about research participation need to be made within hours or days (Levi *et al* 2000). The emotional setting of (pediatric) oncology puts in this way great trust on the acting physician who raises treatment and research options (Ong *et al* 1995; Van Stuijvenberg *et al* 1998). In fact, consent for research is often based on the relationship of trust which exists in the care setting between the physician and the parents (Dermatis and Lesko 1990; Shilling and Young 2009).

Consequently, in the pediatric oncology setting true consent from parents for research is difficult to obtain.

Promoting best interests from a parental point of view

The primary responsibility of parents is to care for and protect their child, also when parents are asked to consider enrolling their child in a pediatric clinical trial (Tait *et al* 1998). This responsibility makes it difficult for them to think of a research setting as detached from the best interests of their child. Of course parents often state that they are motivated to support research that may improve the chances of future patients. They acknowledge that the participation of other children in former trials has improved treatment to the benefit of their own child and they are prepared to do likewise. But protecting their child is fundamental to the parental role and this shapes how they think about trials (Shilling and Young 2009). Some form of altruism can play a role in deciding to let a child participate in research, but only with the firm conviction that the research will not pose any harm to the child, and even more, with the prospect that the research will benefit the child (Singhal *et al* 2002; Reynolds and Nelson 2007).

Parents will take many different factors into account when deciding whether or not to let their child enter an RCT and will not simply accept randomization because an ethics committee has deemed it permissible. For some parents, randomized trials may represent the prospect of receiving a new treatment with a potentially important direct benefit to their child (Kupst *et al* 2003). If this new treatment is only available within a trial, parents may consent to their child's entry for the chance of receiving the assumed benefits (Snowdon *et al* 1997). It can cause them to anticipate regret for not at least trying to get this new treatment through research participation, all from their perspective as guardian of the interests of their child.

The question whether a potential benefit will become available through participation in research is particularly germane. It can be hard for parents to understand that a study involves a new, and in their view potential better therapy for their child, but that research methodology involves randomization, and that the child can also draw the standard therapy (Eiser *et al* 2005). On finding that their child has been allocated to the standard arm, parents sometimes report a sense of missed opportunity, as if the child has been deprived of a known beneficial treatment (Shilling and Young 2009). This may lead to unwanted tensions between parents and physicians at the outset of a long treatment relationship.

On the other hand, parents can also hesitate to participate because of fears for an 'experimental' arm, of being used as a 'guinea pig', or of a computer choosing what therapy will be given (Kupst *et al* 2003).

The treating physician and the investigator are often the same person. This can make parents fear that refusal will have consequences for their future relationship with the physician. Parents frequently indicate that they find it difficult to oppose the proposal of the physician, because they are afraid that this might jeopardize the relationship with the physician, even though consent forms explicitly state the opposite (Appelbaum *et al* 2009; Heneghan *et al* 2004).

Whatever arm of a trial parents think is better for their child, their preference shows that the idea of clinical equipoise held by the expert medical community is not directly transferable to the parent setting. For parents the different arms of a trial are often not in equipoise. Firstly, because they can hold the conviction that one arm is medically superior (Kupst *et al* 2003; Snowdon *et al* 1997; Eiser *et al* 2005). Secondly because the arms may differ in duration or in the amount of extra visits or blood draws. The personal context of a family then determines whether or not a trial arm fits to this family. For example, parents may prefer one trial arm because they live long distance from the hospital and the preferred arm contains less extra visits. *Parental* equipoise would be the point at which the parents are 'maximally uncertain' regarding the relative efficacy, safety and fittingness to their personal situation of comparator interventions. Parental equipoise has not been described before, but could be seen as the 'proxy version' of patient equipoise. When Freedman defined (clinical) equipoise, he stated that it is the expert medical community that ought to be in equipoise (Freedman 1987). In the literature however, it is argued that not only the medical expert community should be in equipoise, but also the trial participants themselves (London 2007; Veatch 2002). London argues that this has consequences for the informed consent process:

> *'There may be reasons that might lead a potential trial participant to prefer one treatment over another even though expert opinion is conflicted. (...) When this is the case, participating in a clinical trial may not be a permissible option for that patient. (...) This example (...) provides a clear focus for the goals of the informed consent process: to ensure that only those individuals participate in research who see the clinical trial as a reasonable option in light of the conflict or uncertainty that exists in expert medical opinion.'* (London 2007, p584).

This resembles Hans Jonas' argument that the people who should be enrolled in a clinical trial should be the ones who most identify with the cause of research (Jonas 1969). The mentioned literature shows that parental equipoise is often very difficult to reach, which leaves parents with the agonizing situation of wanting to do what is best for their child, while not knowing whether research participation is the best course of action to achieve this and being fearful of making the wrong decision (McKenna *et al* 2010).

Therapeutic Misconception

Parents can mix up research and treatment goals (Kodish *et al* 2004; Wiley *et al* 1999; Stevens and Pletsch 2002; Chappuy *et al* 2010). Failure to appreciate the difference between the context of research and treatment, and therefore inaccurately attributing therapeutic intent to research procedures is called 'the therapeutic misconception' (Appelbaum *et al* 1982; Appelbaum *et al* 2004). It refers to the research subject's failure to appreciate that the aim of research is to obtain scientific knowledge, and that any benefit to the subject is a side product of that goal. Though the data are scarce, there is evidence that many trial participants in oncology hold therapeutic misconceptions (Kodish *et al* 2004; Joffe *et al* 2001). One study found that 40-80% of subjects show basic misunderstandings of the research trial design (Appelbaum *et al* 1987).

Due to the fading boundary between research and care in pediatric oncology therapeutic misconceptions can easily arise. This puts another burden on the process of informed consent during which parents will have to be made aware that the proposed treatment is not selected only because of the individual needs of the patient.

The physician's perspective: doctor vs. scientist

Not only parents find it difficult to distinguish treatment and research goals. Physicians and other health personnel may also experience problems when research and clinical care are performed simultaneously. The traditional division of tasks in clinical or research-related is challenged by the emergence of randomized controlled trials (RCTs) and clinical controlled trials (CCTs, see also Table 4) (Taylor 1992). Physicians may ex-

perience tension between their roles as clinicians and scientists, since the latter defies the traditional definition of their core task to place the best interests of patients first. As a solution most oncologists, even those with substantial trial involvement, focus first of all on the possible benefit to their immediate patient and not on the theoretical benefit of future patients. In this way they adopt the perspective of a therapist rather than that of a researcher (Taylor *et al* 1994). Studies show that many oncologists really feel that research participation is in the best interest of the individual child (De Vries *et al* 2010; Joffe and Weeks 2002). This can be understood in two ways. Firstly, physicians feel confident that trials are not *harmful*, and that control by an Institutional Review Board (IRB) protects the child. Secondly, physicians believe that being in a trial, independently of the arm the patient is in, is even better than receiving the same treatment outside of the trial (De Vries *et al* 2010). Enrolling children in clinical trials would ensure that they receive the best treatment. The website of the M.D. Anderson Cancer Center, one of the leading centers for cancer research and care, states underneath a list of diseases for which clinical trials are available:

> *'When you are offered to participate in a clinical trial, your doctor has decided that the best treatment for your condition is provided in that trial'* (MD Anderson Cancer Center 2011).

This suggests that trials are viewed not only as a way to improve treatment in the future, but also as the best treatment for current patients. Pediatric oncologists tend to view trial protocols as clinical practice guidelines (Joffe and Weeks 2002). The statements by many leaders in oncology that clinical trials represent the optimum care for cancer patients are also an expression of this view (Bailes 2000; American Federation of Clinical Oncology Societies 1998).

It could be argued that a RCT does preserve the basic duty to act in the best interest of the child because of clinical equipoise. After all, no subject is randomized to a treatment known to be inferior to the standard treatment. But the fundamental difference between research and treatment is that the treatment setting requires an experienced clinician who selects and monitors the treatment taking into account individual, person-specific factors. The setting of a RCT requires that once a child is thought eligible for participation, the investigator renounces patient specific considerations and uses randomization and a meticulously followed protocol in order to get generalizable results. (Of course taking into account that a child will be removed from a study if it is not in its interests to remain in the study and also that treatments will be adjusted if a child is too unwell to tolerate them.)

Especially when experimental treatments are evaluated, the risks and benefits in randomized trials are less fixed than those in standard medical care. It is the hallmark of randomized studies that it is never known in advance what the actual risks and benefits will be: only after the completion of a study one genuinely knows which arm of the trial showed the best results and whether or not participants were exposed to extra risks and burdens in the intervention arm. Kumar *et al* (2005) described 126 RCTs within the setting of the Children's Oncology Group. They showed that new (experimental) treatments are as likely to be inferior as they are to be superior to standard treatments. Most pediatric oncology trials have Data and Safety Monitoring Plans (DSMP) and suspension rules for the very purpose of dealing with unexpected risks and outcomes.

It has been argued that trial participation is beneficial as compared to non-participation because of the strict adherence to well-defined protocols. Various authors have shown that the use of a treatment protocol improves the end result of that treatment (Stiller and Eatock 1999; Karjalainen and Palva 1989). This would be due to the explicit description of treatment phases and follow up and to strict guidelines indicating how to deal with side effects and relapses. For CCTs one could conclude that participation is beneficial, since CCTs are single arm studies in which the best available treatment is laid down in a protocol (to be able to compare treatment results to historical results). But it is more difficult to apply this to RCTs. A Cochrane review assessed whether there were beneficial effects from participating in RCTs (Vist *et al* 2008). The outcomes of patients who participated in RCTs were compared with outcomes of patients who received similar clinical interventions outside the RCT. On average, the outcomes were similar, suggesting that participation in RCTs does not result in improved outcomes. Peppercorn *et al* (2004) therefore state:

> '*Despite widespread belief that enrollment in clinical trials leads to improved outcomes in patients with cancer, there are insufficient data to conclude that such a trial effect exists. Until such data are available, patients with cancer should be encouraged to enroll in clinical trials on the basis of trials' unquestioned role in improving treatment for future patients*'.

The belief that enrolling children in RCTs ensures that they receive state-of-the-art treatment and that participation is best for the individual child is therefore an example that the therapeutic misperception may also be fostered by physicians (Instone *et al* 2008).

In conclusion, the physician-investigator has a 'hybrid' identity. He serves two different goals: the best interest of the patient and scientific progress (and thereby the best inter-

est of future patients). Physicians are more likely to prefer the perspective of a therapist over that of a researcher, and consequently they may truly come to believe that in the research setting they promote the child's best interests. With this position physicians potentially promote the existence of a therapeutic misconception between them and parents.

Some authors contend that, to reduce misunderstandings about the nature and purpose of research, physician-investigators should restrict themselves to being scientists only and not doctors (Joffe and Miller 2008). In this way the ethical insistence on a clear boundary between research and clinical activity can be secured. This could also partially be achieved by letting research nurses carry out informed consent conversations with parents and children. In both situations, the role of the researcher and the goal of research may be clearer. This solution would however require a fundamental change in the pediatric oncology practice and as such might raise its own problems, for instance regarding the available health personnel and communication problems between physicians and researchers.

Limitations

The studies included in the narrative review have limitations that should be acknowledged. Most studies are interview or questionnaire studies using a retrospective design. In this design there can be uncertainty whether the parents' and physicians' recollections were accurate representations of how they felt and what their thoughts were at the time of diagnosis and inclusion in a trial. Only 3 studies used a prospective design (see Table 5). Most studies have small sample sizes.

Future research with larger samples and a prospective design will be able to ascertain the relationship between the specifics of the informed consent discussion and parental and physician recollection.

CONCLUSION

There is an urgent need for high-quality research in children, to ensure that drugs used in the pediatric setting are both safe and effective (Klassen *et al* 2008). Pediatricians must often rely on evidence that has been generated in adult populations (Cramer *et al* 2005), although both the safety and efficacy profiles of drugs may be significantly different for children (Kearns *et al* 2003). Therefore it is of vital importance to enroll children with cancer in clinical studies. The pediatric oncology practice shows that general implementation of clinical research continuously improves outcomes for children with cancer.

However, when research and clinical care coincide as much as in the pediatric oncology setting, several ethical problems can come up.

Firstly, parental equipoise is almost never reached. Parents cannot (and are not supposed to) think beyond the scope of the best interests of their child. To consider the goals of research *per se* is very difficult, if not impossible for them. Due to the diminishing boundary between research and care, parents are confronted with alleged options and treatment choices, which eventually turn out to be only accessible through research. Some parents are confronted with anticipated remorse when not participating in (promising) research. Others fear trials because of the experimental nature. Many experience a lack of freedom to reject participation. Secondly, the therapeutic misconception may endanger a correct assessment of the pros and cons of participation, because parents might inaccurately attribute therapeutic intent to research procedures. Their focus on the therapeutic effect may hamper understanding of the research purposes. All this could lead to a feeling of emotional stress and limited voluntariness that is reinforced by the trust that is often inherent to the relationship between physician and parents, especially in pediatric oncology (Council for International Organizations of Medical Sciences 2002).

Physicians too are constrained in their options because of their conviction that research constitutes the best available treatment, thereby passing over the greater uncertainty of the risk-benefit ratio as compared to standard medical care.

The challenges that a lack of parental equipoise and the therapeutic misconception pose may be very difficult to overcome. Thorough attention to the quality of communication of research information could improve understanding of the research perspective (Miller and Rosenstein 2003; Appelbaum 2002). In Table 6 we summarize points of awareness with respect to research discussions and give recommendations to improve communication. But even in the case of an enormous communication effort, the question remains whether it is truly possible to explain the nature of research and thereby overcome the emotional conflict of parents who feel responsible for their child's wellbeing. Future research should focus on special efforts that might achieve this.

As it stands today, physicians are bound to react to the individual needs and expectations of parents and children within the context of research. The physician-investigator needs to be convinced that the best interests of the child are warranted. This means that both a therapeutic *and* a scientific orientation are appropriate, and the physician needs to shuttle between clinical care duties and research duties. To do this ethically, he continuously needs to be aware of the potential conflict between research and treatment goals (see Table 6). Having considered all this, professional integrity requires the physician

to treat both the patient's interests and the scientific interests in an honest way without backsliding into a form of therapeutic misconception. After all, he has committed himself to serve both.

Table 6: *awareness points and recommendations for communication in relation to type of research*

Type of research	Awareness*	Recommendations for communication
Randomized Controlled Trials (RCT)	Confidentiality and privacy	Provide information about collection of data and measures taken to protect confidentiality and privacy.
	The potential for a therapeutic misconception: - differences between clinical research and standard care - potential conflict between research and treatment goals	Clarify how the physician-investigator / patient-subject relationship differs from the traditional physician-patient relationship. Mention alternatives to research participation explicitly. Discuss clinical and parental equipoise. Mention voluntariness. Indicate research interventions that are solely performed to measure trial outcomes. Assure freedom to withdraw from the study. Discuss research participation with subjects *before, during and after* the study.
	Consent to treatment does not imply consent to an RCT	Ask explicit consent with a separate consent form than the consent form for treatment. Ask consent for treatment first, and for research later, preferably by a different person than the treating physician, for example a research nurse (with the opportunity to consult with the treating physician)
Clinical Controlled Trial (CCT)	Confidentiality and privacy	Provide information about collection of data and measures taken to protect confidentiality and privacy.
	Consent to treatment does not imply consent to collect patient data	Ask explicit consent with a separate consent form than the consent form for treatment. Ask consent for treatment first, and for research later, preferably by a different person than the treating physician, for example a research nurse (with the opportunity to consult with the treating physician)

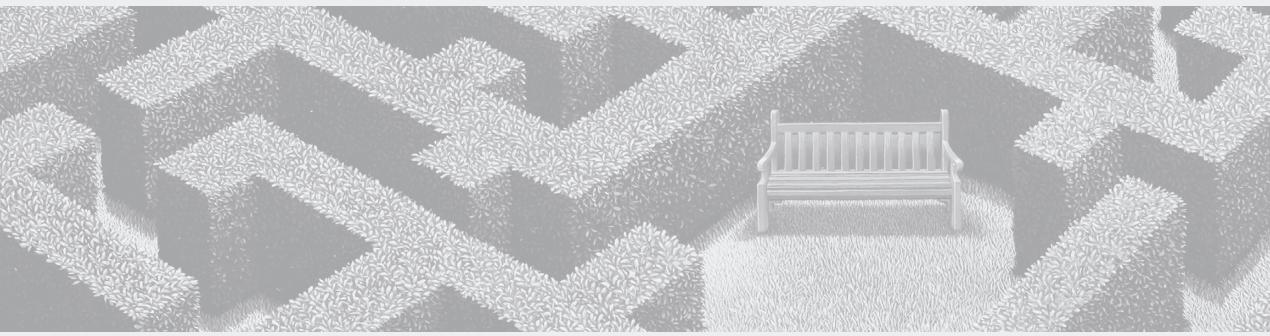
Table 6 continued

Type of research	Awareness*	Recommendations for communication
Laboratory research using tissue from patients	Confidentiality and privacy	Provide information about collection of data and measures taken to protect confidentiality and privacy.
	No therapeutic goal; completely distinct from therapeutic interventions	Mention voluntariness. Indicate that all research interventions to gain tissues are solely performed to gain scientific knowledge.
	The obligation of non-maleficence in this setting differs from that in clinical medicine	Indicate that risks to a patient are justified not because they are outweighed by potential benefits to the patient, but because they are outweighed by the value of the knowledge to be gained from the research.
	Consent to treatment does not imply consent to using or storing human tissues for research purposes	Ask explicit consent with a separate consent form than the consent form for treatment. Ask consent for treatment first, and for research later, preferably by a different person than the treating physician, for example a research nurse (with the opportunity to consult with the treating physician)

* Confidentiality and privacy are not explicitly discussed in this chapter. Apparently, parents and physicians do not experience these concepts as problematic or are not aware of them. Still, confidentiality and privacy are basic concepts in research ethics and should be discussed with parents. For completeness they are mentioned in the Table, in order for the Table to be used as a list to 'tick off' when communicating research with parents.

PART C

Best Interests



Chapter 5

WHAT CONSTITUTES THE BEST INTEREST OF A CHILD? VIEWS OF PARENTS, CHILDREN, AND PHYSICIANS IN A PEDIATRIC ONCOLOGY SETTING

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ABSTRACT

Background. In pediatrics, the 'best interest' standard has become the prevailing standard in decision-making even though it proves difficult to apply in practice. Differences in values can lead to different views by families and physicians of what is in the interest of a child. Our aim was to gain insight into the views of parents, children, and physicians in a pediatric oncology setting.

Methods. We conducted a qualitative multi-center study, using in-depth semi-structured interviews with 21 children aged 8-18 years undergoing cancer treatment, 26 parents, and 15 pediatric oncologists.

Results. At the onset of treatment, parents, children, and physicians had the same views on what is in the interest of the child: survival by following the treatment protocol. In the course of treatment, however, a transition takes place. For families, what constitutes the best interests expands beyond medical considerations, to include the wish to lead a normal life, having control over certain aspects of treatment, and maintaining one's identity (e.g., through religion). These aspects sometimes collide with medical aspects, leading to different professional and familial views about what course of action is appropriate.

Conclusions. In order to recognize personal views and avoid conflicts, physicians should explicitly discuss parent and family concerns and opinions in the course of treatment. We present a model of 'communicative ethics' to make these issues a subject of discussion. The role of the family in determining what is in the best interest of the child should only be limited when it implies a substantial medical risk of (irreversible) harm to the child.

INTRODUCTION

In pediatrics, the 'best interest' standard has become the prevailing standard in decision-making (Kopelman 1997). Often there is no discussion about what constitutes this standard. It is used as if its meaning is self-evident and uncontroversial. For a number of reasons, however, the best interest standard proves difficult to apply (Diekema 2004; Elliston 2007). Close examination of the standard reveals significant problems with its definition and application in practice (Elliston 2007). First, the standard seems incoherent, in that it invokes an absolute duty to do the best for each patient (Veatch 1995). Buchanan and Brock (1989, p88), in their statement of the standard, define absolute duty as 'acting so as to promote maximally the good of the individual.' The best interest standard would then require the surrogate to act so as to always make the decision most favorable to the child. This is impossible because children have conflicting claims, needs, and interests, and often 'the best' is not attainable. Some therefore suggest that the best interest standard should not be used as a maximizing principle, but rather as a minimum threshold of acceptable care (Archard 2003, p41; Diekema 2004). To act in the best interest of the child then means that the care provided should not fall below this threshold (Kopelman 2007).

The best interest standard is also criticized for being too individualistic, attending to the interests of only one person, making their interests paramount, and placing burdens on the interests of others. Moreover, the standard would be blind to the fact that children exist in families and their individual interests are not clearly divisible from those of the family. A child's interests cannot be completely distinguished from those of his or her parents, but are always intertwined with those of parents and siblings. Parents may have competing duties to themselves or other children that should also be considered, as Ruddick (1979, 1989) points out.

Kopelman (1997) tries to invalidate these criticisms by defining the best-interest standard as a standard of reasonableness. This means that it is used to find the most acceptable of the available choices. It instructs us to try to pick the option that most informed rational people of good will would regard as maximizing the child's net benefits and minimizing the net harms to the child without ignoring the rights, needs, and interests of others. Used in this way, the best interest standard does not require people to act in accord with what is literally *best* for a child. Sometimes this means that the least bad alternative for the child should be selected. In this way, a best interest standard seems reasonable to use, when its purpose is to offer good and practical guidance about how to make decisions for those unable to decide on their own (Kopelman 2010).

However, problems can still arise in the use of this standard, namely when reasonable and informed people of good will cannot agree on the interpretation of what is in the best interest of a child. Little controversy exists regarding the interpretation of what is good when medical interventions are available that are reliably expected to prevent serious, far-reaching loss of the patient's health at a reasonable cost (McCullough 2010; Placencia and McCullough 2011), such as treating a bacterial pneumonia with antibiotics. Often, there is professional agreement about these sorts of paradigmatic cases, the relevant outcome data, and the physician's best medical judgment to determine the interpretation of what is best for the child (Leuthner 2001; Pellegrino 1987; Placencia and McCullough 2011; Tan 2002). In other situations it may be more difficult. For instance, it is not easily determined whether it is in the best interest of a child to be vaccinated, circumcised, or treated with complementary therapies. In these and other cases, the notion of best interests is inherently a matter of balancing different values, and not just medical judgment (De Vries, Houtlosser and Egeler 2005; Elliston 2007; Lindemann Nelson and Lindemann Nelson 1995; Kopelman 1997). Best interests are determined not only by outcome data and physician assessment but also by the moral values of the various stakeholders. Introduction of these non-medical facts, values, and preferences may lead to differences in interpretation by parents, children, and physicians, and may result in conflicts (Hinds *et al* 2000).

Until now, most discussions of the best interest standard have focused on neonatal care and end-of-life decision making (Kopelman 2010; Leuthner 2001; Placencia and McCullough 2011; Paddeau 2012). Within pediatric oncology the standard has not received much attention, except when it focused on the end-of-life and the palliative phase (Hinds *et al* 2005; Kars *et al* 2011). When there are no curative options left, family values and preferences become very important. Outside this palliative phase, however, personal values and preferences of parents and children can also play a role in the pediatric oncology setting, when decisional problems related to treatment and care are encountered and it is not directly clear what is best for a child (Masera *et al* 1998).

The purpose of this study was to gain insight into the views of parents, children, and physicians on what is best for the child in a pediatric oncology setting during the curative treatment phase. Specifically, we focus on (1) describing what medical and non-medical factors are important for families and physicians when thinking about what is good for a child and (2) the eventual role of these factors in decision-making. By 'medical' we mean the interpretation from a biomedical view, taking only objective medical data (e.g., outcome data) and the physician's best medical judgment into account. By 'non-medical' we mean an interpretation which takes into account the personal situation of the patient and family values of what is deemed important.

METHODS

Our analysis was based on a data set that was part of a larger qualitative multicenter project in which we explored patients', parents', and physicians' experiences, roles, and considerations in treatment decisions in pediatric oncology. In this project we invited patients (aged 8-18 years) attending the pediatric oncology units of two Dutch university hospitals, their parents, and their physicians to participate in one-to-one, semi-structured in-depth interviews. Interviews were conducted 8-10 weeks after initial diagnosis or diagnosis of relapse. The methodology of the overall project has been described extensively elsewhere (De Vries and van Leeuwen 2010). The project was approved by the Institutional Review Boards at both study-sites (Leiden University Medical Center and VU Medical Center). Informed consent was obtained from all participants.

All physicians, parents, and children were interviewed by the first author. Initial interview topics were formulated after examination of the relevant literature and a preliminary observational study, during which the interviewer spent three months in the children's oncology ward of one of the university hospitals and followed the daily routine and the discussions between parents, children, and physicians. Consistent with standard qualitative research techniques, the interview topics evolved as the interviews progressed through an iterative process to ensure that the questions captured all relevant emerging themes (Britten 1995; Guest, Brunce, and Johnson 2006). The interviews contained general topics and no closed-ended questions. Examples of interview questions relevant for the results reported here are given in Table 7.

The physician interviews lasted between 30 and 60 minutes. The in-depth interview topics covered work experience; general goals of pediatric oncology; the physician–patient-parent relationship, especially concerning decision making during treatment; considerations deemed important in treatment decision making; patient and parent autonomy; and physician's ideas on what is in the best interest of a child.

The child interviews lasted between 30 and 45 minutes. The parent interviews lasted between 60 and 90 minutes. Both were conducted at the hospital. The interview topics covered general characteristics of the patient; the history of the disease; discussions with physicians about the recommended treatment; parents' and child's attitudes to these discussions; considerations deemed important in treatment decision making; and the perceived role of parents and children in decision making during treatment.

All interviews were audio-taped and transcribed verbatim. Data analysis was based on the constant comparative method (Malterud 2006; Strauss and Corbin 1998).We used an iterative process wherein we continually went back to the field to collect more data.

Table 7 *Examples of interview questions*

Children
Can you remember when you were first told that you had cancer? Who told you and what was said?
Can you remember what was said about possible treatments? How was eventually decided what treatment you would get? Was there any choice?
What were important issues for you during discussions about treatment? Do you think the medical team knew what was important for you?
Do you think that you should have an influence in what is decided about your treatments?
Do you have regular meetings / talks with your physician? What do you talk about?
Can you tell me what is important for you now, while on the way in your treatment? Are there things the medical team has to take into account? If yes, do you feel you can discuss these things with the medical team?
Parents
Can you describe the conversations you had with the physician about the cancer diagnosis and treatment options?
What considerations were important for you when treatment options were discussed? Did you discuss these considerations with the medical team?
Did you have any influence in the decision making process? Did your child have any influence in the decision making process?
Now your child is receiving treatment, do you have regular meetings with the treating physician? What do you talk about? Are there important issues for you that the medical team has to take into account? If yes, do you feel you can discuss these things with the medical team?
Physicians
Can you describe the topics discussed when you talk to parents and children about the cancer diagnosis and treatment options?
What considerations are important when treatment options are discussed for a child with cancer? Are there other considerations, next to medical ones?
Do you know the considerations parents and children have? Do you explicitly ask for their considerations?
How much influence do parents get in the decision making process?
How much influence do children get in the decision making process?
Do you ever experience conflict between yourself and a family, or within families about treatment decisions?
Can you describe the topics discussed when you talk to parents and children during the treatment phase?

The following process of data gathering and analysis was used: (1) interviews; (2) transcribing the interview data; (3) open coding, which involved identifying relevant concepts in the text; (4) constantly comparing open codes, looking for conceptual similarities and differences; (5) identifying emerging themes and a theoretical framework; (6) continued sampling and interviewing as theoretical categories emerged and novel questions arose; and (7) continued coding and comparison of codes until nothing new was added to the theoretical categories. Two authors independently coded the full transcripts. An independent researcher (not one of the authors) coded two transcripts to check for consistency and adequacy of the framework. The two authors and the independent researcher engaged in a discussion on the themes each of them had identified from the transcripts. No inconsistencies were found. When no new thematic content was found in the interviews, subject enrollment was stopped. This process, called thematic saturation, is a well-described qualitative method to avoid unnecessarily large and repetitive data sets (Denzin and Lincoln 2000; Guest, Brunce and Johnson 2006).

We used qualitative software (Kwalitan 5.0) for multiple text management, including coding, locating, and retrieving key phrases (Peters 2000). Finally, representative quotations were chosen to illustrate the themes identified. These quotations are included in the text. Quotes were translated from Dutch to English by a native English speaker.

RESULTS

Characteristics of the sample

The sample consisted of 15 physicians, 24 children, and 26 parents of these children. Figure 1 (page 19) shows eligibility criteria and the recruitment process for children and parents. Parents had a mean age of 40 years (range 32-50 years). Their children had a mean age of 13.4 years (range 8-18 years). The parents' occupations varied, indicating social diversity. All families were of Dutch origin. Demographic and clinical characteristics of the parents and their children are given in Tables 1 and 2 (page 20-21).

The group of physicians comprised the entire medical staff of both pediatric oncology units (9 and 6 physicians, respectively). They were the primary providers for the children who participated in the study. Physicians had a mean age of 42.1 years (range 32-52 years) and worked in pediatric oncology for a mean of 7.6 years (range 1.5-20 years); 7 (46.7%) were male. Physician characteristics are shown in Table 3 (page 21).

Framework of the results

The concepts that were identified in the qualitative analysis resulted in a framework that

comprises the following three themes: best interest as deference to medical judgment, transition in the views of what is good for a child, and non-medical goals as a part of the best interests of the child.

Best interest as deference to medical judgment

At the onset of treatment, parents, children, and physicians had the same ideas on what is in the best interest of the child: survival by following the treatment protocol.

[In the beginning] I just wanted to get all the courses of chemotherapy. I just wanted to be sure that the cancer would stay away. Now at the end of treatment I sometimes think 'I don't want this course [of chemotherapy], it takes so long and it is so hard.' But I just have to do it. – Male patient, 12 years, Acute Myeloid Leukemia (AML)

I always tell parents and children that it is essential that we are a team. And that we, as a team, have one main goal: to fight the cancer. –Physician 1

At diagnosis, choices seem limited as there is typically a standard treatment approach, described in (inter)national protocols. All study participants felt there was no choice in treatment options. The way to proceed is to follow the medical protocol.

There was no choice. Well, there was a choice, but that would have been weird. There was only one right choice, to follow the protocol. If I had chosen not to do it, that would have been suicide. – Male patient, 15 years, AML

There is a clear distinction between the medical responsibility and the parental responsibility. It is not that parents have no say in the matter, but in the end the treatment decision is taken on medical grounds, so it is a decision by the medical team. – Physician 6

Physicians state that it is very difficult or even impossible for parents and children to fully discuss treatment options in the period after diagnosis. Parents and children feel ill-equipped to judge all medical information, and put their trust in the physicians, who are seen as experts.

The first twenty-four hours after you have told the diagnosis, parents are numb and hear nothing anymore. And it is exactly then that we have to discuss treatment options. But whatever you say, it doesn't reach them. – Physician 6

We had to let go, although we found that hard to do. But the disease was something we were not able to manage ourselves, it is an area we didn't know anything about. We had to let go, and just trust the physicians in their good intentions. – Mother of male patient, 15 years, with Ewing Sarcoma

I let the people decide who know best and have my interests in mind. These people are my parents and the physicians. If I were to choose myself I would take the easy way, for example skipping one of the chemo courses, because of the side effects. That's why it is better that other people decide. – Male patient, 13 years, with osteosarcoma

Because parents and children feel they have no choice but to follow and agree with the physicians, it comes as a shock to them when they do have to decide on certain issues such as fertility preservation.

That he had to think about the question whether he could produce semen or not, that was really shocking. [...] Of course, to hear that you have cancer is also very shocking. But in a way that just happens to you. It's just a fact. While for this issue we had a choice, we had a choice what to do. – Father of male patient, 13 years, Ewing Sarcoma

Transition in the views of what is good for a child

In the course of treatment, when parents and children regain some control over the situation, other objectives emerge, in addition to the goal of survival. They start to distinguish between the treatment protocol in the strict sense and the care surrounding it. The treatment itself is not questioned. The surrounding care, however, makes parents and children feel that choices *can* be made in the course of treatment. This leads to a re-evaluation of what they think is important.

At the start of treatment there was no choice. But at some point real choices came up. And at that point we wanted to be heard. (...) It is not up to the physicians to determine how much influence parents get. It is up to the parents themselves. We needed time to get things sorted out, but at one point we realized that, well this is it and we have to make the best of it. And at that point we noticed things we wanted to be done differently. It's a process all parents go through. – Mother of male patient, 15 years, with Ewing Sarcoma

Three weeks ago I had to get a new course of chemotherapy. Normally you cannot choose whether you will stay on the ward or in a private room. But it was a new medicine for me and I did not know how I would react. Maybe I would vomit all day, so I refused to be put

on the ward with three other children and maybe a bunch of visitors. Furthermore, it was close to my birthday, so I wanted to come to the hospital earlier, to be home in time to celebrate. In the beginning, I was afraid to ask these sorts of things, but now I just want control over these things. – Male patient, 14 years old, with Ewing Sarcoma

The interpretation of physicians is quite different. They feel that parents and children have limited influence on medical care.

It's only the little things that parents can get a grip on. We're tied to the protocol. That is the only way protocols can function. If everyone would do it in a slapdash manner, we wouldn't have any answers whether we do better than before. Small changes can easily be a violation of protocol, even little logistic changes like starting chemotherapy later due to a birthday or holiday. There is not much room for change. – Physician 3

Non-medical goals within the best interest of the child

Parents and children stated that next to the medical treatment, which is aimed at survival, they develop other goals, namely 'to lead a life as normal as possible' and to protect their identity and (family) values. In the course of treatment, families pick up on their own routines, like their ways of raising their children. This can interfere with the rules and the way things are normally done on the hospital ward. Parents have their own ideas about how to handle their child, but often little room is left for their views.

We know our child best. Better than all nurses and physicians on the ward. Of course we know him best, but this is not recognized. They just don't react to our comments. They do as they think is right. – Father of male patient, 11 years, with ALL

The physiotherapist was just teasing my son. He tried to make my son do nice things. But what is nice for him [the physiotherapist] is not nice for us. We are not used to watching television for a bit of distraction. My son needs to be addressed fitting his environment. Disco, soccer and television are not his environment. To really connect with my son you need to come up with something else. So I asked the physiotherapist why he wanted so badly to provide my son with distraction this way. Although it is not normal for us and we don't like it. – Mother of male patient, 13 years, osteosarcoma

Parents also experience disagreement with physicians on whether or not certain aspects of care belong to the treatment protocol in the strict sense or not, and thus whether they have an influence on it. For example, in the case of nutrition and nasal tube feeding,

there is often disagreement between families and medical team about what is best for the child. Their child's diet is one of the few areas where parents feel they can exert some direct influence or control. Some parents have specific beliefs about the role of nutrition in recovery from disease.

> *Certain juices, like carrot juice, beetroot juice, have a positive influence on his blood count and his immune system. So he drinks these juices every day, we are really onto that. Just as a support. They [the physicians] have no problem with that. But when I asked one of them whether she uses the positive influence of nutritional supplements, she said: no, because we do not believe in it. – Father of male patient, 13 years, Ewing Sarcoma*

Whether or not to start nasal tube feeding is also an important aspect of care where parents want to exert control.

> *After the treatment the medical team wanted [patient] to go home with nasal tube feeding. But we refused. We had gained enough experience with her eating habits after chemotherapy. I call myself an expert in cooking things that [patient] likes. She eats enough when she is at home. In the end we really had a fight with the physician and the nurses about the nasal tube. But we left the hospital without. – Father of female patient, 14 years, Ewing Sarcoma*

Physicians, however, think of nasal tube feeding as part of medical treatment and therefore consider it to be their responsibility.

> *Nasal tube feeding is a medical procedure and I think physicians need to decide on starting it. There is enough evidence that a good nutritional state adds to the chance of survival, so I think it is a medical decision. Chemotherapy is better tolerated for example. Of course we consult the parents, but I think it is part of treatment to secure the nutritional state of the patient. – Physician 3*

Children therefore often feel there is no real choice when nasal tube feeding is proposed.

> *I asked whether I could try and eat more. But they [physicians] said it was better to have the tube feeding, because I wouldn't succeed in eating enough. That's what they told me. And anyway, even if I had refused, they would have put in the nasal tube, I'm sure of that. – Female patient, 14 years, ALL*

For some parents and children, religion is an important aspect of their identity and how they cope with illness. Religion opens a different (non-medical) perspective to the disease, which parents want to share with their physician.

Some friends say that it is stupid to talk about God with a physician who doesn't believe. But for me it is very important. He [the physician] tells me what he thinks, so I tell him how I think about it. This physician for example tells my son repeatedly that the cancer is just bad luck. So I felt that I had to tell him [the physician] that we don't see it as just bad luck. There is a meaning in it, although I don't know which. And the progress my son makes is of course due to the drugs and the treatment, but also because he is in the prayers of our friends and because God is watching over him. – Mother of male patient, 14 years, Ewing Sarcoma

Religious beliefs sometimes become a factor in (curative) medical decision making.

Well the nurse came to take him to the operating room. But I said I won't have it. The portacath cannot be removed. It was a religious thing for us, he had prayed all night and the fever had subsided. He was convinced that prayer is helpful. And then the nurse said they were going to remove the portacath anyway. My first thought was that my son would never trust God again. So I asked the nurse to take the temperature again and to consult with the physician. The nurse slammed the door in anger. But the physician reluctantly gave us the benefit of the doubt and the portacath didn't have to be removed at that moment. And the fever didn't come back. – Mother of male patient, 13 years with osteosarcoma[1]

As a consequence of differing views between the medical team and the families, some parents feel that they have to stand up for their child to get things arranged the way they think is best.

I have become like a lioness fighting for her cub. Oh, yes, I'm not nearly as friendly as I was at the start of treatment! I developed an aspect of myself I knew I had in me, but I never needed before. At the start of treatment I let things happen, I thought that it was all alright. But now I'm more onto things. I question whether certain things are necessary. You grow into that. – Mother of female patient, 10 years, Hodgkin

[1] Because of persistent fever, the patient's portacath, as a potential locus of infection, was scheduled to be removed.

DISCUSSION

At diagnosis, choices are limited as there is typically a standard treatment approach, described in (inter)national protocols. Because parents are often in shock by the diagnosis, and time is of the essence in terms of making treatment decisions, the most common reaction is to defer to what the pediatric oncologist views as necessary to act in the best interests of the child, which is providing life saving treatment. However, as children and parents become familiar with the treatment and medical environment, as shock subsides, and as additional choices to the treatment become apparent, children and parents begin to more actively participate in decision-making. At that point, a transition takes place with regard to the views of what is best for the child. Factors other than medical considerations become important.

This study shows that at the start of treatment children, parents, and physicians have the same view on what is best for the child: being treated according to the best available treatment protocol. Parents and children feel ill-equipped to judge the medical information, and most of the time they let physicians decide on treatment options. Deference to physician authority is a common rule of thumb, especially at the start of treatment. Reinforced by the technological character of the cancer treatment and the psychological turmoil due to the diagnosis, the medical view on what is best for a child prevails. Accordingly, children and parents experience a lack of control. This is also reported by other authors (Levi *et al* 2000; Lowe, Bravery and Gibson 2008; Patiño-Fernández *et al* 2008).

In the course of treatment, parents and children become 'layman-experts' in the treatment protocol. That changes their opinions. Parents and children regain some control and become partners in discussions with physicians. In contrast to the initial 'submission', families become to feel more certain, and think of themselves as more or less equal discussion partners when talking to the physician (De Vries *et al* 2005). This phenomenon is also described by Decker, Phillips, and Haase (2004), and Tuckett *et al* (1985). Parents no longer focus only on the protocol, and the way children are generally treated, but also on *their* child with his or her own ways to cope with the situation. This leads to a re-evaluation of what they think is important. Also, children were able to discuss their considerations in the decision making process. The interpretation of what constitutes best interests starts to contain more than only the medical perspective (see e.g. Kirschbaum 1996). As reported by Young *et al* (2002), parents discover that their child's interests are also affected by control over certain aspects of care (e.g., nutrition), the wish to lead a life as normal as possible (e.g. particulars in upbringing and schooling), and the wish to maintain one's identity and family values (e.g. through religion). These

values can sometimes collide with medical protocols, leading to different professional and family views as to what course of action is appropriate.

Physicians regard parents and children as having limited influence within the treatment protocols. For families, however, it is no longer taken for granted that the best interest of their child can be determined objectively on medical grounds. Best interests turn out to encompass spheres other than the medical, including part of the life perspectives of parents and child (Carroll *et al* 2012; Ruddick 1979, 1989). The influence of this family perspective in the decision-making process initially concerns mostly minor medical decisions, like timing the administration of drugs, placing a new nasal tube, or planning new admissions (e.g. not on the child's birthday). Such routine actions in following protocols may become major issues for patients and parents. Fried *et al* (2002) and Spinetta *et al* (2009) showed that it is important to recognize how these personal aspects in decision making help parents and children to regain some control over the situation, and that respect for those issues may be equivalent to the respect for more fundamental views on life and its meaning.

Sometimes the views of parents and children and the medical perspective differ widely. In our examples, this concerned whether or not to start nasal tube feeding and the removal of a portacath. As described by Hinds *et al* (1997), and Hinds *et al* (2000), such differences may lead to dissatisfaction or even conflicts between parents, the child, and the medical team. Coyne (2007) found that health professionals held the view that parents and children were supposed to follow implicit rules of the ward. Parents who held a view that is not congruent with these rules disrupted the organization of the ward and were labeled 'problem' parents. James and Hilde Lindemann Nelson (1995) even spoke of a 'rivalry of care' regarding the conflict between the ethical approaches of families and physicians.

When family and professional views differ widely, the question inevitably arises whose perspective should prevail. In order to avoid discussions about who is in power to apply an abstract standard of best interests, 'communicative ethics', such as described by Moody (1992) can be followed, meaning that all parties involved, including the patient (when possible), come to an agreement about shared goals and talk about decisions to be made. The aim of the communicative ethics approach is to develop and maintain a shared vision on the course of treatment (D'Aloja 2010; Elwyn *et al* 2000). The central questions are 'What is best for this patient at this moment?' and 'How to share decisions?' instead of 'Who should decide?'. In the model of communicative ethics, the various views of what is best for a child are given a *prima facie* character (Beauchamp and Childress 2009, 14; Kopelman 1997, 276). It is the duty of all actors to reach consensus about the resulting definition of the best interest of the child. The emergence of personal

views that are potentially different from the professional perspective can be recognized, understood, and, if necessary, dealt with (Coyne 2007). This model is in line with models of family-centered care and shared decision-making

Due to the complex and high-tech character of oncology treatments the physician has a substantial role in the decision-making process. Young *et al* (2002) showed that parents are reluctant to act as advocates for their own views in this setting. To recognize the personal views of parents and children, physicians need to actively discuss parents' preferences, customs, and concerns, especially in circumstances when there are tradeoffs possibly involving individual values and preferences (Elliston 2007; Hardart 2000; Tan 2002; Whitney 2006). The physician can also discuss limits to these wishes, as long as mutual understanding, awareness, and reasoning are maintained (D'Aloja 2010; Bensing 2000; Kai 1996).

In some particular circumstances, parental views of what is good for their child may lead to actions that inflict harm. Dedication to their child, which is the prerequisite of good parenting, may then stand in the way of making a responsible, correct decision (Baines 2008). An absolute focus by parents on the survival of their child may, for instance, lead to the demand that painful treatment be continued long after any prospect of cure. In cases like this, parental interpretations can constitute a substantial medical risk of irreversible harm, and then a limit to their influence is reached (Diekema 2004; Kopelman 1997). The moral and legal focus should then be on the professional's point of view of what is medically in the best interest of the child. In these situations, it must be acknowledged that the pediatrician's responsibility to the patient exists independently of parental desires or proxy consent (Committee on Bioethics 1995). Parents can use their own values to decide what is best for their child, but their decisions cannot fall below a certain threshold of acceptable care (Kopelman 2007).

Limitations

Our study is subject to some limitations. First, there is a possible bias due to the refusal rate of parents and children to participate (21%). This may result in an overrepresentation of families who encountered substantial differences between family and professional views on what constituted the best interest of the child. On the other hand, this is more of a problem for quantitative than for qualitative research, as our aim was to explore possible differences in interpretation of best interests, and we were not so much interested in exact numbers regarding the existence of such disagreement. Second, there could be a regional bias in the results, because the study is based on respondents from only two of the eight hospitals in our country where children with cancer are treated. However, the group of respondents was diverse enough for our purpose to explore the differences in

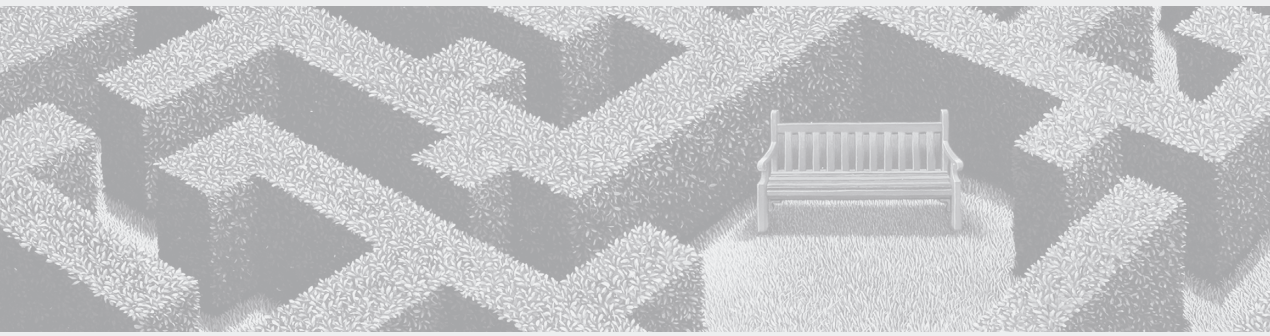
interpretation of best interests between families and physicians. At the same time, the topic was compact enough to reach saturation across the sample: during the last interviews, no new information was yielded.

Conclusion

In conclusion, the interviews give insight in how families define what is good for their child and how they contemplate their child's best interest. Especially in the course of a long treatment, 'what is best for the child' is subject to change, and for families, the answer encompasses spheres other than the medical. It includes parts of the life perspectives of parents and child. Our data suggest that the Best Interest Standard is not defined only by abstract, philosophical, or legal terms. Eventually, the shared intention to do good to children should be guided by a standard that understands best interests as a matter that comes about through consultation. This consultation can be shaped by a 'communicative ethics'. Future research should focus on the best way for physicians to recognize personal views and act on them without losing professional autonomy.

PART D

Child participation versus parental authority



Chapter 6

NORMS VERSUS PRACTICE: PEDIATRIC ONCOLOGISTS' ATTITUDES TOWARDS INVOLVING ADOLESCENTS IN DECISION-MAKING CONCERNING RESEARCH PARTICIPATION

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ABSTRACT

Background. Various regulations and guidelines stipulate the importance of involving adolescents in decision-making concerning research participation. Several studies have shown that in the context of pediatric oncology this involvement is difficult to achieve due to emotional stress, the complexity of research protocols and limited time. Still, up to 80% of adolescents with cancer enter onto a trial during their illness. The aim of this study was to determine physicians' views and attitudes towards enrolling adolescents in research, considering the difficulties surrounding their involvement in decision-making.

Methods. A qualitative multicenter study was performed, using in-depth semi-structured interviews on the informed consent process with 15 pediatric hemato-oncologists.

Results. Four central themes emerged that characterize physicians' attitudes towards involving adolescents in the decision-making process: (1) physicians regard most adolescents as not capable of participating meaningfully in discussions regarding research; (2) physicians do not always provide adolescents with all information; (3) proxy consent from parents is obtained and is deemed sufficient; (4) physician-investigator integrity: physicians judge research protocols as not being harmful and even in the best interest of the adolescent.

Conclusions. Physicians justify not involving adolescents in research discussions by referring to best interest arguments (adolescents' incompetence, proxy consent, and investigator integrity), although this is not in line with legal regulations and ethical guidelines.

INTRODUCTION

Informed consent is a major issue in pediatric ethics, especially when it concerns parents' and children's consent for research (Committee on Bioethics 1995; National Commission for the Protection of Human Subjects 1979). While adults are assumed to have the requisite capacity to provide an informed consent, children are a protected population and in most circumstances are not afforded the legal right to consent. Often, however, children who have not yet reached the legally established age of consent do have the mental capacity to understand the implications of participating in research. Several studies have assessed children's comprehension of trials (Joffe *et al* 2006; Mårtenson and Fägerskiöld 2008). They studies suggest that children as young as 9-10 years can understand research-related information, whereas under optimal circumstances, children aged 14 and older can even approach the understanding expected of adults. Still, it is also recognized that age is at best a proxy for developmental capacity, and that experience, maturity and psychological state are important determinant factors.

Numerous country-specific regulations as well as international treaties stipulate the importance of involving minors in decision making concerning research participation (Jaspan *et al* 2008; Office for Human Research Protections 2009). In addition to the legally required informed consent (permission) from parents, most of these regulations require that assent be obtained from those children who are deemed capable of providing it. Assent is defined as 'a child's affirmative agreement to research participation' (Code of Federal Regulations 1991). Especially in the case of adolescents, serious consideration should be given to their developing capacities for participating in decision making, regardless of legal authority (Committee on Bioethics 1995; Leikin 1993). This mainly implies that meaningful agreement to enroll in a trial should be sought and that any refusal should be respected (Council for International Organizations of Medical Sciences 2002; Council of Europe 2005; Whitney *et al* 2006). The Dutch Act on Medical Research Involving Human Subjects correspondingly states that the consent of the minor should be sought in addition to the written permission of the parents when the minor is aged 12 or over and is deemed capable of participating meaningfully in decision making. It also states a clear duty to inform all children (whatever age) in a developmentally appropriate manner, while refusal of even young children needs serious consideration.

The intensely emotional nature of pediatric oncology makes it difficult to involve adolescents in decision making (Joffe *et al* 2006). Complex treatment and research-related decisions are brought up while facing a potentially life-threatening diagnosis, limiting good communication (Dermatis and Lesko 1990; Oleschnowicz *et al* 2002). Informed participation in decision-making requires the understanding of complex research-relat-

ed concepts such as randomization, voluntariness, and risks. The consent documents explaining these concepts are hard to understand for the layman (Berger *et al* 2009). Furthermore, most pediatric oncologists are also investigators and consequently discussions regarding diagnosis and treatment often include dialog about participation in research. Due to this integration of research and treatment, it is difficult for adolescents to distinguish between scientific goals and treatment objectives (Chappuy *et al* 2008; Susman *et al* 1992; Broome *et al* 2001). Finally, decisions about research participation need to be made within days or even hours (Stevens and Pletsch 2002). Taken together, the above constraints are likely to limit the degree and quality of discussions concerning trial enrolment. Consequently, assent is difficult to obtain (Oleschnowicz *et al* 2002). Still, a remarkable percentage of children with cancer—up to 80% of 0- to 14-year-olds and up to 30% of children over 15—enroll in a trial during their illness, as compared to only 1–4% of adult patients (Bleyer 1997; Ferrari and Bleyer 2007).

Little is known about physicians' attitudes towards involving adolescents in decision making. Few data are available on the presence and degree of participation of children in discussions regarding research (Oleschnowicz *et al* 2002) and what adolescents think of the assent process (Young *et al* 2003). No data are available on our research question: what are the views of physicians concerning their ethical and legal obligation to involve children in decision-making and how do they justify the limited extent to which assent is obtained? As we aimed to explore views, experiences, and attitudes, a qualitative interview design was used (Patton 2002; Denzin and Lincoln 2000). The research setting is defined as the situation in which the patient will not receive person-specific standard treatment but will instead be treated according to a clinical research protocol (with or without randomization) in order to obtain generalizable results. Adolescents are defined as minors between the ages of 10 and 18 years.

METHODS

The study sample was drawn from data collected as part of a larger qualitative multicenter project exploring patients', parents' and physicians' experiences of the informed consent process for treatment and research decisions after initial cancer diagnosis or after relapse. The project was approved by the Institutional Review Boards at the study sites. Informed consent was obtained from all participants. The present study is based on the interviews with the subgroup of physicians. One-to-one, in-depth, semi-structured interviews were conducted with the entire medical staff of two pediatric oncology centers in two academic hospitals (n=15). Children and adolescents up to the age of 18 are generally treated in these centers. The interviews were carried out from June to August 2007.

Interview procedure and analysis

All physicians were interviewed by the author of this thesis. Initial interview topics (see table 8) were formulated after examination of the relevant literature and a preliminary observational study in the children's oncological ward of one of the hospitals. In accordance with qualitative research techniques, the interview topics evolved as the interviews progressed through an iterative process to ensure that the questions captured all relevant emerging themes (Britten 1995; Guest *et al* 2006). The interviews contained general topics and no close ended questions, and lasted between 30 and 60 minutes. Thematic saturation was reached after the 11th interview.

The interviews were recorded and transcribed verbatim. Data analysis was based on the constant comparative method (Strauss and Corbin 1998; Malterud 2001). Two of the authors (MdV and EvL) independently coded the transcripts by identifying and labeling discrete units of texts that referred to one or more concepts relevant to the purpose of the study. Through comparison across transcripts, the open codes were developed into higher order themes to provide a framework for coding subsequent transcripts. An independent researcher coded two transcripts to check for consistency and adequacy of the framework. No inconsistencies were found.

We used qualitative software, Kwalitan 5.0 (Peters 2000), for multiple text management including coding, locating, and retrieving key phrases. Finally, representative quotations were chosen to demonstrate the themes identified. These quotations are included in the text.

Table 8. *Interview Topics*

The in-depth interview topics covered:
• Characteristics of pediatric oncology: integration of research* and treatment, emotional setting
• Possible difficulties in explaining research and treatment goals and risks
• Physician-patient-parent relationship concerning treatment and research decisions
• Adolescent's participation in decision making
• Ethical and legal obligations to involve adolescents in decision-making
• Parents and patient autonomy
• Physician's ideas on non-maleficence and beneficence

*When talking about research, we confined ourselves to discussing phase III-trials, in which the overall contribution of a new approach ('protocol') was evaluated, often in a large, randomized controlled trial (RCT) setting in which the new approach was compared with the previously evaluated best standard therapy. Most 'front-line' pediatric cancer studies are phase III studies.

RESULTS

All 15 physicians who were contacted agreed to participate. The physicians varied in age, sex and working experience (see table 3, page 21). The physicians from center B were younger and had less working experience in pediatric oncology. There were, however, no differences in outcomes according to site.

In line with previous studies, almost all physicians stated that meaningful assent from adolescents, although an ethical (and legal) requirement, is difficult to obtain (12 of the 15 physicians, 80%). Four central themes that characterize the physicians' attitudes towards involving adolescents in decision-making concerning research were identified. These themes emerged consistently in all interviews.

Theme 1: physicians regard most adolescents as not capable of meaningful participation in research discussions

The interviews show that the physicians in our study started from the presumption that adolescents are incapable of participating meaningfully in research discussions, mostly because of the overwhelming situation. All physicians stated that most adolescents are unable to judge correctly what a research setting entails, even after ample discussion.

> *In my opinion, these children are not able to judge these things at the time of diagnosis. As soon as I get the idea that they can, I try to involve them in the decision-making. But I think that only concerns the children who really have reached puberty, not the 12- and 13-year olds. Most of them sit and watch their parents. – Physician B4*

Four physicians stated that sometimes they did encounter adolescents who were capable of understanding what research entails, mainly because they were facing a relapse and had previous experience in participating in research.

> *It is true that children who suffer relapse, well they are sometimes wiser than you would expect. Not all of course, but some are. – Physician A5*

Children who had almost reached the legally established age of maturity (in the Netherlands: 18 years) were also attributed more capabilities but this was not seen as a general rule. Physicians also encountered older adolescents who were too overwhelmed to participate in research discussions.

Theme 2: Physicians do not always provide adolescents with all information

The majority of physicians (11 of the 15 physicians, 73%) will omit information when talking to adolescents because they think they are too vulnerable. Sometimes information is also considered not to be useful for them at that particular moment.

> *Most of the times I talk to parents and the child separately, because I'm more honest to parents than to the child about the ins and outs of the research protocol and possible complications. (...) It's not that I lie about things, but some things you just don't have to mention to a child. You don't have to burden a child with things that might not happen at all. But we do have the obligation to articulate these things to parents. – Physician A3*

> *If you have to explain randomization to a young adolescent, that is often very difficult. You can explain aspects of the treatment in general. [...] But more difficult issues, like randomization and risks, I discuss with parents separately. – Physician B3*

Adolescents hear about their condition, the proposed treatment and side effects (especially short term side-effects, like vomiting and hair loss), but they get little or no information on certain research issues, such as risks (stated by 9 of 15 physicians), randomization (2 of 15 physicians), alternative treatments (5 of 15 physicians) and extra burdens (2 of 15 physicians). Leaving out information and thus enabling only incomplete participation in decision making was justified with the following arguments: first, proxy consent from parents was obtained (theme 3); and second, physicians judge research protocols as being not harmful and even in the best interest of the child (physician-investigator integrity, theme 4).

Theme 3: physicians regard proxy consent as a necessity

All physicians were confident that parents generally want to promote the welfare of their child and that parents understand the research setting. Therefore, proxy consent was seen as sufficient justification for enrolment.

> *Some adolescents just don't understand what they are signing. Then I count on the parents' wishes. Parents always want what is best for the child. – Physician A6*

Theme 4: Physician-investigator integrity: research is not harmful

Thirteen of 15 physicians (87%) felt confident to include a child in a study since their own knowledge of the trial (e.g., its risks and burdens) and the Institutional Review Board (IRB) approval convinced them that the study was not inferior to known treatment options. Their own integrity and IRB control would protect the child.

I've seen the development of this trial and that's why I'm very aware of what we offer the child. It is not something horrifying but something I can support completely. Well, that's why I don't have any difficulty that I let the child sign for a trial, although he doesn't understand the ins and outs of it. – Physician B5

The accuracy that studies need to have these days to be accepted by IRB ruling...; then you can wholeheartedly say that it is not harmful. And that's why I'm a vigorous advocate of studies and I always try enroll a child. – Physician A4

Some clinicians (3 of 15) said participation in a trial, independent of the arm the patient is in, ameliorates the treatment which could be received outside a trial.

I think that parents should become more familiar with the fact that studies actually provide a qualitatively better treatment. There is better control, there are fixed rules we have to abide by concerning inclusion, exclusion, adjusting chemotherapy because of side-effects, etc. That's why I'm more inclined to think that participating in a study is an advantage, rather than a disadvantage. – Physician A4

Two physicians were skeptical about the benefits for children.

It's not true that participation in research is completely harmless. We are fallible. Sometimes experimental arms of research turn out not to work at all. Also, little things can go wrong during the treatment. It's all human work. – Physician A6

All physicians felt bound to enroll children in the, usually international, clinical trials, because they considered it the state-of-the-art treatment and because the oncological team conformed itself to participate in these trials.

We also explain how things work in the Netherlands, that our hospital works with uniform protocols, that all children get the same treatment in the Netherlands. (...) I have to admit that I explain things [to parents] as if they have no choice. I usually say: your child has leukemia, or whatever form of cancer, and then most of the times I already made copies of the trial protocol outline and I say: well, In the Netherlands all children with this disease are treated this way. – Physician B1

DISCUSSION

In pediatric oncology, treatment is often combined with research. The intertwinement between research methodology and clinical care has led to much progress in therapeutic options, but it makes the informed consent procedure difficult to perform. The physicians in our study confirmed that they often do not fully involve adolescents in decision-making concerning research participation. Assent by the adolescent is acknowledged as ethically and legally necessary but is said to be difficult to obtain.

The four themes that characterize the physicians' attitudes towards involving adolescents in research discussions can be summarized as follows: Adolescents are not capable of meaningful participation in these discussions (theme 1) and are not fully involved in decision-making (theme 2). This is, however, not a problem, because proxy consent (theme 3) and investigator's integrity (theme 4) safeguard the adolescent's best interest in a trial. Not involving adolescents in research discussions is justified by physicians with the use of best interest arguments (adolescents' incompetence, proxy consent, and investigator integrity). Discussion should focus on the appropriateness of these best interest considerations in a research setting.

Best interest and research participation

Almost all pediatric oncologists in our study sincerely believed that enrolling children in clinical trials was in their best interest and constituted state-of-the-art treatment. These observations support Joffe *et al*'s findings about enrolment of children in trials and best interest considerations (Joffe *et al* 2002).

At first sight, it seems rather safe to rely on a best interest standard in research decisions since the same standard is used in treatment decisions. In a research context, however, proxy consent and the best interest standard are not so easily applied. First, the function of proxy consent can be troublesome: literature shows that parents also have difficulties in understanding research related topics (Stevens and Pletsch 2002; Kodish *et al* 2004; Wiley *et al* 1999). What is more, there is evidence that there is a potential for disagreement between adolescents and parents on research participation (Young *et al* 2003). One study even reports a consistent 40% discordance in views between adolescents and parents across a variety of asthma research protocols (Brody *et al* 2005). It seems that the physicians we interviewed are unaware of the basic lack of understanding of research-related concepts in parents and the potential for disagreement between adolescents and parents. At least it does not change the importance the physicians attach to proxy consent. Based on the literature however, it can be argued that parents may not be equipped to make decisions about research participation on behalf of their children.

Secondly, the contexts of treatment and research are fundamentally different and require different ethical approaches (National Commission for the Protection of Human Subjects 1979; Miller and Brody 2003; Spinetta *et al* 2003). In the treatment relationship, the best interest of the individual child is prevailing in the selection of the best available treatment. Any new knowledge generated is incidental to the overriding goal of providing therapy. The concept of presumed or implicit consent is often used in the therapeutic setting. Pediatricians routinely carry out medically indicated procedures on children without obtaining assent, or even despite a child's vigorous objections. This is acceptable because it is the interest of the child which is the sole motivation prompting the intervention (Lee *et al* 2006). In the context of research, however, the researcher seeks to advance knowledge to improve the care of future children as well as to serve other interests, like building an academic profile. Therapeutic benefits to the individual are, from a methodological perspective, secondary to the overriding goal of obtaining robust data and new knowledge (Miller and Brody 2003). The goals of research often require that children undergo non-therapeutic procedures, such as additional blood samples, spinal taps and (PET) scans. These procedures may cause considerable pain, discomfort, inconvenience, or even harm (Miller and Brody 2003). Therefore, the research setting leaves no room for presumed consent. Subjects should voluntarily enter the research setting, with adequate information and only after explicit consent, because the best interest standard is not the only demanding principle (National Commission for the Protection of Human Subjects 1979).

Sometimes it is argued that an RCT preserves the basic treatment related duty to act in the best interest of the child through clinical equipoise, the uncertainty principle. After all, no subject is randomized to a treatment known to be inferior to the present standard. For example, Kumar *et al* (2005) found that new treatments in childhood cancer tested in randomized controlled trials are, on average, as likely to be inferior as they are to be superior to standard treatments, confirming that the uncertainty principle has been operating. However, the uncertainty principle also means that it is never known in advance what the actual risks and benefits will be: only after the completion of a study one genuinely knows which trial arm showed the best results and whether or not participants were exposed to extra risks and burdens. Most pediatric oncology trials have Data and Safety Monitoring Plans (DSMP) and stopping rules for the very purpose of dealing with unexpected risks and outcomes.

The physicians in our study argued that trial participation is beneficial as compared to non-participation because of a strict adherence to well-defined protocols. Various authors have stated that the use of treatment protocols improves the end result of treatment (Stiller and Eatock 1999; Karjalainen and Palva 1989; Stiller 1994). This could be

the result of the explicit description of the treatment phases and their follow up. Other authors, however, show that there are insufficient data to conclude that such a trial effect exists (Vist *et al* 2008; Peppercorn *et al* 2004). Until such data are available, patients with cancer should be encouraged to enrol in clinical trials on the basis of trials' unquestioned role in improving treatment for future patients.

In conclusion, recognition of the fundamental conceptual difference between the care orientation and the research orientation is crucial in deciding to obtain explicit assent of adolescents. One cannot justify wavering assent from an adolescent for research elements in a protocol by pointing to the best interest standard, as the physicians in our study did.

Can adolescents decide for themselves?

The other reason given by the clinicians for not obtaining assent is that adolescents would not be capable of participating meaningfully in research discussions and that therefore obtaining proxy consent suffices. However, several studies have shown that children aged 14 and older can approach the level of understanding of adults (Joffe *et al* 2006; Mårtenson and Fägerskiöld 2008). Some studies even conclude that relatively young children (as young as 7 years) can participate meaningfully in the consent process (Committee on Drugs 1995). One study indicates that emotional factors are more frequently related to understanding the implications of research participation than are age or cognitive development (Dorn *et al* 1995). This suggests that providing a medical environment that decreases anxiety and increases a sense of control may enhance adolescents' understanding of the research process, however difficult this may be to achieve in the situation of a child with newly diagnosed disease or relapse. The ability to understand research issues may also relate to experience rather than to age, as even young children appear to understand complex issues (British Royal College of Pediatrics 2000). The physicians in our study confirmed these latter findings. Some mentioned that they do encounter children who are wiser than expected and that their approach then is different, involving these children more in the decision-making process. From these data, we can at least conclude that adolescents as a class should not be regarded as incapable, but that an assessment is needed in each individual case. We must aim at avoiding two kinds of mistakes: imposing complex research decisions on adolescents who are unwilling or unable to make them, and excluding capable adolescents who desire to participate in decision making (Joffe *et al* 2006). Therefore, a case-by-case (psychological) assessment prior to concluding the consent process is necessary in order to evaluate the decision-making capacity of the adolescent (Abrams *et al* 2007). Thus, justice may be done to the ethical ideal of respect for the developing autonomy of children in making decisions, as

stipulated in several international regulations and guidelines [Code of Federal Regulations 1991; Directive 2001/20/EC 2001; Spinetta *et al* 2003). Unless they have a very pertinent reason to do so, physicians cannot put their judgment about the child's best interest in place of the child's consent to participate. The opinion of the adolescent should be actively sought, which will sometimes mean that the views of parents will have to be overridden by oncologists. We would suggest that in the case of an adolescent with the capacity to understand the implications of research participation, both the adolescent and the parents need to consent to research participation. Especially an adolescent's refusal needs serious consideration; in our view conducting research is not acceptable if this means overruling an adolescent's refusal, even if parents did consent to it.

It is extremely difficult to explain complex research concepts to lay persons in a situation of acute, serious medical illness as well as emotional strain. Well-crafted information materials (booklets, visual aids) could aid investigators in explaining to potential child research participants and their parents what these concepts mean, and which elements of their treatment are research procedures (for example additional blood samples or spinal taps) (Ungar *et al* 2006).

Chapter 7

ATTITUDES OF PHYSICIANS AND PARENTS TOWARDS DISCUSSING INFERTILITY RISKS AND SEMEN CRYOPRESERVATION WITH MALE ADOLESCENTS DIAGNOSED WITH CANCER

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ABSTRACT

Background. In pediatric oncology, the risk of infertility due to treatment constitutes an important problem. For sexually mature male adolescents, sperm cryopreservation is an option, but discussing the topic is complex because of the sensitive nature and the limited timeframe. In this chapter we determine attitudes and preferred roles of physicians and parents towards discussing sperm banking with male adolescents.

Methods. Qualitative multi-centre study, using in-depth semi-structured interviews with 14 physicians and 15 parents of male adolescents undergoing cancer treatment.

Results. Although physicians and parents agreed that infertility would have a major impact on the future quality of life, they sometimes disagreed on whether the topic should be discussed with adolescents. Physicians always wanted a separate discussion with adolescents because of the sensitive nature and the experience that parents sometimes misjudged the stage of maturity of their son. Parents, however, wanted control over whether physicians discussed the topic with their child and what was said. Physicians did not accept this control and, when necessary, were willing to bypass the parents and discuss the topic with the adolescent even when parents refused consent.

Conclusions. Physicians face the difficult task of balancing between their ideas of what is in the (future) interest of the adolescent and accommodating parental wishes. We argue that, because of the private character of sexuality and the potentially inadequate maturity assessment by parents, semen cryopreservation should be discussed separately with adolescent and parents. In addition, there should be an open communication with parents to address potential discomforts.

INTRODUCTION

Children treated for cancer are increasingly likely to survive. For all childhood cancers 5-year overall survival has improved markedly over the past 30 years, from less than 20% to nearly 80%, due to improved treatments and better supportive care (American Cancer Society 2007). However, long-term survivors may face serious long-term side effects, including damage to the reproductive system. Rates of compromised fertility after cancer treatment vary and depend on many factors, like the chemotherapeutic agent or radiation field, the dose, dose-intensity, method of administration, disease, age, sex and pre-treatment fertility (Fallat *et al* 2008; Lee *et al* 2006a; Schrader *et al* 2001; Wallace *et al* 2001). Most at risk are those who are intensively treated with a treatment modality encompassing successive multiple toxicity, like bone marrow transplantation.

The inability to father genetically own children has a high impact on the future quality of life (Lee *et al* 2006; Saito *et al* 2005; Schover *et al* 1999; Schover *et al* 2002a; Schover 2005; Van den Berg and Langeveld 2007). Both male and female cancer survivors report a large degree of stress regarding fertility (Schover 2005; Green *et al* 2003; Zebrack *et al* 2004).

In male adolescents with a risk of infertility, sperm banking can be offered, provided that the adolescent is sexually mature. Cryopreservation of semen for eligible adolescent boys is a well established and proven technique which should be considered routine (British Fertility Society 2003). The availability of ICSI makes it worthwhile to cryopreserve almost all semen samples, even when the sperm has extremely poor characteristics of count, motility and morphology (Tournaye *et al* 2004). In adolescents who are at risk for infertility and have had spontaneous nocturnal ejaculations, but are unable to produce semen by masturbation, transrectal electro-ejaculation under general anaesthesia is an option (Hovav *et al* 2001; Schmiegelow *et al* 1998).

Notwithstanding the technical possibilities, semen collection in male adolescents can be complex because of communication difficulties. Discussing sperm banking involves sensitive topics like body changes and developing sexuality, the grief of confronting infertility as a side effect, the necessity of using masturbation to collect a semen sample, and the use of pornographic materials as an aid (Schover 1999; Crawshaw *et al* 2007). Eligible patients and their parents must consider preserving fertility during the stressful period after having received a potentially fatal diagnosis. Usually the time frame until cancer treatment starts is short, which further adds to the experienced pressure.

Because of the large variation in the stage of maturity among teenage boys, it is difficult to select the boys eligible for cryopreservation. Not only the Tanner stage is important in assessing possible success, but also whether the boy has spontaneous

nocturnal semen emissions and/or masturbates. To gain insight in the stage of maturity, this sensitive topic is often discussed with parents first and subsequently with the patient (Müller *et al* 2000). The decision to initially talk with the parents requires ethical consideration. Talking to the parents first may be embarrassing for adolescents, because they value their privacy in this matter. But parents of teenagers may be protective and may prefer to have topics such as sexuality and reproduction not addressed without their consent. This may pose a dilemma for the oncology team about who to talk to first (Schover 1999). This dilemma raises special concern because of the need to balance the extent to which adolescents are able to participate in the discussion and the extent to which parents are able to judge the stage of maturity of their sons.

To date, not much data is available on the practice of discussing fertility preservation in the pediatric oncology setting. Most studies assessed the adult oncology setting (Green *et al* 2003; Quinn *et al* 2007). Previous reports on pediatric oncologists only concern their knowledge about infertility risks and fertility preservation techniques, and whether fertility issues are discussed before the start of treatment (Anderson *et al* 2008; Goodwin *et al* 2007). There are no data on how the topic is discussed and on physicians' ideas about who should be present during the discussion. With regard to parents, there are publications on their knowledge about the infertility risks for their child (Van den Berg *et al* 2007), their concerns about fertility Oosterhuis *et al* 2008) and their presence during initial discussions (Ginsberg *et al* 2008), but none about the preferred roles of parents in the discussion about this topic.

The purpose of the present study was to clarify the attitudes of parents and physicians concerning various aspects of discussing fertility issues. Specifically, this study was conducted to: (1) assess the current communication practice of pediatric oncologists regarding fertility preservation, with emphasis on role delineation of physician, parents and adolescent, (2) explore the experiences of physicians and parents regarding their roles in fertility preservation communication, and (3) explore the ethical issues involved. Insight into the attitudes of physicians and the discomforts and preferences of parents may contribute to successful communication, and thereby positively affect parental satisfaction with communication (Zwaanswijk *et al* 2007).

METHODS

Participants and design

Our sample was drawn from data collected as part of a larger qualitative multi-centre project in which we explored patients', parents' and physicians' experiences with the

informed-consent process for treatment after initial cancer diagnosis or after relapse. In this project we invited patients (aged 8-18 years) attending the pediatric oncology units of two Dutch university hospitals, their parents and their physicians to participate in semi-structured interviews about the informed consent process.

The present study is based on the interviews with the subgroup of parents of male adolescents (n=14) and their physicians (n=15). Since we only focused on fertility preservation techniques available in the two clinics where the study was conducted (cryopreservation of semen collected through masturbation (both clinics) or electro-ejaculation (one clinic)), we did not use the interview data of the parents of prepubertal male patients or female patients. We had hoped to also include an analysis of the interviews with the male adolescents, but most of them were reluctant to talk about semen cryopreservation in the context of the broader research project. These interviews generated not enough data for assessment in this study.

Figure 4 shows eligibility and recruitment of parents. Parents had a mean age of 42.8 years (range 36-50 years). Their sons had a mean age of 13.8 years (range 11-17 years). The parents' occupations varied, indicating social diversity. All families were of Dutch origin. Demographic and clinical characteristics of the parents and their sons are given in Table 9.

The group of physicians comprised the entire medical staff of both pediatric oncology units. Physicians had a mean age of 42.1 years (range 32-52 years), worked in pediatric oncology for a mean of 7.6 years (range 1.5-20 years) and 7 (46.7%) were male. The project was approved by the medical ethics committees at the study sites. All parents gave written informed consent.

Interview procedure and data collection

All families were interviewed by the author of this thesis. The parent interviews lasted between 60 and 90 minutes and were conducted at the hospital. The interview topics covered general characteristics of the patient; the history of the disease; discussions with physicians about the recommended treatment and possible side effects like infertility; parents' attitudes to these discussions, and the perceived role of parents in decision making regarding cancer therapy and related treatments, like fertility preservation options.

Each physician was interviewed in their office. The interview lasted between 30 and 60 minutes. The in-depth interview topics covered work experience; general goals of childhood oncology; the physician–patient-parent relationship, especially concerning decisions regarding therapy and related treatments, like fertility preservation options; patient and parent autonomy, and physician's ideas on what is in the best interest of a child.

Table 9: *characteristics of parents and their sons*

Parent number	Age patient (yrs)	Diagnosis	Treatment	Parent interviewed	Age parent	Education parent	Marital status parent
1	11	ALL	chemotherapy	father	37	Middle level high school	married
2	12	AML	chemotherapy	father	36	Middle level high school	married
3	15	AML relapse	HSCT	mother	43	Advanced vocational	divorced
4	12	AML	chemotherapy	mother	39	Middle level high school	married
5*	13	MDS	HSCT	father	41	Lower level high school	married
6*	13	MDS	HSCT	mother	39	Lower level high school	married
7	13	NHL	chemotherapy	father	49	Middle level high school	married
8	17	NHL relapse	HSCT	father	50	Middle level high school	married
9	16	Hodgkin relapse	HSCT	father	47	Middle level high school	divorced
10	14	Ewing sarcoma	chemotherapy	mother	46	Advanced vocational	married
11	15	Ewing sarcoma	chemotherapy	mother	41	unknown	married
12	14	Ewing sarcoma	chemotherapy	father	46	Middle level high school	married
13	14	Ewing sarcoma	chemotherapy	father	39	Advanced vocational	married
14	13	Osteosarcoma	chemotherapy	mother	46	Advanced vocational	married

Abbreviations: ALL=acute lymphoblastic leukaemia; AML=acute myeloid leukaemia; MDS=myelodysplastic syndrome; NHL=non Hodgkin's lymphoma; HSCT=haematopoietic stem cell transplantation

* Parent 5 and 6 were parent of the same child.

Data Analysis

All the interviews were audiotaped and transcribed verbatim. Data analysis was based on the constant comparative method (Malterud 2001; Strauss and Corbin 1998). The authors, MdV and EvL, independently coded the full transcripts by identifying and labelling discrete units of texts that referred to one or more concepts relevant to the study. Through comparison across transcripts, the open codes were developed into higher order themes to provide a framework for coding subsequent transcripts. The simultaneous inclusion of parents and physicians enabled comparison of themes between the two groups. An independent researcher coded two transcripts to check for consistency and adequacy of the framework. When no new thematic content was found in the parent interviews, subject enrolment was stopped. This process, called thematic saturation, is a well-described qualitative method to avoid unnecessarily large and repetitive data sets (Guest *et al* 2006; Denzin and Lincoln 2000).

We used qualitative software (Kwalitan 5.0, Peters 2000) for multiple text management, including coding, locating, and retrieving key phrases. Finally, representative quotations from parents and physicians were chosen to demonstrate the themes identified.

RESULTS

We identified four central themes from the interviews: concerns about the future quality of life, child participation, parental control, and timing and approach for fertility discussions. We discuss these themes for physicians and parents separately.

Attitudes of physicians on communicating fertility issues

Concerns about the future quality of life

For all physicians, infertility was seen as having a major impact on the future quality of life of patients. All physicians therefore felt a duty to bring up the issue and offer cryopreservation.

> *I think it's our duty as oncologists to offer fertility preservation, because only before start of treatment is there the possibility to do so. Once they have had chemotherapy, it's over. And maybe later on, when they are 25 years old they come back to me and ask: doctor, why didn't you offer it to me? – Physician A8*[1]

[1] For the quotes: physician numbers refer to the physician numbers in Table 3 (page 21). Parent numbers refer to the parent numbers in Table 9.

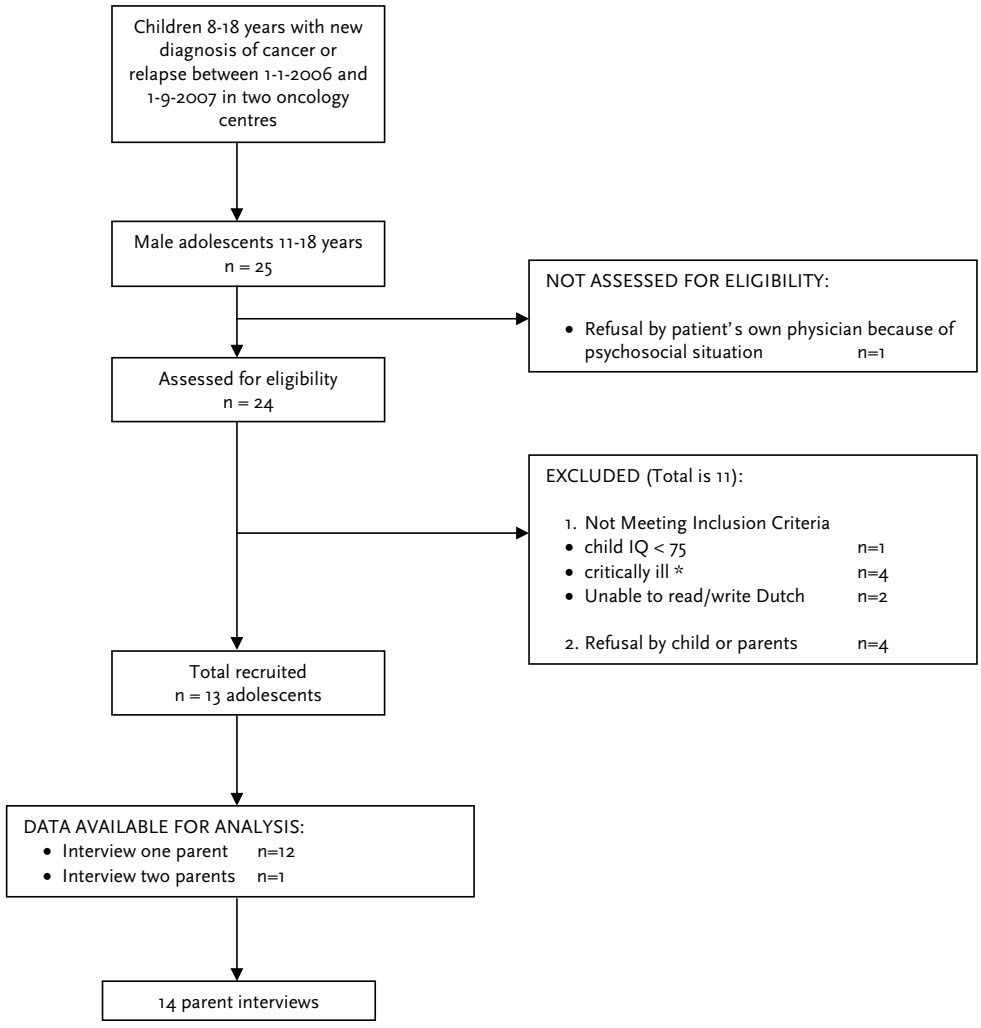

Figure 4. *Enrollment, eligibility and recruitment of parents.*

** For critically ill adolescents, therapy had to start immediately and there was no time to cryopreserve semen*

Child participation and parental control

There was unanimity among physicians that children should participate in the decision-making process. Most of the times physicians talked to the parents first to find out their thoughts on the sexual development of their child. Subsequently, the opinion of the child was sought.

> *I always first discuss it with the parents. Even with older adolescents I first talk to the parents and ask them whether they think that the boy is ready to discuss the topic and produce semen. Only after that I talk to the boy. – Physician A7*

Physicians, however, knew from experience that parents cannot always correctly predict whether their child masturbates or has nocturnal semen emissions.

> *I remember one mother who had it completely wrong. She thought her son didn't do anything yet, but he was [masturbating]! She just didn't know and she was shocked to find out, because she thought she knew her child very well, but now found out that she didn't. – Physician B4*

> *We have been mistaken once or twice. Parents sometimes said that their child was not ready, but then we talked to the child alone, and it turned out that the child was ready. And that he was able to produce sperm for preservation. On such occasions we almost let a chance pass by because parents had said that the boy was not ready. I learned from those experiences that you always have to talk to the adolescent alone, and not leave the issue to the parents. – Physician B3*

Because of the alleged inability of the parents to make reliable predictions on this topic, and the importance of the issue, the physicians always talked to the adolescent, even if parents doubted whether the issue should be discussed with their son.

> *If you think that a patient will become infertile from the treatment, and the boy has reached an age at which sperm can be preserved, then I think it's your duty to do so. You can only do it once. I think it should be offered and I feel justified in passing over the parents. If I think the child is ready and parents doubt that, then I think it's in the best interest of the child to go ahead. – Physician A3*

Fourteen of the 15 physicians would even discuss the topic with the adolescent when parents straightforwardly refused them permission to talk to their son. Only one physician

said she would then follow the preferences of the parents. Because of the delicate issues to be discussed, physicians in fact sometimes talked to the adolescent alone, without the parents knowing.

Once, with a 14-year old boy, I first talked to the boy, without his mother knowing. Because I thought it was too delicate an issue to discuss with everyone present. The mother was furious when she found out. 'It's MY child and I have a right to know!', she claimed. I replied that she had a right to know, but that the child had the right to know FIRST, because with this issue you enter a private domain. – Physician B4

Experiences of parents

Concerns about the future quality of life

Just like the physicians, many parents were thinking of the future quality of life of their son when pondering over the fertility issue.

What counted for us was the thought that, well, let's suppose that he wants to start a family, that his future wife has a strong child wish, and we would have blocked the way. If you say no [to fertility preservation], then that's final. That would be too much control from our side. In my opinion, that would be unwise. – Parent 14

For him to have a choice in the future to start a family or not, that was the reason why we made the decision to preserve semen. It is his life after all. And I don't want to intervene in it. I don't want to deny him choices in the future by deciding for him now. – Parent 13

Child participation and parental control

In contrast to the physicians, there was no unanimity among parents with respect to their views on the participation of children in the decision making process. Some parents were explicit in their views that it is eventually the child who decides what happens, because it relates to his own future.

He [the child] initially said that we [the parents] had to decide what to do. Well, that was something! I thought it was too much. We couldn't decide over something that he might regret 10 years from now. So we talked it over with him. And he eventually cut the knot. And we supported him. He generally very easily passes the buck to us. As soon as he has to think something through, he makes us decide. But in this case that was not realistic. It's about your life, I told him. – Parent 14

Many parents (8 of 14) however doubted whether the issue should be discussed with their son. They wanted to protect their child from this information, or at least wanted control over what was being discussed with their child.

At one point I said to the nurse: 'I want to protect him from this [fertility] conversation with the physicians. I will tell him myself what he needs to know'. – Parent 6

[Patient was approached first, without his mother knowing] Well, the fact that they approached him first, that they let him decide, I found it hard to come to terms with that. His whole life I've been responsible and the one people talked to concerning him. Of course we always discuss things, me and the children, but in the end, I'm the one with the most life experience. So I take the final decisions. But now, they approached the child directly. So I said to them [the physicians]: 'I think the sequence is wrong. You should first contact me, when you want to discuss things with my child.' – Parent 3

The main reason parents wanted control over the discussion was because they doubted whether their son was sexually mature.

We had to think about whether he already has ejaculations. I just knew this was not the case. I mean, he is almost 14 years old, but it's just not the case. Is it reasonable then to confront him with this side-effect? We told the physician not to mention it to him. – Parent 5

Three parents were reluctant to discuss the issue because they felt that the conversations were ill-timed and confronting due to the sensitive nature.

The evening before the start of the chemotherapy he [the child] was told about possible infertility and semen preservation. Later on we told them [the physicians] that the timing was really bad. For a child to be in such a big hospital and then to have to think about something like that. Even adults wouldn't be able to do that. We felt it was mentioned too late. They should have mentioned it during the first conversation. (...) Because then the child has 2 or 3 weeks to think about it in his own environment. – Parent 11

That he had to think about whether he could produce semen or not, that was really shocking. He had to make such a leap in his development. Of course, to hear that you have cancer is also very shocking. But in a way that just happens to you. It's just a fact. While for this issue we had a choice, we had a choice what to do. – Parent 13

DISCUSSION

Unanimity existed among parents and physicians with respect to the impact of possible infertility on the future life of the child. The child's best interest in the context of treatment was seen as to include both its present interests in surviving and future interests such as fertility preservation. Maintaining future options is a well-known theme in pediatric ethics, and various authors have argued that physicians and parents act unethical if they make choices that limit a child's range of future options (Feinberg 1992; Davis 2001). A child's right to fertility preservation is acknowledged in bioethical literature as a right in trust. If the medical risk is acceptable, it seems that parents have an ethical right to ask for fertility preservation and an ethical duty not to constrain the choices of their children regarding future reproduction (Fallat *et al* 2008; Davis 2001).

Although physicians and parents agreed that infertility would have a major impact on the future quality of life of their child, they sometimes disagreed on how the topic should be discussed. Physicians always wanted a separate discussion with adolescents because of the sensitive nature of the topic and the experience that parents can misjudge the stage of maturity of their son. Some parents, however, felt that there were barriers to discussing the topic with their son because they felt he was too immature and under pressure of time. Discussing infertility with adolescents was a sensitive topic for parents and they wanted control over whether physicians discussed the topic with their child and what was said. In the literature this control over physician-child communication has been described before and termed strategic control. Parents tend to filter and modulate what children are told by their physicians, relegating children to a passive role in medical decision-making (Tates and Meeuwesen 2000, 2001). Literature shows that physicians normally deem this mode of communication acceptable (Levetown *et al* 2008). Studies in pediatric oncology describe a general tendency from physicians to protect children from too much information (Young *et al* 2003; Olechnowicz *et al* 2002). Parents and physicians jointly discuss the ways to encounter the child, whether to involve the child in the decision making process and the information given to the child. The parents in our study wanted to exert strategic control in fertility issues as with other topics. The physicians we interviewed, however, did not accept this strategic control when fertility preservation was involved. The future potential of fertility seemed too important to them and they wanted to discuss it with the child, even when the parents did not give consent. This confronts physicians with the difficult task of finding a balance between their view of the (future) interest of the adolescent and accommodating parental wishes. Most physicians in our study were ultimately willing to bypass the parents. This could potentially lead to an undesirable situation of conflict between parents and physicians at the outset of a long treatment relationship.

Because of the potential differences in opinion between parents and physicians, fertility preservation can be used as an example case to discuss the limitations of parental discretion to regulate information disclosure to their child. In general, parents want to promote the welfare of their children. It is this intention that makes parents the presumed decision makers for their children and legitimises parental discretion to act as they think is best for them (Ross 1998). In the delicate issue of fertility discussions however, the parental role can become problematic and it could be assumed that the adolescent is the most appropriate discussion partner and does not need a custodian. After interviewing young cancer survivors, Schover *et al* (2002b) came to the conclusion that the fertility topic should first be raised with the adolescent in private and then be discussed separately with the parents. The patients in the study by Schover *et al* reported that it was acutely uncomfortable to be informed about sperm banking in front of their parents. Ginsberg *et al* (2008) showed that almost half of the male adolescents would have preferred to have initial discussions without their parents present. One study suggested that male adolescents may be more successful at masturbation if a parent does not accompany them to the sperm bank (Bahadur *et al* 2002). Various guidelines and protocols state that adolescents can in some circumstances be considered mature enough to give or refuse informed consent for medical procedures, without the need for parental involvement, especially when reproductive health services are at stake (so-called mature minor doctrine) (British Fertility Society 2003; Sigman and O'Connor 1991; Committee on Bioethics 1995; Dickens and Cook 2005). Strategic control from parents therefore seems inappropriate concerning fertility discussions.

There can be many reasons not to discuss fertility preservation with an adolescent, like the inclination to prioritize discussions about treatment and its immediate side-effects, emotional discomfort with discussing fertility issues, lack of time or the prediction that the adolescent is probably not mature enough (Lee *et al* 2006; Vadaparampil *et al* 2007). The ease with which physicians can discuss fertility issues also depends on the existing practice of educating teens about sexuality, which may differ from country to country. However, if we want to preserve future reproductive choices for adolescents and if we take the adolescents' ability to discuss their own sexual development and behaviour seriously, these reasons do not relieve physicians and parents of the obligation to initiate early discussions with adolescents in private about conservation of future fertility potential.

It should be noted that communication, especially on a potentially difficult topic such as fertility, is culturally sensitive. A basic knowledge of the norms and values about sexuality and fertility associated with specific groups is helpful for this purpose. On the other hand, we need to be aware that there is also a great diversity *within* groups, communi-

ties, and families. Simon and Kodish (2005) therefore emphasize the danger of making assumptions based on ethnicity or socioeconomic factors, which may contribute to the omission of important information for families.

In our study, 3 of 15 parents were surprised by the late announcement of fertility problems and cryopreservation options. Other studies show that adolescents and parents want information regarding sperm cryopreservation early (within a week of diagnosis) in order to have the opportunity to think about it and to avoid unnecessary delays in treatment (Ginsberg *et al* 2008). Two surveys suggest that lack of timely information is the most common reason for not banking sperm (Schover *et al* 1999; Schover *et al* 2002a). Therefore, fertility preservation should be mentioned as early as possible, and should not be delayed because of the sensitive nature or a feeling of inappropriateness during a time of emotional stress. An educational brochure answering key questions could help facilitate discussion in a time of medical urgency and initial lack of relationships of trust between physicians, adolescents and parents (Nagel *et al* 2008).

CONCLUSION

Discussing the storage of sperm of an adolescent with cancer is a challenging aspect of pediatric oncology care. Because of the private character of the issue and the potentially inadequate assessment by parents of the stage of maturity of the adolescent, semen cryopreservation deserves to be discussed with the adolescent in private. In addition, there should be timely, open communication with parents, in which it is made clear that the issue is private and deserves separate discussion with their child. Addressing potential discomforts of parents about approaching their child may contribute to parents' eventual satisfaction with communication.

Future research should address adolescents' opinions on timing and approach for fertility discussions, as well as how to proceed once an adolescent wants to bank sperm (for example timeframe, use of erotic material, design of collection rooms). Since these topics turned out to be so sensitive for the adolescents, this research should be done anonymously (for example by using a questionnaire) or by a sexologist / andrologist to gain a better insight into their views.

Chapter 8

GENERAL DISCUSSION

In the following paragraphs, the principal results of this thesis are put into perspective. We will focus on two issues: first, we will give methodological considerations: does our methodology prove valuable for answering ethical questions in practice, and what are the limitations?; and second, what are the implications of our study for our thinking about child participation, the use of a best interests standard and parental authority in pediatric oncology and in pediatrics in general? Finally, directions for future research are given.

METHODOLOGICAL CONSIDERATIONS

The use of third person moral experiences in empirical medical ethics. Reflective equilibrium and empirical data

A familiar criticism of bioethics charges it with being more conceptual than practical - having little to do with the 'real world' and its moral issues. In order to answer this criticism and to keep its feet on the ground, bioethics has started to utilize methods from the social sciences. Empirical research data are believed to provide the bridge between conceiving a moral vision of a better world, and actually enacting it (Solomon 2005). This belief is not without counteraction, causing a debate about the question whether empirical studies can truly inform ethical reasoning (Pellegrino 1995, Düwell 2009). By using empirical data, are we not confusing the descriptive, the analytical-metaethical, and the normative domains of ethics? In short, ethics is not a democratic process. In this field of tension and debate, empirical ethics is still developing, and studies actually using empirical data, as well as studies on how to combine the 'is' and 'ought' are increasingly published (Salloch *et al* 2012).

In chapter 2, we defended our version of a Reflective Equilibrium (RE) method, namely the Network Model with Third Person Moral Experiences, which allows for a two-way relation between empirical and normative data. We concluded that various aspects can strengthen the search for coherence between the various data used (theories, principles and considered moral judgments) and eventually the credibility of the moral judgment of the 'thinker'. All these aspects have to do with using empirical data.

Our methodology can be questioned. First, one can ask why we use coherence as starting point to develop our methodology, and not deductivism or inductivism. Deductivism and inductivism both have attracting features (Beauchamp and Childress 2009). Deductivism rightly notes that once we have a fairly settled body of guidelines, in many cases a direct appeal to these guidelines leads to satisfactory moral judgments. And inductivism rightly emphasizes the role of new experiences and problems to refine guidelines. On the other hand, accounts only from the 'top' (principles, rules) and the

'bottom' (cases, individual intuitions) both have their problems. The content of rules and principles is often too abstract to determine the acts we should perform. Principles need to be made specific for cases. Furthermore, a top-down model creates a potentially infinite demand for final justification. And no single normative theory has shown yet to be a sufficient basis for moral justification. Case analysis needs illumination from general principles or norms to link and interpret various cases. Furthermore, a solely bottom-up approach cannot identify unjust practices or prejudice by the persons who make the judgments about cases. Eventually, neither general principles nor paradigm cases can guide the formation of justified moral beliefs. As Beauchamp and Childress (2009) state: 'there is no fixed order of inference or dependence from general to particular or from particular to general' (p 381). That is why we support a coherence theory. Justification is a reflective testing of our moral beliefs, moral principles, theoretical postulates, and the like, to make them as coherent as possible (Rawls 1971; Daniels 1979). If we want to develop realistic ethical constructs, we need to understand the ethical norms as well as the empirical data.

Then, is it truly possible to reach a reflective equilibrium? How do we refrain from merely looking for evidence for our own (prejudiced) opinion, and conveniently disregarding other evidence? As discussed in chapter 2, the subjective character and therefore the credibility of considered judgments are often questioned. With our interpretation of the initial judgment of the 'thinker' as a hypothetical equilibrium we at least try to be transparent about what elements or premises constitute this judgment. Furthermore, judgments can alter during the RE process. In this way, the RE process itself can function as a filter, which can separate reliable from unreliable judgments. The process of weighing and balancing judgments, principles, background theories and empirical data can let us identify judgments that are apparently wrong or prejudiced. The 'thinker' consequently gains a distanced view, while remaining attached to the concrete situation (cf. Nagel 1986). The Network Model with Third Persons Experiences gives the opportunity for the 'thinker' to stay susceptible to a wide range of experiences and facts, and to accept that his own judgments can change due to the RE process (the 'conversion').

Finally, how much time does reaching a RE need? Is it not too time consuming, and therefore not practical in a medical setting, especially when we include empirical data (which we have to find first)? We admit that there is no reason to expect that the process of revising moral judgments and specifying and balancing principles will come to an end in a perfect equilibrium. It is continuous work in a dynamic process. Our basic postulate is therefore that moral experiences, values, virtues and norms are part of a constantly moving process in which we create stability by using moral frameworks which are inherently temporary. Instead of a fixed rationalized framework built on principles we there-

fore face a never-ending search for coherence which is challenged by counterexamples to our beliefs, and by novel situations, technological possibilities and scientific insights that challenge the relative stability of our moral framework (Beauchamp and Childress 2009; Rawls 1971).

Qualitative research: moral experiences and considerations of parents, children and physicians in treatment and research decisions in pediatric oncology

In order to enrich the deliberation of 'the thinker' in RE with the norms and practical wisdom of the field of pediatric oncology, we collected experiences of relevant actors in our qualitative interview study. Several aspects of how we conducted our qualitative study warrant discussion. Many of them have already been discussed in chapters 3, 5, 6 and 7. First, our interview study used a retrospective design. This means there can be uncertainty whether the parents', patients', and physicians' recollections were accurate representations of how they felt and what their thoughts were at the time of diagnosis and during treatment decisions. Examining parents' and children's narratives of decision making is not tantamount to studying decision making per se. The introspective gap between 'true' decision-making processes and those that subjects report is a limitation in this realm of research, and could introduce biases. Second, the study had small sample sizes. These two limitations could be partially surmounted by other study designs, like direct observation of decision making, recorded conversations between parents, child and physician, or mixed methods research in combining questionnaires with qualitative methods, but only by departing from the complexity and weight of real-world decision-making experiences. Future research with larger samples and a prospective design will be able to ascertain the relationship between the specifics of the informed consent discussion and parental, child and physician recollection. Third, we interviewed only parents and children who were willing to participate in the study. This may have resulted in an overrepresentation of families who had outspoken ideas on patient-parent-physician interaction or who had encountered substantial differences between family and professional views on the research topics. Although this kind of bias constitutes a well-known pitfall for quantitative methodology, in qualitative research it poses less of a problem, as our aim was to explore the moral content of experiences in decision making in pediatric oncology, and we were not so interested in quantifying the variety of experiences in statistics. Finally, there could be a regional bias in the results, because the study is based on respondents from only two of the eight hospitals in our country where children with cancer are treated. However, the group of respondents was diverse in its social demographics and well spread over the western part of the country. For our purpose to explore the moral experiences of families and physicians, the interviews were saturated

with participants from various moral backgrounds. The only group missing were immigrants (with limited comprehension of the Dutch language). Furthermore, the topic was compact enough to reach saturation across the sample: during the last interviews, no new information was yielded.

Eventually, one central question remains: can our results be generalized to pediatric oncology in general and even pediatrics in general?

Generalizability refers to the applicability of findings to settings and contexts different from the one in which they were obtained. The goal of our RE, however, and thus of the use of empirical data herein, is firstly to understand what is happening in a concrete situation of decision-making. The equilibrium reached does not exist outside this concrete situation, since the description of and experiences within the context of the situation are an integral part of the equilibrium. In that sense, speaking of generalizability within our use of RE is a bit odd. As described in chapter 2, the RE enterprise is continuous work in progress, in which we readjust an equilibrium reached whenever new data come along. Although the results of the RE in terms of a moral framework - e.g. how principles like the respect for autonomy are experienced, used and evaluated by the actors – cannot be generalized, the construct of the RE can prove to be an adequate instrument in the ethics of decision-making in pediatric oncological care. Our empirical data are robust enough to be used in a RE, and can also be the starting point to develop our understanding of the use of the concepts of best interests, child participation and parental authority in the concrete context of pediatric oncology. This understanding can subsequently be used as a new starting point, a so-called hypothetical equilibrium (see chapter 2) for reaching a new empirical reflective equilibrium, after obtaining new empirical data in other pediatric contexts. The process which evolves could imply that we end up with an unworkable situation, in which we are ad infinitum looking for a new equilibrium. By using the 'Third Person' perspective, which implies mainly a rationalization of the RE that has been reached, we however arrive at a relatively stable framework, which stands until new empirical data force us to rethink the equilibrium. In that sense parallels can be made with the falsifiability principle of Karl Popper (1959). Knowledge is irreducibly hypothetical, including moral knowledge, and we have to look for data that contradict it. In other words, as long as our empirical reflective equilibrium is not totally shaken, stirred or refuted, it stands as an understanding of the use of the concepts of best interests, child participation and parental authority.

DISCUSSION OF RESULTS

Best interests, child participation and parental authority

This thesis has highlighted several issues which combined show the shapes that the concepts of best interests, parental authority and child participation take in pediatric oncology. In every chapter, we confronted the experiences of relevant actors, collected in our interview study, with existing theoretical ethical concepts about pediatrics and child welfare. In other words, the theoretical ethical concepts were the starting point and were subsequently enriched by the emergent themes from the interviews. The experiences of parents, children and physicians give us unique insights in pediatric oncology practice and the way ethical concepts function in this practice. Because we use empirical findings we come much closer to the reality of the ethical challenges faced than a theoretical view could.

Central themes that emerged from the interviews were:

1) *The nature of the pediatric oncology practice, with its almost complete integration of research and treatment*. In this context, it is a demanding requirement to bring diverse moral commitments together, like putting the patient's interests first, clinical equipoise, generation of new knowledge, true informed consent and voluntariness.
2) *Interpretations of best interests*. In the course of a long treatment, 'what is best for the child' is subject to change, and for families, the answer encompasses spheres other than the medical. It includes parts of the life perspectives of parents and child.
3) *Difficulties to demarcate parental authority to balance future and present interests in decision making*. Sometimes parental authority goes no further than to guide a child to adulthood with as many opportunities open as possible. In other situations, parents have substantial discretion to act on personal views.
4) *Difficulties to ascribe decision making capacities to children*. The same adolescent in one situation can be deemed capable and in another situation incapable of decision making.

In what follows we will take these themes together and try to integrate them in a reflective equilibrium.

The concept of the child's best interest at the interface of clinical care and research

The 'best interest' standard has become the prevailing standard in pediatric decision-making (Kopelman 1997). Like most of bioethics' ventures, best interests can be formulated in ways that sound appropriate or even compelling. However, as shown in chapter 5, close examination of the standard reveals significant problems with its definition and application in practice.

There have been many attempts to formulate 'objective' criteria for the best interest standard in pediatrics. Some authors claim that every child has a right to reach adulthood with as many opportunities left open as possible. Maintaining future options is a well-known theme in pediatric ethics, and various authors have argued that physicians and parents act unethically if they make choices that constrain a child's range of future options (Feinberg 1992; Davis 2001). Feinberg (1992) proposed recognition of a child's 'right to an open future', in which a child has a right 'while he is still a child [ ] to have [ ] future options kept open until he is a fully formed self-determining adult capable of deciding among them'. Feinberg's 'right to an open future' relies upon giving the child the opportunity to take advantage of those talents that her genetic traits, her 'initial bias from heredity' confer. In chapter 7 on discussing fertility issues with male adolescents diagnosed with cancer, we showed an example of using the child's right to an open future. In our interviews, physicians stated that they would always discuss fertility preservation, because they wanted to maintain future options for the adolescent.

Other authors, like Kopelman (1997; 2010) describe the best interest standard as a standard of reasonableness. The best interest standard 'requires us to focus on the child and select wisely from among alternatives, while taking into account how our lives are woven together. It instructs us to try and pick the option that most informed, rational people of good will would regard as maximizing the child's net benefits and minimizing the net harms to the child without ignoring the rights, needs, and interests of others.' (Kopelman 1997)

However, calling on an uncertain future or on 'informed, rational people of good will' still does not solve the problem of what the best interest standard should require when the actual clinical practice is so maddeningly complex and varied as is pediatric oncology. First, chapter 3 showed that in pediatric oncology there is an unprecedented integration of research and care, which leads to an intertwinement between patient interests and research interests. In this setting, uncertainty (for example, over which arm one will be randomized in) is a new dimension. Furthermore, the starting point of treatment within a research setting is what children have in common, not how they differ. Parents' role on the other hand is to promote *their* child's best interests, also when they are asked to consider enrolling their child in a trial. Parents are almost never in equipoise on trial participation, which leaves them with the agonizing situation of wanting to do what is best for their child, while being fearful of making the wrong decision. Furthermore, a therapeutic misconception endangers correct assessment of participation, making parents inaccurately attribute therapeutic intent to research procedures. Chapter 3 and 6 showed that

physicians prefer the perspective of a therapist over a researcher. Consequently they may truly believe that in the research setting they promote the child's best interests, which maintains the existence of a therapeutic misconception between them and parents.

Second, chapter 5 showed that in the course of a pediatric oncology treatment we can distinguish a medical and a patient-family domain. At that point, the notion of best interests turns out to inherently be a matter of balancing different values, and not only of medical judgment. In the course of treatment, as the initial shock of diagnosis subsides, children and parents begin to more actively participate in decision-making. Parents no longer focus only on the protocol, and the way children are generally treated, but also on their child with his or her own ways to cope with the situation. This leads to a re-evaluation of what they think is important. The interpretation of what constitutes best interests starts to contain more than only the medical perspective. Parents discover that their child's interests are also affected by control over certain aspects of care (e.g., nutrition), the wish to lead a life as normal as possible (e.g., particulars in upbringing and schooling), and the wish to maintain one's identity and family values (e.g., through religion). These values can sometimes collide with medical protocols, leading to different professional and family views as to what course of action is appropriate.

Third, chapter 7 showed that, when thinking about the interests of a child, there is always a friction between future and present needs, which is not so easily settled, even when future needs seem evident, like fertility preservation.

In conclusion, the pediatric oncology context is so complex that it depends on the point of view one takes (research versus treatment, medical versus personal, future versus present), how one interprets what is in the interest of the child. And every point of view can be refuted or put in perspective by another point of view. Only a comprehensive analysis of all points of view gives insight in what best interests can mean in the pediatric oncology practice. In short, and to phrase Hegel (2000): 'Das Wahre ist das Ganze'.

In adult medicine, multiple models have been proposed to resolve disagreement over what constitutes the best interest of the patient, including informed decision making and shared decision making (Bensing 2000; Charles 1997). Both these models use an ethical paradigm in which the principle of respect for autonomy has general priority to the principle of beneficence. Physicians are expected to respect an adult patient's autonomous wishes to refuse treatment, even if those wishes are not what the physician thinks is in that patient's medical interests. This 'adult' paradigm puts a strong focus on patient participation in clinical decision making by taking into account the patients' perspective, and tuning medical care to the patients' needs and preferences (Bensing 2000).

In contrast, in the 'pediatric' paradigm, the principle of beneficence has general priority to the principle of respect for autonomy (Miller 2003, p 2-3). However, since the complexity of the context and our pluralistic beliefs about child-rearing and child welfare do not lead to a uniform interpretation of what is in the best interests of the child, also in the 'pediatric' paradigm we need to find a way to discuss the weight of various perspectives, and to give guidance as to *how* a decision should be reached, which considerations apply, and how future, as yet unknown life perspectives should be weighed.

To do that, we need to discuss the various ways to look at parental discretion and child participation.

How far does parental discretion go? Parental authority and physicians' professional autonomy

The family is a cardinal moral institution and a major source of moral as well as bioethical controversy (Wang *et al* 2010). It seems obvious to state that the primary responsibility of parents is to care for and to protect their children, and that parents are devoted to promote the interests of their children. Some philosophers therefore state that parental authority can only be instrumental to the best interest of the child. This interpretation can already be found in Kant's philosophy (Kant 1986). According to Kant, a child is not the property of parents. Parents cannot freely decide over their children, but have the duty to provide for and take care of their children. Their rights as parents derive from this duty to care: they have the right to keep the child with them and raise it. Childhood is defined as a passing phase of impaired maturity.

'Der Mensch aber braucht eigene Vernunft. Er hat keinen Instinkt und muß sich selbst den Plan seines Verhaltens machen. Weil er aber nicht sogleich imstande ist, dieses zu tun, sondern roh auf die Welt kommt, so müssen es andere für ihn tun.' (Kant 2005, p697)

It is in the interest of the child to be disciplined, cultivated, civilized and moralized to grow into maturity (Schapiro 1999). The possible wishes and desires of parents are only dealt with indirectly, as far as they promote or harm the interests of the child.

Other thinkers share this view. Dupuis (Dupuis 1991, p175) for example states that the aim of parental authority is to guide a child to self-determination, not to assign an inalienable dispositional right over their children. And Leenen (2007, p168) adds: parental authority exists not for the sake of the parents, but for the very reason to protect the child. In the early eighties, Feinberg (1992) developed his, abovementioned, influential theory on 'the right to an open future'. It was a reaction on the US Supreme Court decision that permitted the Amish, a self-sufficient religious farming community in America,

to end their children's public schooling at 14, two years short of the legal limit. According to the Amish, sending their children to public schools would undermine their community as they would be influenced by the modern secular world. The Court majority accepted the Amish argument that the continued existence of their 19th century religious farming community was at stake: if their children attended public high school, they would be less likely and less able to take up their roles in the community. Feinberg criticized the US Supreme Court decision. He argued that the Amish violate their children's 'right to an open future,' namely, the right to be 'permitted to reach maturity with as many open options, opportunities, and advantages as possible.' This complex right has as its general basis the right to autonomy or self-determination, that is, 'the sovereign authority to govern oneself, which is absolute within one's own moral boundaries'. The child's right to autonomy is a right-in-trust, to be fully granted when a child has developed the capacities necessary for its exercise. On this view, it is a principal parental duty to help a child to develop the capacity for autonomy, and in that sense parenthood is only instrumental to reaching the goal of self-determination, with as many options open as possible. In Feinberg's footsteps, Davis (1997) formulated it as follows: 'All parenthood exists as a balance between fulfillment of parental hopes and values and the individual flowering of the actual child in his or her own direction. (...) Good parenthood requires a balance between having a child for our own sakes and being open to the moral reality of that the child will exist for her own sake, with her own talents and weaknesses, propensities and interests, and with her own life to make'. In chapter 7 we showed an example of describing parental tasks as instrumental to the child's right to an open future. When the moral focus is on preserving as many options as possible for the future child, then the physician's task is to do all that is possible to protect a child's future health, using only medical facts as starting point for proposed treatments. In these situations the pediatrician's responsibility to his or her patient exists independently of parental desires or proxy consent (Committee on Bioethics 1995).

Other authors repudiate the thought that parental authority is only instrumental. Schoeman (1985) claims in this context that: 'Certain decisions seem legitimate when made within the context of a family, even though they seem to violate the liberal principles for treating incompetents'. And: 'the family is to be thought of as an intimate arrangement with its own goals and purposes. It is inappropriate to impose upon that arrangement abstract liberal principles'. A family has his own complex of values, relationships and goals that is highly autonomous. In the discussion in the early eighties on the schooling of Amish children, the American philosopher William Ruddick came to a nuanced conclusion. He did not support either the Amish viewpoint, since it gives parents too

much power over their children's future lives, nor Feinberg's right to an open future, that gives parents too little power (Ruddick 1988). To steer between the parental extremes of parental self-perpetuation and parental self-denial, Ruddick developed a family-centred use of the best interest standard, the 'Life Prospect Principle' (Ruddick 1988). In his theory he uses an analogy of gardener and guardian when talking about parents and the way they have to fill in the interests of their child. The gardening analogy reflects the fact that a child is a parent's product, the result of intentional effort, but a product with the unique capacity to become the equal of its producers. Hence, child-producers may not treat children as if they were and would remain artifacts or property. Children have the capacity for becoming autonomous beings, and a presumed interest in becoming that imposes restraints on their producers and requires protection. Hence, the virtue of the (legal) metaphor of parents as guardians. A parent is, as it were, a Guardian-Gardener, a provider of 'life prospects'. This reflects a child's product-origin and its autonomous future, while respecting parental productive hopes (Ruddick 1979). A child cannot be fully distinguished from his parents and surroundings. 'In short, there are no criteria for individuating child from parent, or for defining the beginning or end of parenthood and childhood. In various respects at various times, parent and child are not distinct individuals' (Ruddick 1979, p124). That means that we cannot easily use an individual noting of interests. The child's interests are always intertwined with those of his parents. This description fits more with the view on parental authority as described in chapter 5, where we described that families have substantial discretion to act on personal views, as long as their decisions do not fall below a certain threshold of acceptable care. In this view, the physician needs to put medical facts into the context of familial values, and needs to discuss how to weigh the medical facts in this specific context.

Child participation

Children develop powers of self-determination as they mature, and this affects all interactions between adults and young people. Pediatrics is special as compared to other specialties that deal with incompetence (like geriatrics) in the hope that the incompetence ends, and in the investment in bringing a child to competence.

Several studies have assessed and reviewed children's capacity to participate in medical decision making (Dorn *et al* 1995, Mårtenson and Fägerskiöld 2008, Ondrusek *et al* 1998). The data on this topic have been ambiguous. All that these studies suggest is that the major period of rapid change and individual variability in children's capacities occurs between age 9 and 14 years. Some have concluded that relatively young children can participate meaningfully in the assent process (Committee on Bioethics 1995), whereas others raise doubts about what children can understand (Wendler and Shah 2003; Par-

tridge 2010). When interpreting these studies, it is important to realize that the way in which researchers define assent drives their conclusions. It greatly depends on the capacities one requires for children to be deemed capable of providing assent (Miller and Nelson 2006). The closer the definition of these capacities comes to the capacities needed to be an ideal adult, the older the child will be before it can meet the criteria. In fact, it also depends on the broader social context of ascribing moral capacities and rights to children (James and Prout 1990; James *et al* 1998; Jenks 1996). Childhood as an institution (not individual children) is a set of beliefs and practices determining how children are treated and how they respond (Hilliard 1981). It differs radically in time and place; individuals aged twelve years are treated as responsible adults in one society and as fairly helpless dependants in another. Beliefs about childhood influence assessment of competence and also whether adults inform children and encourage them to take decisions, and whether children want and feel able to learn, choose and act. The care of children in hospitals is affected as much by changing beliefs about childhood, as by the changing medico-legal context (Alderson 1996).

Our study confirmed that it is not so straightforward to ascribe decision making capacities to children, even though the Netherlands have specific regulations that stipulate the age at which minors should be involved in decision-making concerning their treatment (Ministry of Health 1995). In chapter 7 on discussing infertility risks and semen cryopreservation with adolescents, physicians in general deemed the adolescent capable of participating in these discussions. In chapter 6 on involving adolescents in decision making concerning research participation, however, physicians deemed (the same!) adolescent incapable of participating in these discussions, even leading to the provision of a lower level of information to adolescents than to their parents. In both situations, physicians seem to be directed by their interpretation of what is in the best interest of the child in the concrete context at hand. Concerning research, physicians deemed research protocols in the best interest of their patients, and therefore they were confident to include an adolescent in a trial. Physicians recognized that the intense emotional context in which decision-making occurred, the extremely complex research protocols being explained to families, and the relatively short time frame during which treatment decisions had to be made introduced barriers to integrating adolescents into decision-making. Physicians therefore used attention to the best interest (also ensured by proxy consent and investigator integrity) as a substitute for the adolescent's true consent. Quite the reverse, in the context of fertility discussions, physicians used their interpretation of what is in the best interest of the child (namely future fertility preservation) as a reason for *involving* adolescents in the decision making process, even though the topic was delicate.

In chapter 7 we described the term strategic control: the parental control over physician-child communication. Parents tend to filter and modulate what children are told by their physicians, relegating children to a passive role in medical decision making. Literature shows that physicians normally deem this mode of communication acceptable (Levetown 2008). Chapter 6 shows that for research discussions physicians use the same 'strategic control', when informing adolescents. Other studies in pediatric oncology describe the same tendency from physicians to protect children from too much information (Olechnowicz *et al* 2002; Young *et al* 2003). In other words, parents and physicians determine the ways to encounter the child, whether to involve the child in the decision-making process and the information given to the child.

Concluding, in the complex, emotional practice of pediatric oncology, there seems to be a constant weighing by physicians of burdens versus benefits in involving adolescents in decision making. This explains why the same adolescent in one situation can be deemed capable and in another situation incapable of decision making. In pediatric oncology, respect for adolescents accounts for their developing capacities as well as their vulnerability due to their illness and the emotional situation they are in.

A uniform decision making framework: the moral landscape of pediatric oncology

We can conclude from the above paragraphs that in the case of parental authority, physician's professional autonomy and child participation there are different points of view. Again, as was the case with the interpretation of best interests, it depends on the concrete context which view is acceptable. Due to the complexity of the pediatric oncology context and due to our pluralistic beliefs about child development, child-rearing, child welfare and parental discretion herein, we cannot present a uniform interpretation of what is in the best interest of the child and how far child participation and parental discretion should go. Using RE, we may however come to a uniform *decision making framework*. Our RE framework describes the moral landscape of pediatric oncology as a complex interaction between seemingly incompatible viewpoints: research versus treatment, medical versus personal, technological perfection versus communication skills, future versus present, family versus individual, competent versus incompetent. In this moral landscape, physicians are challenged to provide medically effective care while respecting the wishes of the parents and children involved. Inevitably there are conflicts. Some conflicts are minor and would be resolved by more compassion or flexibility on the part of physicians (for instance, more respect for family beliefs and values), and by a similar adjustment on the part of the parents and children. Some conflicts are severe, as when parents refuse lifesaving therapy. These are discussed in chapter 5. And some conflicts are in the middle zone, raising challenging questions of which decision should

be taken when doctors and families disagree. As described in chapter 5, in these middle zone situations, the model of 'communicative ethics' can guide us. The aim of communicative ethics, as described by Moody (1992), is that all parties involved, including the patient (when possible), come to an agreement about shared goals and talk about decisions to be made. The emergence of personal views that are potentially different from the professional perspective can be recognized, understood, and, if necessary, dealt with (Coyne 2007). The various viewpoints are given a prima facie character (Beauchamp and Childress 2009, p14; Kopelman 1997, p276). We can (almost) never assume a completely clear-cut scenario in which one viewpoint prevails. As stated above, even the basic rules 'put the patient's interests first' or 'child participation needs to be encouraged' are not absolute when we consider the moral landscape of pediatric oncology. It is an acceptable starting premise, a *hypothetical* equilibrium, but not acceptable as final conclusion. For a final conclusion we need to weigh it against other viewpoints. It is a demanding requirement first to identify and then bring together the diverse moral commitments that function in pediatric oncology. Sometimes an external party (for example an ethicist) is needed to function as the 'thinker' and to make the moral landscape explicit, and position the various viewpoints.

Due to the complex and high-tech character of oncology treatments the physician has a substantial role in the decision-making process. Parents and children can be reluctant to act as advocates for their own views in this setting (Young *et al* 2002). To recognize the personal views of parents and children, physicians need to actively discuss parents' preferences, customs, and concerns, especially in circumstances when there are tradeoffs possibly involving individual values and preferences (Elliston 2007; Hardart 2000; Tan 2002; Whitney *et al* 2006). The physician can also discuss limits to these wishes, as long as mutual understanding, awareness, and reasoning are maintained (D'Aloja *et al* 2010; Bensing 2000; Kai 1996). Eventually, it is the duty of all actors to reach consensus about what course of action is appropriate. When someone's view is outweighed or overridden, it does not simply disappear. It leaves a 'moral trace' (Beauchamp and Childress 2009, p16), which should be reflected in the course of action eventually taken. A 'communicative ethics' structured in this way leads to a shared decision in which the contribution of all actors is considered. Furthermore, in our RE the third person moral experiences are rationalized in a way that remains focused on the specific context, while at the same time makes it open for accountability to people who were not involved in the decision making process.

CONCLUSION

There is still a great deal to learn about the complex processes that underlie joint decision-making in the context of pediatrics. Process-oriented qualitative methodologies, such as those employed in this thesis, lend themselves well to an examination of the multiple factors that contribute to this decision-making.

The moral landscape drafted in our RE can prove to be an adequate instrument in the ethics of decision-making in pediatric oncological care, and maybe in pediatric care in general. When the shared intention to act in the best interest of the child is based on a decision making framework that understands it as a matter that comes about in true consultation, the decision making process can nurture and enlarge children's and parents' understanding, trust and confidence, through the sharing and transferring of insights and responsibilities between physicians, children and parents.

FUTURE RESEARCH

The empirical reflective equilibrium we reached gave us an understanding of the use of the concepts of best interests, child participation and parental authority in the concrete context of pediatric oncology. As mentioned, this understanding can subsequently be used as a new starting point, the so-called hypothetical equilibrium for reaching a new empirical reflective equilibrium. We therefore need to obtain novel empirical data in other pediatric treatment and research contexts. We are currently gathering new empirical data from children who are asked to participate in medical research to answer the question whether these children can and want to be approached as moral subjects concerning research participation. These data can subsequently modify our hypothetical RE about child participation in research. We are planning a new empirical study on the ethical issues regarding puberty suppression in adolescents with gender identity disorder. The data gathered in this study will give us insight in whether children are competent to make far-reaching decisions, the role of parents and the role of society to define illness and health.

Not only new research will inform our RE. In the future we will also need to be aware of new realities, like the development of 'personalized' medicine, and the impact of whole-genome sequencing technology. All these realities will influence a future equilibrium reached.

Eventually, the aim of future projects and modifications of our RE will be to develop a stable decision making tool which incorporates the best interest standard, parental authority and child participation, and is practical in a wide range of treatment decisions.

Chapter 9

SUMMARY

Few medical specialties encounter so many ethical challenges as pediatrics does. It is a specialty that inherently has features that are morally charged. Pediatric ethics examines the broad issues of (1) the concept of the child's best interest; (2) parental responsibility and authority in decision-making about the life and health of a child; (3) the emerging desire and capacity for self-determination of an older child, and (4) the professional obligation of a pediatrician to act in the best interests of the child. Much is written about these issues, but often the literature on these topics is either 'academic' and theoretical in nature, or casuistic. It remains difficult to utilize what is written in the reality of pediatric practice. In this thesis we reflect on the question how the concepts of best interests, parental authority and child participation can and should be translated and made operational in the everyday encounter between parents, physicians and children. We therefore combine theoretical conceptions of the best interest standard, child participation and parental authority with a close look on how these concepts actually function in pediatric practice, and how they are conceived by actors in the pediatric field. Taking the view that people's actual moral beliefs, intuitions, experiences and reasoning in a (medical) practice yields information which is meaningful for the operationalization of ethical concepts, we refine an existing empirical ethical methodology that successfully combines empirical research and ethical reflection, namely Reflective Equilibrium. Subsequently, we use this methodology to study one specific pediatric medical practice, namely pediatric oncology. Our goal is to describe in detail the forms that the concepts of best interests, child participation and parental authority take in the studied pediatric oncology practice. Furthermore, we reflect on the question whether the insights gained in this particular research setting can be translated to pediatric oncology in general and, where possible and appropriate, even to pediatrics in general.

Chapter 1 gives a general introduction to the thesis. We describe the philosophical quintessence of pediatrics and the aims of the thesis. We subsequently explain our reasons to use an empirical ethical approach. Empirical ethics denies the structural incompatibility of empirical and normative approaches, and believes in their fundamental complementarity. It is an answer to the critique of bioethics for being too abstract, too general, too dogmatic, too top-down as well as too far removed from clinical reality, insensitive to the peculiarities of specific situations. The alliance with practice is a prerequisite for practicing ethics well-informed and pro-actively and for avoiding armchair philosophy. Attention to the experienced reality of pediatric practice however raises the question how to integrate experiences from clinical practice in ethical theory and analysis. Although intuitions and experiences are highly valuable as moral markers, it is generally stated that in ethics they need to be subjected to systematic, rational analysis in order to prevent

violation of the so-called 'fact-value distinction'. In other words, if one wants to use information from practice, one needs to reflect on the methodology applied to integrate this information in normative-ethical analysis and decision making. This reflection is done in chapter 2, in which we justify the use of Reflective Equilibrium.

We end chapter 1 with a description of the pediatric oncology practice and of the interview study, which produced the empirical data we incorporate in our reflective thinking. Our interview study comprised a qualitative multicenter project in which we explored patients', parents' and physicians' experiences with the informed-consent process for treatment and research decisions in pediatric oncology. We invited patients (aged 8-18 years; n=24) attending the pediatric oncology units of two Dutch university hospitals, and their parents (n=26), to participate in semi-structured in depth interviews about the informed consent process. We also interviewed all pediatric oncologists (n=15) from the two hospitals.

Chapter 2 describes our methodology of Reflective Equilibrium (RE) in detail. First, we discuss the use of RE as method of justification in ethics. RE tries to facilitate a real dialogue between theory and practice by not assigning a preferential status to either of them. Considerations on different levels of abstraction have an equal status at the start of the ethical enterprise. Justification is a reflective testing of our moral beliefs, moral principles, theoretical postulates, and other elements, to make them as coherent as possible. Coherence is achieved by an interaction between the different elements in RE, which can have an effect on all these elements. Thus, some elements need to be altered or removed, others kept. The equilibrium reached is a dynamic one; it can change due to new elements in the reasoning process. In RE the reasoning is normally done by one individual, whom we will call: 'the thinker'.

Second, we describe the adjustments we made to the traditional RE method, to come to our own methodology: the Network Model with Third Person Moral Experiences. In this model, empirical data, namely the moral experiences of the various actors in a practice, are added to the elements used in reflective thinking. We explain the need to include empirical data in RE (especially third-person experiences): one reduces the risk of self-justification, prejudiced judgments and bias by the 'thinker', and subsequently increases the credibility of the RE reached. The risk of self-justification is one of the main weaknesses of the RE model: coherence is not a sufficient guarantee for credibility or moral truth. By including third-person experiences, one reduces the risk of self-justification in two ways: since the experiences of many are brought into the RE process, there is a good chance of getting a pluralistic view on the matter at hand. Furthermore, minority positions can also gain attention in the process of reasoning. The process of weighing and

balancing judgments, principles, background theories and empirical data can let us identify judgments that are apparently wrong or prejudiced. In this way, the RE process itself can function as a filter, which can separate reliable from unreliable judgments of the 'thinker'. The 'thinker' consequently gains a distanced view, while remaining attached to the concrete situation. The Network Model with Third Persons Experiences gives the opportunity for the 'thinker' to stay susceptible to a wide range of experiences and facts, and to accept that his own judgments can change due to the RE process (the so-called 'conversion').

Chapter 3 is a theoretical introduction to the ethical concepts studied empirically in chapter 4. Pediatric oncology has a strong research culture. Most pediatric oncologists are investigators involved in both clinical care and research. Consequently, various concepts studied in research ethics are relevant for our investigation. We describe the ethical criteria for valid informed consent: knowledge, competence and voluntariness. We pay extra attention to the concept of therapeutic misconception, i.e. the tendency to mistake the scientific aim of the trial for the therapeutic aim of a treatment. Subjects may have difficulty to recognize that the aim of the trial is to obtain scientific information, and that potential benefits for the subjects themselves are formally a mere by-product of gaining such information. We conclude with the fundamental point of departure in research ethics, namely the important distinction between the treatment relationship which exists between clinician and patient, and the research relationship which exists between researcher and subject.

In *Chapter 4* we discuss the ethical consequences of the unprecedented integration of research and care in pediatric oncology from the perspective of parents and physicians. We use an empirical ethical approach, combining (1) a narrative review of (primarily) qualitative studies on parents' and physicians' experiences of the pediatric oncology research practice, and (2) comparison of these experiences with existing theoretical ethical concepts about (pediatric) research. Analysis of the 22 studies reviewed revealed that the integration of research and care has consequences for the informed consent process, the promotion of the child's best interests, and the role of the physician (doctor vs. scientist). True consent to research is difficult to achieve due to the complexity of research protocols, emotional stress and parents' dependency on their child's physician. Parents' role is to promote their child's best interests, also when they are asked to consider enrolling their child in a trial. Parents are almost never in equipoise on trial participation, which leaves them with the agonizing situation of wanting to do what is best for their child, while being fearful of making the wrong decision. Furthermore, a therapeutic mis-

conception endangers correct assessment of participation, making parents inaccurately attribute therapeutic intent to research procedures. Physicians prefer the perspective of a therapist over a researcher. Consequently they may truly believe that in the research setting they promote the child's best interests, which maintains the existence of a therapeutic misconception between them and parents. We conclude that the challenges that a lack of parental equipoise and the therapeutic misconception pose may be very difficult to overcome. Thorough attention to the quality of communication of research information could improve understanding of the research perspective. We summarize points of awareness with respect to research discussions and give recommendations to improve communication.

Chapter 5 describes the various interpretations by parents, children and physicians of the best interest of the child in the course of a pediatric oncology treatment. In pediatrics, the 'best interest' standard has become the prevailing standard in decision-making. Often there is no discussion about what constitutes this standard. It is used as if its meaning is self-evident and uncontroversial. For a number of reasons, however, the best interest standard proves difficult to apply. We first summarize the various problems with the standard. Subsequently, we describe the most commonly used solution to these problems, namely the definition of the best interest standard as a standard of reasonableness by Loretta Kopelman. This definition states that we must try to pick the option that most informed rational people of good will would regard as maximizing the child's net benefits and minimizing the net harms to the child without ignoring the rights, needs, and interests of others. Used in this way, the best interest standard does not require people to act in accord with what is literally best for a child. Sometimes this means that the least bad alternative for the child should be selected. However, problems can still arise in the use of this standard, namely when reasonable and informed people of good will cannot agree on the interpretation of what is in the best interest of a child. Differences in values can lead to different views by families and physicians of what is in the interest of a child. With our interview study we aimed at gaining insight into the views of parents, children, and physicians in the pediatric oncology setting. The study shows that at the start of treatment children, parents, and physicians have the same view on what is best for the child: being treated according to the best available treatment protocol. Parents and children feel ill-equipped to judge the medical information, and most of the time they let physicians decide on treatment options. Deference to physician authority is a common rule of thumb. The medical view on what is best for a child prevails. In the course of treatment, however, a transition takes place. For families, what constitutes the best interests expands beyond medical considerations, to include the wish to lead a normal life, having

control over certain aspects of treatment, and maintaining one's identity (e.g. through religion). These aspects sometimes collide with medical aspects, leading to different professional and familial views about what course of action is appropriate. When family and professional views differ widely, the question inevitably arises whose perspective should prevail. Integrating the empirical data and theories on shared decision making we present a model of 'communicative ethics' to make the differing views a subject of discussion. In the model of communicative ethics, the various views of what is best for a child are given a prima facie character. It is the duty of all actors to reach consensus about the resulting definition of the best interest of the child. The emergence of personal views that are potentially different from the professional perspective can be recognized, understood, and, if necessary, dealt with.

Chapters 6 and 7 deal with the possibilities of true child participation. *Chapter 6* discusses child participation in decision making concerning research participation. Various regulations and guidelines stipulate the importance of involving adolescents in this decision-making. Literature shows that in the context of pediatric oncology this involvement is difficult to achieve due to emotional stress, the complexity of research protocols and limited time. Still, a remarkable number of adolescents with cancer enter onto a trial during their illness. We performed an empirical study to determine physicians' attitudes towards enrolling adolescents in research and towards involving adolescents in decision making concerning research participation. The physicians' views can be brought together into four themes: (1) physicians regard most adolescents as not capable of participating meaningfully in discussions regarding research; (2) physicians do not always provide adolescents with all information; (3) proxy consent from parents is obtained and is deemed sufficient; (4) physician-investigator integrity: physicians judge research protocols as not being harmful and even in the best interest of the adolescent. In other words, physicians justify not involving adolescents in research discussions by referring to best interest arguments (adolescents' incompetence, proxy consent, and investigator integrity), although this is not in line with legal regulations and ethical guidelines. Integrating theoretical knowledge from research ethics and our empirical data, we argue that the fundamental differences between a research and treatment relationship should be seen as an incentive to truly involve adolescents in decision-making and not simply rely on best interest considerations. Physician-investigators should assess the capabilities of adolescents on a case-to-case basis and, when appropriate, should thoroughly explain the differences between research and standard care.

In *Chapter 7* we present another discussion on child participation in decision making. This time the focus is on parental discretion to regulate information disclosure to their child, thus influencing true child participation. In pediatric oncology, the risk of infertility due to treatment constitutes an important problem. For sexually mature male adolescents, sperm cryopreservation is an option, but discussing the topic is complex because of the sensitive nature and the limited time frame. In our empirical study, both parents and physicians spontaneously mentioned the problem of infertility discussions as an example of involving children in decision making. Although physicians and parents agreed that infertility would have a major impact on the future quality of life, they sometimes disagreed on whether the topic should be discussed with adolescents. Physicians always wanted a separate discussion with adolescents because of the sensitive nature and the experience that parents sometimes misjudged the stage of maturity of their son. Parents, however, wanted control over whether physicians discussed the topic with their child and what was said. Physicians did not accept this control and, when necessary, were willing to bypass the parents and discuss the topic with the adolescent even when parents refused consent. Integrating our empirical data with ethical theories on the child's 'right to an open future', parental authority, and child participation, we conclude that physicians face the difficult task of balancing between their ideas of what is in the (future) interest of the adolescent and accommodating parental wishes. We discuss the concept of 'strategic control': the parental control over physician–child communication. Parents tend to filter and modulate what children are told by their physicians, relegating children to a passive role in medical decision making. Literature shows that physicians normally deem this mode of communication acceptable. Parents and physicians jointly discuss the ways to encounter the child, whether to involve the child in the decision-making process and the information given to the child. We conclude however in the fertility case that, because of the private character of sexuality and the potentially inadequate maturity assessment by parents, semen cryopreservation should be discussed separately with adolescent and parents. In addition, there should be an open communication with parents to address potential discomforts.

Finally, in *Chapter 8* the principal results of this thesis are put into perspective. We focus on two issues. First, we give methodological considerations by answering additional methodological questions, of which the most important is: can our results be generalized to pediatric oncology in general and even pediatrics in general? Generalizability refers to the applicability of findings to settings and contexts different from the one in which they were obtained. The goal of our RE, however, and thus of the use of empirical data herein, is firstly to understand what is happening in a concrete situation of decision-making. The equilibrium reached does not exist outside this concrete situation, since the description

of and experiences within the context of the situation are an integral part of the equilibrium. We conclude therefore that speaking of generalizability within our use of RE is a bit odd. We do argue however, that, by using the 'Third Person' perspective, which implies mainly a rationalization of the RE that has been reached, we arrive at a relatively stable framework, that stands until new empirical data force us to rethink the equilibrium. In that sense parallels can be made with the falsifiability principle of Karl Popper. Knowledge is irreducibly hypothetical, also moral knowledge, and we have to look for data that contradict it. In other words, as long as our empirical reflective equilibrium is not totally shaken, stirred or refuted, it stands as an understanding of the use of the concepts of best interests, child participation and parental authority.

Second, we reflect on the implications of our empirical study for our thinking about child participation, the use of a best interests standard and parental authority. We take the themes from the interviews together and try to integrate them in a reflective equilibrium with existing theories, norms and principles. We conclude that due to the complexity of the pediatric oncology context and due to our pluralistic beliefs about child development, child-rearing, child welfare and parental discretion herein, we cannot present a uniform interpretation of what is in the best interest of the child and how far child participation and parental discretion should go. Using RE, we may however come to a uniform decision making framework. Our RE framework describes the moral landscape of pediatric oncology as a complex interaction between seemingly incompatible viewpoints: research versus treatment, medical versus personal, technological perfection versus communication skills, future versus present, family versus individual, competent versus incompetent. In this moral landscape, physicians are challenged to provide medically effective care while respecting the wishes of the parents and children involved. We can (almost) never assume a completely clear-cut scenario in which one viewpoint prevails. Even the basic rules 'put the patient's interests first' or 'child participation needs to be encouraged' are not absolute when we consider the moral landscape of pediatric oncology. It is an acceptable starting premise, in our methodology: a hypothetical equilibrium, but not tolerable as final conclusion. For a final conclusion we need to weigh it against other viewpoints. It is a demanding requirement first to identify and then bring together the diverse moral commitments that function in pediatric oncology. Sometimes an external party (for example an ethicist) is needed to function as the 'thinker' and to make the moral landscape explicit, and position the various viewpoints. Eventually, when the shared intention to act in the best interest of the child is based on a decision making framework that understands it as a matter that comes about in true consultation, the decision making process can nurture and enlarge children's and parents' understanding, trust and confidence, through the sharing and transferring of insights and responsibilities between physicians, children and parents.

Addendum

REFERENCES

ABBREVIATIONS

SAMENVATTING

CURRICULUM VITAE

DANKWOORD

PUBLICATIONS

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LIST OF ABBREVIATIONS

ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
CCMO	Centrale Commissie Mensgebonden Onderzoek (Central Committee on Research Involving Human Subjects)
CCT	Clinical Controlled Trial
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
HSCT	Haematopoietic Stem Cell Transplantation
MDS	Myelodysplastic Syndrome
NHL	Non-Hodgkin Lymphoma
IRB	Institutional Review Board
RCT	Randomized Controlled Trial
RE	Reflective Equilibrium
SKION	Stichting Kinderoncologie Nederland
WMO	Wet Medisch-wetenschappelijk Onderzoek met Mensen (Medical Research with Human Subjects Act)

SAMENVATTING

In de kindergeneeskunde wordt men bijna dagelijks geconfronteerd met ethische vragen. Het vakgebied heeft unieke kenmerken die maken dat veel behandelbeslissingen ethisch geladen zijn. De kindergeneeskunde houdt zich bezig met de gezondheid en de fysieke en mentale groei en ontwikkeling van ieder kind, vanaf de geboorte tot in de adolescentie, met als uiteindelijke doel zo gezond mogelijke volwassenen af te leveren. Kinderen zijn kwetsbaar en verdienen bescherming. Meestal zijn het de ouders die in de medische setting opkomen voor de belangen van hun kind. Soms ontstaat echter twijfel of de ouders die belangen wel juist zien en of ze de beste vertegenwoordigers zijn van hun kind. Kinderen zijn ook in ontwikkeling en verdienen op een gegeven moment de vrijheid om zelf te beslissen over hun lijf en leven. Maar kunnen ze dat altijd even goed? De ethiek van de kindergeneeskunde houdt zich bezig met vragen over de interpretatie van wat goed is voor een kind, de grenzen van de ouderlijke macht en de grenzen van professionele bemoeienis. Kort maar krachtig gezegd onderzoekt zij de volgende kwesties: (1) wat moeten we verstaan onder het belang van het kind; (2) hoever reiken de ouderlijke verantwoordelijkheid en het ouderlijk gezag om beslissingen te nemen over leven en gezondheid van een kind; (3) hoe moeten we omgaan met het toenemende vermogen en verlangen van oudere kinderen tot zelfbeschikking, en (4) hoever reikt de professionele plicht van de kinderarts om in het belang van het kind te handelen?

Er is veel over deze kwesties geschreven, maar de literatuur is vaak ofwel te theoretisch, ofwel juist te casuïstisch. Het blijft daardoor moeilijk om het geschrevene toe te passen in de alledaagse kindergeneeskundige praktijk. Dit proefschrift draait om de vraag hoe we de concepten ‘het belang van het kind’, ‘ouderlijke macht’ en ‘kindparticipatie’ kunnen vertalen en bruikbaar kunnen maken in de dagelijkse ontmoetingen tussen artsen, ouders en kinderen. Om die vraag te beantwoorden combineren we theoretische noties van het belang van het kind, kindparticipatie en ouderlijke macht met een nauwkeurige beschrijving van de manier waarop deze concepten daadwerkelijk functioneren in de kindergeneeskundige praktijk en hoe ze worden geïnterpreteerd door de verschillende actoren in het kindergeneeskundige veld. Het uitgangspunt daarbij is de overtuiging dat de ervaringen, intuïties en gedachten van mensen in een (medische) praktijk informatie opleveren die van toegevoegde waarde is bij het bruikbaar maken van ethische concepten. In dit proefschrift verfijnen we een al bestaande empirische ethische methode die empirische data (de ervaringen, intuïties en gedachten) combineert met ethische reflectie, namelijk het Reflectief Evenwicht. Vervolgens passen we deze methode toe in een specifieke kindergeneeskundige praktijk, te weten de kinderoncologie. Ons doel daarbij is om in detail de vormen te beschrijven die de concepten het belang van het kind, kind-

participatie en ouderlijke macht aannemen in de kinderoncologische praktijk. Bovendien reflecteren we op de vraag of de inzichten die we in deze research setting verkrijgen ook vertaald kunnen worden naar de kinderoncologie in het algemeen en eventueel zelfs naar de kindergeneeskunde in het algemeen.

Hoofdstuk 1 is een algemene introductie op het proefschrift. We beschrijven de filosofische kwintessens van de kindergeneeskunde en de doelstellingen van het proefschrift. Vervolgens lichten we toe waarom we een empirische ethische methode gebruiken. De empirische ethiek ontkent dat empirische en normatieve benaderingen incompatibel zijn, maar gelooft juist dat ze elkaar aanvullen. De empirische ethiek is het antwoord op de vaak gehoorde kritiek dat de bioethiek te abstract, te algemeen, te dogmatisch, te top-down, en te ver verwijderd is van de klinische realiteit, ongevoelig voor de bijzonderheden van specifieke situaties. De alliantie met de praktijk is een voorwaarde voor het goed geïnformeerd en proactief praktiseren van de ethiek en voor het vermijden van ivoren-toren filosofie. Het leidt echter ook direct tot de vraag hoe ervaringen uit een klinische praktijk geïntegreerd kunnen worden in een ethische analyse en in ethische theorievorming. Natuurlijk zijn intuïties en ervaringen waardevol als morele markers, maar in de ethiek moeten ze onderworpen worden aan een systematische, rationale analyse om te voorkomen dat men verstrikt raakt in het zogenaamde feit-waarde-probleem. Anders gezegd, als je informatie uit de praktijk wilt gebruiken, moet je ook reflecteren op de toegepaste methodologie om deze informatie te integreren in een normatief-ethische analyse en in besluitvorming. Deze reflectie wordt uitgevoerd in hoofdstuk 2, waarin een rechtvaardiging wordt gegeven voor het gebruik van Reflectief Evenwicht als methode.

Hoofdstuk 1 eindigt met een beschrijving van de kinderoncologie en van de interviewstudie die de empirische data opleverde om te integreren in ons reflectief denken. De interviewstudie betrof een kwalitatief multicenter project waarin we de ervaringen van kinderen, ouders en artsen hebben verkend met de informed-consentprocedure voor behandeling en wetenschappelijk onderzoek in de kinderoncologie. We nodigden kinderen (leeftijd 8-18 jaar; n=24) uit die behandeld werden op de afdeling kinderoncologie van twee Nederlandse Academische ziekenhuizen om deel te nemen aan semigestructureerde diepte-interviews. We interviewden ook de ouders van deze kinderen (n=26) en alle kinderoncologen van de twee ziekenhuizen (n=15).

Hoofdstuk 2 beschrijft in detail onze methode, het Reflectief Evenwicht (RE). Allereerst bespreken we het gebruik van RE als rechtvaardigingsmethode in de ethiek. RE probeert een echte dialoog te bewerkstelligen tussen theorie en praktijk door geen van de twee een voorkeursstatus te verlenen. Overwegingen op verschillende niveaus van abstractie

hebben een gelijke status aan het begin van de ethische onderneming. Volgens het RE ligt de rechtvaardiging van morele uitspraken in een reflectief testen en coherent maken van onze morele intuïties, morele principes, theoretische postulaten en andere elementen. Coherentie wordt bereikt door een interactie tussen de verschillende elementen in RE, waarbij deze interactie een effect kan hebben op al deze elementen. Sommige zullen veranderd of verwijderd moeten worden, andere juist behouden. Het evenwicht dat wordt bereikt is dynamisch; het kan veranderen ten gevolge van nieuwe elementen in het redeneerproces. In RE wordt het redeneren over het algemeen uitgevoerd door één individu, genaamd 'de Denker'.

Vervolgens beschrijven we de aanpassingen die we hebben gemaakt op de gangbare RE-methode om te komen tot onze eigen methodologie: Het Netwerk Model met Morele Ervaringen van Derden. In dit model worden empirische data, namelijk de morele ervaringen van verschillende actoren in een praktijk, toegevoegd aan de al bestaande elementen uit het reflectief denken in RE. We leggen uit waarom deze empirische data nodig zijn in RE: hiermee wordt de kans op zelfrechtvaardiging verminderd en worden vooringenomen oordelen en bias bij 'de Denker' voorkomen. Uiteindelijk leidt dit tot een toename van de geloofwaardigheid van het bereikte reflectief evenwicht. Vooral het risico op zelfrechtvaardiging is een van de voornaamste zwakten van het RE-model: coherentie is niet een voldoende garantie voor geloofwaardigheid en morele waarheid. Door de ervaringen van derden toe te voegen verkleint men de kans op zelfrechtvaardiging op twee manieren. Aangezien de ervaringen van velen in het RE-proces worden ingebracht, is de kans groot dat er een pluralistische kijk op het bestudeerde onderwerp ontstaat. Bovendien krijgen minderheidsstandpunten ook aandacht in het redeneerproces. Het proces van afwegen en balanceren van oordelen, principes, achtergrondtheorieën en empirische data zorgt ervoor dat we oordelen herkennen die kennelijk verkeerd of bevooroordeeld zijn. Op deze manier functioneert het RE-proces als een filter, dat geloofwaardige van ongeloofwaardige oordelen van 'de Denker' kan onderscheiden. Dientengevolge verkrijgt 'de Denker' een afstandelijk gezichtspunt, maar blijft tegelijkertijd verbonden met de concrete situatie. Het Netwerk Model met Morele Ervaringen van Derden geeft 'de Denker' de mogelijkheid om gevoelig te blijven voor een diversiteit aan ervaringen en feiten, en om zijn eigen oordeel te veranderen door het RE-proces (de zogenaamde 'conversie').

Hoofdstuk 3 is een theoretische inleiding op de ethische concepten die empirisch bestudeerd worden in hoofdstuk 4. De kinderoncologie kent een sterke onderzoekscultuur. De meeste kinderoncologen zijn ook onderzoekers en betrokken bij zowel klinische zorg als wetenschappelijk onderzoek. Dientengevolge zijn verscheidene concepten die

bestudeerd worden binnen het vakgebied van de onderzoeksethiek ook relevant voor onze onderneming. We beschrijven de ethische criteria voor een valide informed consent: kennis, wilsbekwaamheid en vrijwilligheid. We besteden extra aandacht aan het concept 'therapeutische misvatting', de tendens om de wetenschappelijke oriëntatie van het onderzoek te verwarren met de therapeutische oriëntatie van een behandeling. De therapeutische misvatting werd voor het eerst beschreven in 1982 als de misvatting dat deelname aan een wetenschappelijk onderzoek hetzelfde is als het krijgen van een door een arts op de persoon afgestemde behandeling. Proefpersonen kunnen moeite hebben om in te zien dat het doel van het onderzoek is om wetenschappelijke kennis te verkrijgen; zij kunnen soms moeilijk inzien dat eventueel voordeel voor de proefpersoon zelf formeel slechts een 'bijproduct' van die kennis is.

We eindigen met het beschrijven van het belangrijkste uitgangspunt in de onderzoeksethiek, namelijk de gedachte dat er een fundamenteel verschil is tussen de behandelrelatie (tussen arts en patiënt) en de onderzoeksrelatie (tussen onderzoeker en proefpersoon).

H*oofdstuk 4* beschrijft de ethische consequenties van de ongekende integratie van wetenschappelijk onderzoek en zorg in de kinderoncologie vanuit het perspectief van ouders en artsen. Er wordt gebruik gemaakt van een empirisch-ethische benadering, waarin een narratieve review van (voornamelijk) kwalitatieve studies naar de ervaringen van ouders en artsen met de kinderoncologische onderzoekspraktijk wordt gecombineerd met een vergelijking van deze ervaringen met bestaande theoretische ethische concepten over (pediatrisch) onderzoek.

De analyse van de 22 studies in de review toont aan dat de integratie van research met zorg gevolgen heeft voor de informed-consentprocedure, het behartigen van het belang van het kind, en de rol van de arts (dokter versus wetenschapper). Een valide geïnformeerde toestemming voor onderzoek is moeilijk te verkrijgen door de complexiteit van studieprotocollen, de stress rondom de diagnose kanker en de afhankelijkheid die ouders voelen ten opzichte van de behandelend arts. De rol van ouders is het behartigen van het belang van hun kind, ook wanneer hun wordt gevraagd na te denken over deelname aan wetenschappelijk onderzoek van hun kind. Ouders zijn echter bijna nooit in equipoise over onderzoeksdeelname, waardoor ze zich in de onmogelijke situatie bevinden dat ze die strategie willen kiezen die het beste is voor hun kind, maar steeds angstig zijn dat ze de verkeerde beslissing nemen. Bovendien bedreigt de therapeutische misvatting een juiste beoordeling van onderzoeksdeelname, waarbij ouders onterecht therapeutische intenties toeschrijven aan onderzoekshandelingen.

Artsen handelen over het algemeen meer vanuit het perspectief van dokter dan van onderzoeker. Dit kan tot gevolg hebben dat ze oprecht geloven dat ze binnen een onderzoekssetting het belang van het kind behartigen, waarmee ze het bestaan van een therapeutische misvatting tussen henzelf en ouders in stand houden. We sluiten af met de stelling dat de therapeutische misvatting en het ontbreken van equipoise bij ouders moeilijk te voorkomen zijn. Nauwgezette aandacht voor de kwaliteit van het bespreken van wetenschappelijk onderzoek zou echter wel het begrip voor het research-perspectief kunnen vergroten. Als handvat om de communicatie te verbeteren geven we een opsomming van aandachtspunten die van belang zijn bij het bespreken van wetenschappelijk onderzoek.

Hoofdstuk 5 beschrijft de verschillende interpretaties van het belang van het kind door ouders, artsen en kinderen zelf gedurende de kinderoncologische behandeling.

In de kindergeneeskunde is 'het belang van het kind' de overheersende norm geworden bij behandelbeslissingen. Er is zelden discussie over wat deze norm (of, in het verlengde van het Engels, 'standaard') inhoudt. 'Het belang van het kind' wordt gebruikt alsof de betekenis ervan vanzelfsprekend en onomstreden is. Er zijn echter meerdere redenen waarom deze standaard moeilijk toepasbaar is in de praktijk. We beginnen het hoofdstuk met een samenvatting van de verschillende problemen met de standaard. Vervolgens beschrijven we de meest gebruikte oplossing voor deze problemen, namelijk de definitie door Loretta Kopelman van de standaard als een 'standaard van redelijkheid'. Deze definitie houdt in dat we moeten proberen om die optie te selecteren waarvan de meeste goed geïnformeerde, rationele mensen van goede wil zouden beamen dat deze de meeste netto voordelen heeft en de minste netto schade voor het kind, zonder echter de rechten, behoeften en belangen van anderen te veronachtzamen.

Gebruikt op deze manier, vereist de standaard 'het belang van het kind' niet dat we altijd moeten handelen in overeenstemming met wat letterlijk het beste voor het kind is. Soms betekent het bijvoorbeeld dat het minst slechte alternatief voor het kind gekozen moet worden.

Ondanks deze mooie definitie kunnen er nog steeds problemen ontstaan met het gebruik van de standaard, namelijk als ook rationele en goed geïnformeerde mensen van goede wil het niet eens kunnen worden over wat nu in een specifieke situatie in het belang van het kind is. Verschillen in waarden en levensperspectieven kunnen leiden tot verschillende opvattingen bij ouders, kinderen en artsen over wat nu in het belang van het kind is.

Met onze interviewstudie beoogden we inzicht te verkrijgen in de opvattingen van ouders, kinderen en artsen over het belang van het kind in de kinderoncologische prak-

tijk. Onze studie toont aan dat aan het begin van de behandeling ouders, kinderen en artsen dezelfde ideeën hebben over het belang van het kind, namelijk behandeld worden volgens het beste beschikbare behandelingsprotocol. Ouders en kinderen voelen zich slecht toegerust om de medische informatie te begrijpen en meestal laten ze de behandelbeslissingen over aan artsen. Het zich voegen naar de autoriteit van de arts is eerder regel dan uitzondering. Versterkt door het medisch-technisch karakter van de oncologische behandeling heeft het professionele perspectief de overhand. Ouders ervaren deze eerste periode als een tijd van enorm controleverlies.

In de loop van de behandeling vindt een omslag plaats. Voor ouders en kinderen gaat het belang van het kind meer behelzen dan alleen medische overwegingen. Het omvat dan ook een persoonlijke visie, waarin begrepen de wens om een zo normaal mogelijk leven te leiden, het willen controleren van sommige aspecten van de behandeling en het vasthouden aan de eigen identiteit (bijvoorbeeld door middel van religie). Deze persoonlijke visie botst soms met de medische overwegingen, wat kan leiden tot verschillende visies bij het gezin en bij het medisch team over het te volgen beleid. Wanneer persoonlijke en professionele opvattingen ver uiteen lopen, komt onvermijdelijk de vraag op wiens perspectief de overhand moet hebben. We beantwoorden deze vraag door in het reflectief-evenwichtmodel onze empirische data te integreren met onder andere theorieën over 'shared decision making'. We presenteren vervolgens een model van 'communicatieve ethiek' waarin de verschillende gezichtspunten onderwerp van gesprek kunnen worden. In het 'communicatieve ethiek-model' krijgen de verschillende visies op het belang van het kind een prima facie karakter, dat wil zeggen dat geen van hen bij voorbaat de overhand heeft. Het is vervolgens de taak van alle betrokken actoren (medisch team, ouders, kind) om in gesprek consensus te bereiken over de uiteindelijke definitie van het belang van het specifieke kind. Persoonlijke gezichtspunten die potentieel kunnen afwijken van de professionele visie kunnen in dit gesprek herkend en begrepen worden, en er kan in gezamenlijkheid een behandelplan ontwikkeld worden.

Hoofdstukken 6 en 7 behandelen de mogelijkheden van het kind zelf om te participeren in de besluitvorming.

Hoofdstuk 6 bespreekt het meebeslissen van het kind over onderzoeksdeelname. De Nederlandse wetgeving en ook verscheidene (internationale) richtlijnen schrijven voor dat kinderen vanaf een bepaalde leeftijd (in Nederland 12 jaar) betrokken moeten worden bij de besluitvorming over deelname aan wetenschappelijk onderzoek. Recente studies laten echter zien dat in de context van de kinderoncologie deze betrokkenheid moeilijk te realiseren is door de ervaren stress rondom de diagnose kanker, door de complexiteit van researchprotocollen en door de ervaren tijdsdruk. Desondanks participeert een

opmerkelijk grote groep kinderen met kanker in wetenschappelijk onderzoek. In onze interviewstudie onderzochten we de opvattingen van kinderoncologen over het includeren van kinderen in wetenschappelijk onderzoek en over het betrekken van (oudere) kinderen bij de besluitvorming over onderzoeksdeelname.

De opvattingen van de kinderoncologen kan samengevat worden in vier thema's: (1) zij achten kinderen (ook degenen ouder dan 12 jaar) over het algemeen niet in staat om zinvol te participeren in gesprekken over wetenschappelijk onderzoek; (2) zij geven de (oudere) kinderen niet alle relevante onderzoeksinformatie; (3) de toestemming van ouders wordt wel verkregen en wordt over het algemeen als voldoende gezien; (4) integriteit van de onderzoeker: de artsen oordelen dat onderzoeksdeelname niet schadelijk is en zelfs in het belang van het kind kan zijn, omdat binnen een onderzoeksprotocol de beste behandeling wordt gegeven. Met andere woorden: de kinderoncologen rechtvaardigen het niet betrekken van (oudere) kinderen bij gesprekken over wetenschappelijk onderzoek door te verwijzen naar aandacht voor het belang van het kind - gewaarborgd door proxy consent en integriteit van de onderzoeker -, hoewel dit niet strookt met wettelijke voorschriften en ethische richtlijnen.

Vervolgens integreren we in ons reflectief-evenwichtmodel deze empirische data met theoretische kennis vanuit de onderzoeksethiek. We concluderen dat het verschil tussen de *onderzoek*srelatie (onderzoeker-proefpersoon) en de *behandel*relatie (arts-patiënt) zodanig fundamenteel is, dat dit juist gezien moet worden als een impuls om oudere kinderen werkelijk te betrekken bij de besluitvorming en niet kortweg af te gaan op overwegingen van het belang van het kind. Arts-onderzoekers zouden van geval tot geval het vermogen van kinderen om mee te beslissen moeten beoordelen en duidelijk moeten zijn over het verschil tussen wetenschappelijk onderzoek en de standaard behandeling.

In hoofdstuk 7 wordt een andere discussie beschreven rondom kindparticipatie, namelijk de discretionaire ruimte van ouders om de informatievoorziening aan hun kind te reguleren en daarmee de betrokkenheid van het kind bij besluitvorming te beïnvloeden.

In de kinderoncologie vormt het risico op infertiliteit door de behandeling een groot probleem. Voor jongens die al in de puberteit zijn is semencryopreservatie een optie, maar het bespreken hiervan is complex door de gevoeligheid van het onderwerp en de beperkte tijd om sperma voor opslag te produceren.

In onze interviewstudie benoemden zowel ouders als artsen spontaan de gevoeligheden rondom het bespreken van infertiliteit als een voorbeeld van het wel of niet betrekken van kinderen bij de besluitvorming. Hoewel ouders en artsen het met elkaar eens waren dat onvruchtbaarheid een enorme impact zou hebben op de toekomstige kwaliteit van leven, verschilden ze soms van mening over de vraag of het onderwerp besproken

moest worden met adolescenten. De kinderoncologen waren unaniem in hun mening dat er altijd een apart gesprek met adolescenten moet plaatsvinden over infertiliteit en semencryopreservatie. Hun argumenten hiervoor waren de gevoeligheid van het onderwerp en hun ervaring dat ouders de puberteitsontwikkeling van hun kind niet altijd goed inschatten. Ouders daarentegen wilden controle over *of* het onderwerp besproken werd met hun zoon en over *wat* er besproken werd. De kinderoncologen accepteerden deze controle niet en waren zelfs bereid om voorbij te gaan aan de wil van ouders en het onderwerp met de adolescent te bespreken ondanks de weigering van ouders.

In ons reflectief-evenwichtmodel integreren we deze empirische data met ethische theorieën over 'het recht op een open toekomst', ouderlijk gezag en kindparticipatie. De kinderoncologen zien zich voor de moeilijke taak gesteld om te balanceren tussen hun ideeën over wat in het (toekomstig) belang van het kind is en de wensen van ouders. We bespreken het concept 'strategische controle': de controle die ouders willen hebben over de gesprekken tussen arts en kind. Ouders neigen tot het filteren en moduleren van de medische informatie aan hun kind, waarmee ze het kind automatisch een passieve rol in de besluitvorming toebedelen. Recente literatuur laat zien dat artsen deze manier van communiceren vaak acceptabel vinden. Ouders en artsen bespreken samen de manier waarop het kind benaderd moet worden, of het kind betrokken moet worden in de besluitvorming en welke informatie het kind mag krijgen. We beargumenteren dat in het geval van het bespreken van infertiliteit deze strategische controle niet acceptabel is, vanwege het privékarakter van seksualiteit en de mogelijk inadequate inschatting van de puberteitsontwikkeling door ouders. Semencryopreservatie moet daarom altijd apart met een adolescent besproken worden. Aanvullend moet er een open communicatie zijn met ouders om eventuele zorgen bespreekbaar te maken.

Tenslotte worden in *hoofdstuk 8* de voornaamste resultaten van dit proefschrift in perspectief geplaatst. We concentreren ons daarbij op twee kwesties. Allereerst bespreken we opnieuw onze methodologie en beantwoorden de volgende vraag: kunnen onze resultaten gegeneraliseerd worden naar de kinderoncologie in het algemeen en misschien zelfs naar de kindergeneeskunde in het algemeen?

Generaliseerbaarheid verwijst naar de mate waarin onderzoeksresultaten en conclusies van een onderzoek ook opgaan voor personen, situaties en gevallen die in dat onderzoek niet onderzocht zijn. Het doel van ons Reflectief Evenwicht, en dus van de empirische data die erin zijn gebruikt, is echter op de eerste plaats om te begrijpen wat er in een concrete situatie van besluitvorming gebeurt. Het bereikte evenwicht bestaat niet buiten deze concrete situatie, aangezien de beschrijving van en de ervaringen binnen de context van de situatie een integraal onderdeel vormen van het evenwicht. We

concluderen derhalve dat het spreken over generaliseerbaarheid binnen onze versie van het Reflectief Evenwicht eigenlijk een beetje merkwaardig is. We beargumenteren echter dat, door het gebruik van het perspectief van derden (wat hoofdzakelijk een verdere rationalisering inhoudt van het bereikte evenwicht), we uitkomen op een relatief stabiel raamwerk dat stand houdt totdat nieuwe empirische data ons dwingen om het evenwicht te heroverwegen. Dit is te vergelijken met het falsificatieprincipe van Karl Popper. Kennis, ook morele kennis, is onvermijdelijk hypothetisch van aard en we moeten steeds op zoek zijn naar data om deze kennis te weerleggen. Anders gezegd, zolang ons empirisch reflectief evenwicht niet door elkaar wordt geschud of wordt weerlegd, geldt het als een inzicht in het gebruik van de concepten belang van het kind, kindparticipatie en ouderlijk gezag.

Vervolgens reflecteren we op de implicaties van ons empirisch onderzoek voor het denken over het belang van het kind, kindparticipatie en ouderlijk gezag. We nemen de thema's van de interviews samen en proberen ze te integreren in een reflectief evenwicht met bestaande theorieën, normen en principes. We concluderen dat door de complexiteit van de kinderoncologische context en door onze pluralistische opvattingen over de ontwikkeling van een kind, het welzijn van het kind en de discretionaire ruimte van ouders, we geen uniforme interpretatie kunnen geven van wat het belang van een kind inhoudt en hoe ver kindparticipatie en ouderlijke discretionaire ruimte zouden moeten gaan. Door het gebruik van het Reflectieve Evenwicht kunnen we echter wel komen tot een uniform raamwerk voor besluitvorming. Ons reflectief raamwerk beschrijft het morele landschap van de kinderoncologie als een complexe interactie tussen ogenschijnlijk onverenigbare gezichtspunten: onderzoek versus behandeling, professioneel versus persoonlijk, technologische perfectie versus communicatievaardigheden, toekomst versus heden, gezin versus individu, wilsbekwaam versus wilsonbekwaam. In dit morele landschap worden artsen steeds uitgedaagd om effectieve zorg te leveren en tegelijkertijd de visies van ouders en kinderen op zorg en onderzoek te respecteren. Slechts zelden is er sprake van een overduidelijk scenario waarin één gezichtspunt overheerst. Zelfs basisregels als 'het belang van de patiënt gaat voor alles', of 'de stem van het kind moet gehoord worden' zijn niet absoluut wanneer we het morele landschap van de kinderoncologie beschouwen. Het zijn acceptabele premissen, in onze methodologie: een hypothetisch equilibrium, maar niet aanvaardbaar als laatste conclusie. Voor een definitieve conclusie moeten we deze premissen afwegen tegen andere gezichtspunten. Het is een zware taak om de verschillende morele verplichtingen die functioneren in de kinderoncologie te identificeren en vervolgens bij elkaar te brengen. Soms kan een externe partij (bijvoorbeeld een ethicus) van waarde zijn om te functioneren als 'de Denker' en om het morele landschap en de verschillende gezichtspunten inzichtelijk te maken. Wanneer uiteinde-

lijk de gezamenlijke intentie om in het belang van het kind te handelen gebaseerd is op een raamwerk voor besluitvorming dat dit belang begrijpt als een zaak die tot stand komt in werkelijk overleg, dan pas kan het besluitvormingsproces het begrip en het vertrouwen van kinderen en ouders vergroten, namelijk door het delen en overdragen van inzichten en verantwoordelijkheden tussen artsen, kinderen en ouders.

CURRICULUM VITAE

Martine de Vries was born on the 3th of September 1974 in Gouda, The Netherlands.

She attended secondary school at the 'Stanislas College' in Delft and passed her gymnasium ß exam in 1992 *(cum laude)*. From 1992 till 1993 she studied Greek language and history at the Aristotle University in Thessaloniki, Greece (certificate of Greek Language competency). From 1993 till 2000 she studied Medicine and Philosophy (specialty: Medical Ethics) at Leiden University, The Netherlands. She was awarded the Pieter van Foreest incentive prize for medical humanities for her doctoral thesis on complex treatment decisions in Pediatrics ('Besluitvormingsprocessen bij complexe behandelingsvraagstukken in de Kindergeneeskunde'). During her studies she worked as a teaching assistant at the educational center of the Leiden University Medical Center (LUMC).

In 2000 she started her clinical training at the LUMC and obtained her medical degree in 2002 (*cum laude*). Hereafter, she worked for a short while as a resident (ANIOS) at the Department of Pediatrics at the MCH Westeinde Hospital in The Hague, and as a physician in the refugee centers of Leiden, Waddinxveen and Alphen aan den Rijn.

In September 2003 she started her research on ethical issues in Pediatrics at the Departments of Philosophy and Medical Ethics (head: Prof. E. van Leeuwen) and the Division of Pediatric Oncology/Hematology (head: Prof. G.J.L. Kaspers) of the VU Medical Center, Amsterdam and the Departments of Pediatrics (head: Prof. J.M. Wit) and Medical Ethics and Health Law (head: Prof. D.P. Engberts) of the LUMC. As from September 2005 she combined her training in Pediatrics with the research resulting in this thesis. She started her specialization in Pediatrics at the Reinier de Graaf Hospital in Delft (head: dr. N. van der Lely) and is now fulfilling her specialization at the LUMC (head: Prof. H.A. Delemarre-van de Waal; presently: Prof. F.J. Walther).

As of July 2012 she is project leader of a guideline development trajectory, funded by the Dutch Ministry of Health, on due diligence of pediatric researchers throughout the research process, dealing with the informed consent procedure, creating a child-friendly setting, giving voice to the child-participant and monitoring expressions of objection from young children. She is also co-investigator in two ZonMw-funded research projects, one dealing with the development of information material for children on research participation, and the other dealing with the development of a standardized instrument for assessing children's competence to consent to research.

She is member of the board of the Society for Philosophy and Medicine, and member of the Committee on Medical Ethics and Health Law of the Dutch Pediatric Association (NVK).

Martine de Vries and her wife have two sons.

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