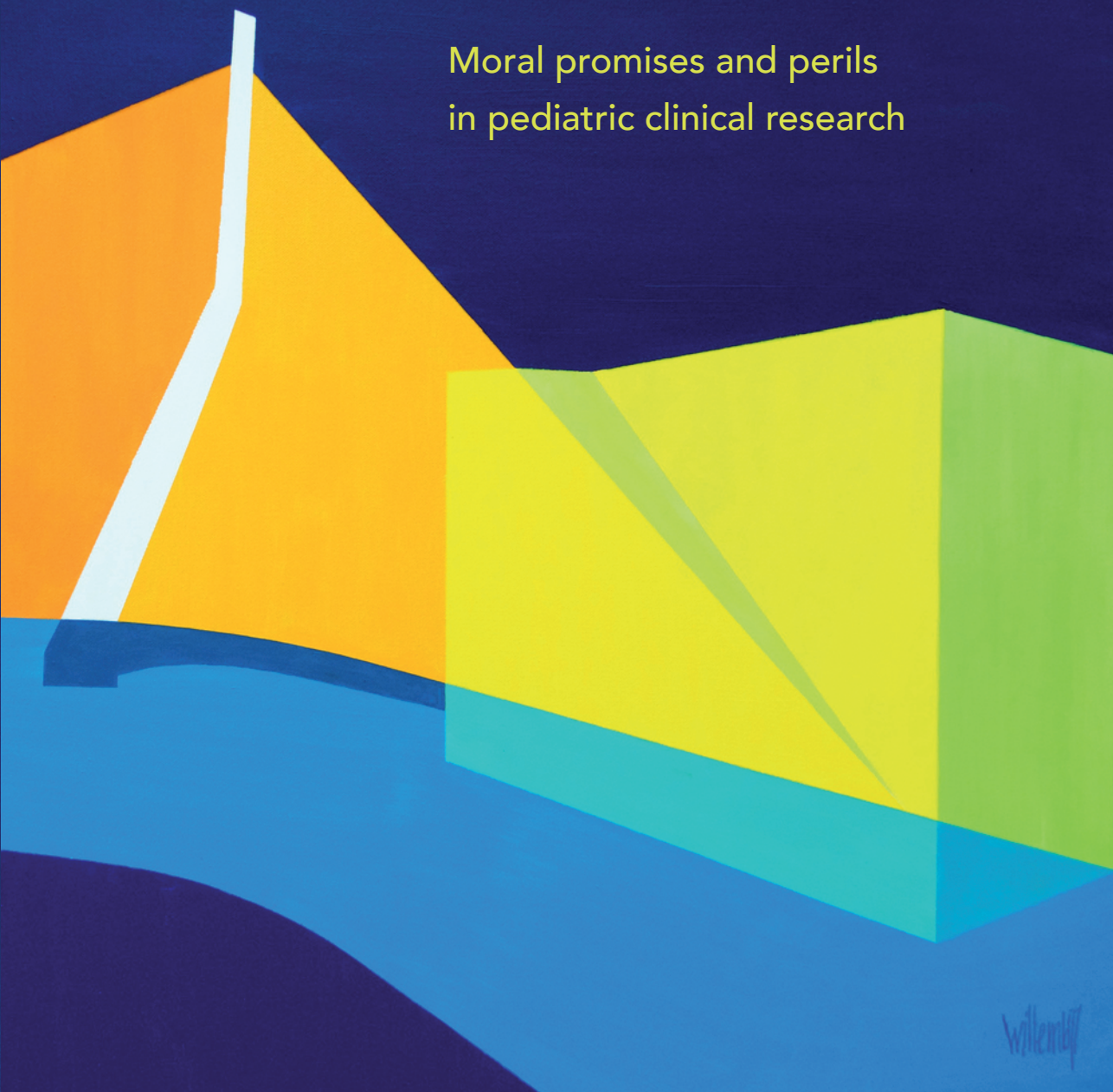
BETWEEN PROTECTION AND PARTICIPATION

KRISTA TROMP

Moral promises and perils
in pediatric clinical research



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Krista Tromp

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Between Protection and Participation

Moral promises and perils in pediatric clinical research

Tussen bescherming en deelname

Morele beloften en gevaren in medisch-wetenschappelijk onderzoek met kinderen

Proefschrift

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TABLE OF CONTENTS

CHAPTER 1

General introduction

"Yes, I think it's ambivalent, because on the one hand, if my child gets a medicine that has never been tested, I think that's bad. But on the other hand, I also find it very bad when my child ... that he will test that medicine."

Mother, focus group (chapter 6)

This mother is spot-on. I interviewed her in one of the empirical studies in this thesis. She describes the ethical dilemma that ethicists, philosophers, researchers, physicians, members of research ethics committees and other professionals have been wrestling with for many years regarding performing clinical research involving children. How can we conduct clinical research to advance scientific knowledge and develop much-needed treatment options for children while protecting children against harm from research? In this thesis, I aim to contribute to finding a balance in this dilemma.

ETHICAL DILEMMA IN PEDIATRIC CLINICAL RESEARCH

The core ethical dilemma in pediatric clinical research centers on finding a balance between advancement and protection.[1,2] It is not one or the other but a balancing act that will allow us to advance science and maximally protect children.

We need to realize that without clinical research, every treatment in daily practice is actually an experiment. Clinical research with children is essential; otherwise, children turn into 'therapeutic orphans'.[3] Clinical research generates new data that we can use to develop new treatments for children, and these treatments are much needed. A lack of knowledge about drugs and other treatments in children may cause treatment failure and adverse events in children in clinical practice.[4,5] There are some unfortunate examples, such as the treatment failure that was observed in neonates on extracorporeal membrane oxygenation (ECMO) with disseminated herpes simplex virus infection after they were given unresearched doses of acyclovir.[6,7] There are no alternatives: performing research involving adults and extrapolating these data to children is not the solution either. Children are not small adults. For example, treatment of neonates with doses of chloramphenicol that were derived from research results in adults caused gray baby syndrome and even death in neonates.[8,9]

Fortunately, there are some initiatives to stimulate pediatric clinical drug research. In 2006, the European Commission launched a directive that offered incentives to pharmaceutical companies to generate data in children.[10] A similar initiative was set up in the United States (US).[11] Unfortunately, these initiatives have not resulted in the expected reduction in off-label drug use in children for which they were designed.[12,13] Off-label use

of drugs in children in diverse hospital settings still ranges from 10 to 65%.[14] In children admitted to the Pediatric Intensive Care Unit (PICU) and in neonates, these numbers even go up to 70-90%.[15 16] It seems there is still a discrepancy between the therapeutic needs and therapeutic offers, due to a lack of clinical research in children. [17] Therefore, clinical research is essential to provide safe and effective treatments for children.

At the same time, children need and deserve protection against the harm associated with research participation. In addition, this protection is and should be more stringent for them than for adults.[1 2] Children are more vulnerable, as their distinct physiology puts them at increased risk of being harmed during research. Moreover, children are (relatively) incapable of protecting their own interests because of their dependency on others and due to their developing decision-making capacities. Because of this fact and a lack of legal competence, children (partly) rely on their parents to make decisions for them. Their parents decide for them, while the children are the ones participating in the research.

INFORMED CONSENT IN PEDIATRIC CLINICAL RESEARCH

Before children can participate in research, someone needs to make decisions about their research participation and consent to their participation. For children, this someone, in most cases, is their parent. To be precise, both parents need to consent to their child's participation, and children need to co-consent or assent to research participation. An informed consent process empowers parents and children to make an informed decision about participation in clinical research. The importance of informed consent in pediatric clinical research is hardly ever questioned, but its effectiveness and validity are always a concern in practice. To illustrate these, I distinguish three values of informed consent in pediatric clinical research: legal, moral and instrumental values.

LEGAL VALUE OF INFORMED CONSENT IN PEDIATRIC CLINICAL RESEARCH

The legal value of informed consent in pediatric clinical research concerns the arrangement of the rights and duties between (the parents of) the pediatric research participants and researchers. What then has been laid down in legislation about informed consent for pediatric research? Variation exists in the national legislative requirements for informed consent in pediatric clinical research worldwide.[18] However, there are some common core elements. The core guideline concerning clinical research is as follows: no participation without prior informed consent of the research participant.[1 2 19-21] Children have a special position in this issue. As mentioned earlier, children generally cannot make an autonomous, well-considered decision concerning research participation on their own

and therefore cannot consent to research. Their parents (or legal guardians)[1i] need to consent for them, which is called proxy consent. In the Netherlands, proxy consent is arranged in the Medical Research (Human Subjects) Act (WMO), precisely art. 6:1.[21]

How the views of children themselves are being taken into consideration in informed consent requirements differs by country. In many countries, an assent procedure is used for children. This means that although children cannot consent for themselves, to respect children's developing autonomy, they do need to assent to research participation. However, assent is very differently used in daily practice, and no consensus exists on an operational definition in legislation and guidelines.[22]

In the Netherlands, we go a step further in recognizing children's decision-making capacities.[23] In the Netherlands, children aged 12 years and older also need to officially consent for themselves next to their parents' consent (art. 6:1.b WMO 1998). This is called dual consent or co-consent.[23] For children below 12 years of age, researchers do not have to ask official consent but must ensure that children are informed about the research by an appropriately trained person in a manner befitting their ability to understand (art. 6:7 WMO 1998). For this purpose, authors have suggested using illustrations or even comic strips to support the informed consent process for children.[24] Children's willingness to participate is also respected and reflected in a clause that states that when a child objects to or resists research procedures, the research will not commence or will not be continued (art 10.a:1 WMO 1998). During the time of the research on which this thesis is based, the legal age of consent for clinical research in the Netherlands shifted from 18 years of age to 16 years of age.[ii] This revision of the WMO came into force in March 2017 (art 6:1 WMO 1998) and was a result of a long-lasting discussion that had started with the '*Committee Doek*' in 2009.[25 26] This shift brought the age threshold in line with the thresholds used in the Dutch Medical Treatment Contracts act and incorporated new insights into children's developing decision-making capacities.[23 27]

These legal requirements are, of course, crucial, but too much focus on the legal value of informed consent creates an informed consent process that is actually just a one-time achievement and, moreover, creates informed consent documents and conversations with complex scientific terminology, technical jargon and information that is irrelevant for decision-making but required from a legal perspective.[28-30] In that way, the informed

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i In the remainder of this chapter, whenever there is mention of 'parents', one can also read this term as 'parents or legal guardians'.

ii At the time of the empirical work presented in this thesis, the former legislation was still in force and dual consent of both the child and the parents was needed for 16- and 17-year-olds. As a result, the perspectives of (the parents of) children who are 16 and 17 years of age are included in the empirical work in this thesis.

consent process might be legally correct but often is inadequate in moral and instrumental terms.

MORAL VALUE OF INFORMED CONSENT IN PEDIATRIC CLINICAL RESEARCH

The moral value of informed consent in general is the implementation of the ethical principle 'respect for persons'. Respect for persons means that people are treated as autonomous agents and that people with diminished autonomy have a right to protection.[19] To reach a complete meaningful and valid consent, five elements are distinguished: transmission of information, comprehension of this information, voluntariness (no coercion by others), competence to make a decision, and actual consent.[31] These moral elements are particularly under pressure in pediatric clinical research.

The information related to clinical research is very complex: Advances in medicine have created complex clinical research protocols resulting in elaborate and complicated information to be conveyed to potential research participants and their parents during an informed consent process.[28 30 32] Comprehension of such information is difficult for both the child and the parent.[32-37] A study in the Netherlands indicated that material targeted to children was difficult for even adults to read and understand.[32] In a study by Unguru and colleagues, half of the children were unaware that their treatment was in fact a research intervention.[37] Chappuy and colleagues showed that after informed consent, half of the parents were not able to explain the aim of the research their child was participating in or to describe the potential benefit for their child.[34] Furthermore, the competence of children varies greatly due to children's developing decision-making capacities.[38] Finally, due to children's lack of legal competence, the actual consent for research is arranged by proxy consent of their parents. All these factors make the informed consent process more complicated for pediatric clinical research than for clinical research with adults.[23 39]

INSTRUMENTAL VALUE OF INFORMED CONSENT IN PEDIATRIC CLINICAL RESEARCH

The instrumental value of informed consent in pediatric clinical research lies in the effect that informed consent can have on participation. Whereas the participation of children in pediatric research is a prerequisite for successful research, pediatric trials often have recruitment problems. One-third of RCTs in the PICU are generally terminated before the needed sample size is reached.[40] An adequate informed consent process can increase the willingness to participate and decrease drop-out rates during participation in research.[41 42] When parents and children are not threatened by the complexity and amount of information but receive information that they consider helpful for their decision, they are probably more willing to participate, thereby increasing participation rates. By creat-

ing realistic expectations of research participation during the informed consent process, potential participants and their parents know what they are getting themselves into, and the risk of surprises during the research is minimized.

INFORMED CONSENT AND MOTIVATIONS IN PEDIATRIC CLINICAL RESEARCH

This thesis focuses mainly on the moral and instrumental values of informed consent in pediatric clinical research and seeks a way to tailor the process of recruitment and informed consent to the perspectives and needs of children and their parents. I would not state it as boldly as Waisel did in an editorial: *"Let the patient drive the informed consent process: ignore legal requirements"*.[43] However, in my opinion, the legal value of informed consent should be the operationalization of the moral and instrumental value. In legislation, we lay down the requirements that are needed to achieve our moral and instrumental aims of informed consent.

Most national legislation specifies which aspects a person needs to be informed about when asked about research participation. For example, the Dutch WMO prescribes that people need to be explicitly informed about the objectives, nature and duration of the trial; the risks that the trial would present to the participant's health; the risks that premature termination of the trial would present to the participant's health; and the possible burden of the trial on the participant (art 6:5 WMO 1998). The rationale behind this requirement is that we see these aspects as crucial elements that must be understood in order to give meaningful and valid informed consent. However, are these the informational aspects that parents and children actually use in their decision? If they attach importance to completely different things and use other aspects in their decision but haven't been informed about those other aspects, can we still call their agreement informed consent?

To learn to what parents and their children attach importance to, we should learn more about their motivations to participate in research. If we learn the motivating and discouraging factors for their decision, we will know what information they use in their decision and about what factors they should be informed. This approach increases both the moral and instrumental value of informed consent; we obtain more *informed* consent and probably *more* informed consent. During the course of this research, legislation in the US changed. Formerly, the prerequisite for valid informed consent consisted of only a list of facts that needed to be provided. Now the information that people use in their decision and the reason why they participate are central for informed consent.[44 45]

US legislation concerning clinical research (The Common Rule) now explicitly states the following: *"Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate…"* (XIV.116.a.5i 49 CFR Part 11 2017).[45] This legislation operationalizes the moral and instrumental value of informed consent by incorporating the motivations of potential participants directly into the legal requirements for informed consent.

In this thesis, I use a similar approach to optimize the recruitment and informed consent process in pediatric clinical research and tailor the process to the needs and perspectives of children and their parents. I study and incorporate their views, motivations and expectations in the recruitment and informed consent process for pediatric clinical research. This analysis teaches us what information parents and children want and need to make a valid informed decision.

SCOPE OF THIS THESIS

With this thesis, I aim to contribute to the optimal inclusion of children in pediatric clinical research in such a way that we can further clinical research to advance scientific knowledge and develop much-needed treatment options for children while protecting children against harm from research.

Ethicists, researchers and physicians have extensively discussed the precarious balance between advancement and protection in pediatric research. However, how do children and their parents view this balance? Do they also weigh the possible harm against the benefits when they are approached for participation in clinical research? Or do they have other reasons and put other factors into the equation? Because children and their parents are the key decision-makers and children are ultimately the ones participating and undergoing the risk and burden of the research, it seems obvious that their views about this balance are crucial.

Why do children and parents want to participate (or not)? What are their motivations and what is important to them in their decision? What expectations do they have of participation? Answers to these questions are indispensable in order to incorporate their views into the pediatric research enterprise and tailor the process of recruitment and informed consent to their needs and perspectives. When we know why children and parents consent or dissent to research and what elements they use in their decision, we

know what they attach importance to in their decision. From this data, we learn which information they want and need to make a valid informed decision. This information helps us to increase both the moral and instrumental value of informed consent in pediatric clinical research.

RESEARCH AIMS

Following the above, the main research aims of this thesis are as follows:

1. To explore children's and their parents' motivations, views and expectations during recruitment and informed consent processes in pediatric clinical research.
   - What are their motivations to consent/assent to participation in pediatric clini cal research? What factors influence their decisions?
   - What are their views on recruitment and informed consent?
   - What are their expectations of research?
2. To analyze these motivations, views and expectations and the factors that shape them from an ethical and legal perspective.
3. To develop a normative framework to support research professionals in the ethically sound inclusion of children in pediatric clinical research. This framework tailors the process of recruitment and informed consent to the perspective and the needs of children and their parents, who have the key role in decisions on research participation.

METHODOLOGICAL APPROACH

Combining normative thinking with empirical research has become increasingly common in bioethics.[46] However, as much as its use has increased, this combination has also been criticized.[47-49] As can be distilled from my introduction and research aims, I am not one of these critics. To achieve my research aims, I have used a variety of research methods by combining ethical theory with empirical research. Although I recognize that one cannot conclude that an action is in fact ethically right from an empirical finding that people believe the action is ethically right, in this thesis, I use results from empirical research others have carried out as well as the results of empirical research that I have performed myself to inform my normative reasoning.[47 50] To explore and evaluate people's moral beliefs, intuitions, behavior and reasoning in practice holds information that is meaningful for normative reasoning about that specific practice.[51] To look into someone else's views enables us to reflect on our own views and adapt them when nec-

essary. Moreover, I believe this use of results from empirical research makes the results of my normative deliberation more ready for application in practice. It gives me insights in the practice I am reflecting on and trying to improve. In addition, this approach is imperative, especially in the field of research ethics, since the aim of research ethics is to evaluate research practices and to foster ethical research practices.[52]

It is, of course, crucial that the results extracted from empirical research are relevant and valid for my normative reasoning and are based on accepted standards of conduct for empirical research methods.[53 54] Therefore, I have used several different types of research methods to collect relevant and valid qualitative and quantitative empirical results.[50] I have collected morally relevant facts, studied morally relevant perspectives and combined them with relevant moral principles and background theories to achieve a reflective equilibrium.[55 56]

I have collected morally relevant facts among others by a review of the relevant rules and regulations concerning clinical research. For example, an evaluation of European pediatric research legislation (e.g., chapter 2) and guidelines concerning informed consent/assent (e.g., chapter 3) are included.

I have studied morally relevant perspectives (e.g., motivations, views, expectations and intuitions) of children and their parents by performing a systematic review of the existing literature concerning motivations (chapter 4) and by performing two qualitative studies: an interview study with children and parents from three hospital/research settings (chapters 5 and 8) and a focus group study with parents from the general public (chapter 6).

Relevant moral principles and background theories that I have used encompass, among others, the value of informed consent, the role of trust in decision-making (chapter 8) and the consequences and desirability of gatekeeping (chapter 7).

I have combined the above-mentioned empirical and normative elements into a reflective equilibrium to reach a coherent normative view that results in a normative framework for an ethically sound recruitment and informed consent process for pediatric clinical research (chapter 9).

OUTLINE OF THIS THESIS

Chapter 2 sketches the European regulatory landscape for pediatric clinical research and shows how specific ethical issues regarding clinical research with children, such as informed consent/assent and risk-benefit thresholds, are incorporated into the relevant legislation.

Chapter 3 gives an overview of the ethical challenges that arise when planning and conducting clinical research with a specifically vulnerable group of children, namely, critically ill children in the PICU. This chapter discusses ethical challenges concerning study design, informed consent and risk and burden and proposes several solutions to these ethical challenges.

Chapter 4 reviews the empirical literature concerning motivations of children and their parents to consent and dissent to pediatric clinical drug research. This chapter provides a comprehensive overview of the motivating and discouraging factors that influence children's and their parents' decisions to participate in pediatric clinical drug research reported in the empirical literature.

Chapter 5 reports on a qualitative interview study aimed at gaining insight into children's and their parents' motivations, views and expectations during the process of recruitment and informed consent for pediatric clinical research. This interview study presents perspectives from three different hospital settings: children and their parents in pediatric oncology, pediatric pulmonology (subdivision: cystic fibrosis) and the PICU.

Chapter 6 reports on a qualitative focus group study aimed to explore parents' perspectives on decisions to participate in pediatric clinical research. This focus group study was performed with parents from the general public to add the intuitions and motivations of non-professionalized (non-hospitalized) parents to the body of empirical evidence.

Chapter 7 discusses the phenomenon of gatekeeping in the recruitment for pediatric clinical research. Gatekeeping is a practice in which research professionals have implicit inclusion and exclusion criteria that lead to not approaching all eligible research participants. This chapter argues that although this practice is understandable in pediatric clinical research, it is ethically undesirable.

Chapter 8 discusses the different types of trust that children and their parents have in the research enterprise illustrated with empirical results from the interview study presented in chapter 5. This chapter also sketches how this trust influences their decision-making

and how it emphasizes the necessity of prior review of a research ethics committee and its filtering task.

Chapter 9 concludes this thesis with a general discussion in which I combine the main findings of the preceding chapters into a normative framework for research professionals to include children in an ethically sound manner in pediatric clinical research. This framework tailors the process of recruitment and informed consent to the perspective and the needs of children and their parents.

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CHAPTER 2

Pediatric clinical research: The regulatory landscape

Wendy Bos*, Krista Tromp*,
Dick Tibboel, Wim Pinxten.

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*[*shared first authorship]*

ABSTRACT

Over the past decades, clinical research has increasingly been subjected to ethical requirements and legal regulation. The specific focus of ethical and legal frameworks on competent adults (which serve as the paradigmatic research subject), however, has created an ambivalent attitude towards pediatric clinical research. On one hand, minors are regarded as a vulnerable population that deserves additional protection against the risks and burdens involved in clinical research. On the other hand, the population of minors should not be denied (or not get timely) access to the benefits of clinical research.

In this chapter, we will explore the legal regulation and ethical guidance that currently governs pediatric clinical research in the European Union and discuss the future challenges in this field. In addition, we will discuss major ethical concerns in pediatric clinical research, with a focus on the acceptability of research risks and the informed consent process. In the discussion, we will address key concerns in both regulating pediatric clinical research and implementing ethical and legal requirement in the actual pediatric research conduct.

INTRODUCTION

Over the past decades, clinical research has increasingly been subjected to ethical requirements and legal regulation. Since the Second World War, landmark codes of ethical research conduct have been drafted and legal regulation has been issued in the US, the European Union (EU), and many other countries. Despite the considerable diversity in ethical and legal requirements, there has always been consensus on the cornerstones of ethical research conduct. For example, the doctrine of informed consent, the premise that the interest of science and society should not prevail over those of the individual, and the fact that human subjects should never be exposed to unnecessary risks in clinical research have been widely endorsed from the very start.

The historical efforts to secure an adequate protection of human subjects in clinical research have been grafted on a paradigmatic research subject: the competent adult. This specific focus, however, has created an ambivalent attitude towards pediatric clinical research. On the one hand, minors are regarded as a vulnerable population that deserves additional protection against the risks and burdens involved in clinical research. Such a protection could not be maximized further than in a full exclusion of minors from clinical research. On the other hand, the population of minors should not be denied (or not get timely) access to the benefits of clinical research. The impressive share of drugs that are prescribed off-label or off-license in pediatric practice,[1] however, clearly indicates that research in competent adults does not automatically generates timely advancements in the diagnosis, care, and treatments for minors. Minors are not just small adults, and omitting to conduct clinical trials in the population of minors turns minors into 'therapeutic orphans'.[2 3] By consequence, the conduct of pediatric clinical trials is indispensable to catch up with the lack of licensed drugs that are labelled for pediatric use.

From an ethical and legal point of view, however, the conduct of pediatric clinical trials is a precarious enterprise, as it often remains difficult to balance scientific advancement with the adequate protection of minors.[4 5] In addition, several hurdles such as difficult recruitment, market issues (e.g., a problematic return on investment for pediatric clinical research), and restrictive regulation (e.g., risk thresholds for non-beneficial research) may be hard to surpass.

In this chapter, we will explore the legal regulation and ethical guidance that currently governs pediatric clinical research and discuss the future challenges in this field. In this respect, it must be emphasized that the applicable ethical and legal frameworks are often formulated in general terms, while pediatric research is a very heterogeneous landscape. As such, these frameworks may fail to respond directly to the specific ethical

issues that come to the surface in practice. Certain issues therefore call for an appropriate ethical approach, which cannot be derived easily from the available ethical and legal guidance. Table 1 lists a number of such issues.

Table 1: Recognized problems from a clinical point of view in critically ill minors

Recognized problems from a clinical point of view in critically ill minors
1. The compassionate use at an individual base as a last resort drug (Imatinib) for pulmonary hypertension original labelled as an anti-cancer drug.
2. The conduction of first in men studies such as new amino acid composition for parenteral nutrition in extreme low birthweight infants in the absence of adult data.
3. The application of a therapeutic modality (for instance liquid ventilation with an organ preservation substance) in the absence of safety data.
4. Invasive fetal treatment modalities guided by industrial progress and not supported by properly designed RCTs.
5. Opportunistic sampling of residual blood samples from routine laboratory test, as well as dry blood spot sampling with the aim to determine drug levels.
6. Diagnostic procedures such as PET-scans to obtain normal values for the age-dependent distribution of opioid receptor isoforms in the central nervous system needed radioactive labelled substance.

THE REGULATION OF ETHICAL ISSUES IN PEDIATRIC CLINICAL RESEARCH IN THE EU

THE LEGAL REGULATION GOVERNING PEDIATRIC CLINICAL RESEARCH IN THE EU

In the EU, various supranational and national regulations that have been promulgated by diverse legislative bodies over the past 15 years aim to harmonize existing standards of good clinical practice and to facilitate and encourage pediatric clinical research.[6] At the supranational level, three different regulations govern pediatric research conduct. First, the Council of Europe issued the European Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine in 1997 (further, the Oviedo Convention).[7] In 2005, this convention was supplemented with an additional protocol on biomedical research.[8] To date, the Oviedo Convention is binding for the 17 EU member states (and 12 countries outside the EU) that have signed and ratified it. The Convention specifically addresses the issue of pediatric research in Article 17 (Table 2).

Second, Directive 2001/20/EC (further, the Clinical Trials Directive) mainly aims at a harmonization of the provisions regarding good clinical practice and the facilitation of multicenter clinical trials across the borders of individual EU member states.[9] All EU member states were bound to implement this directive into national law, with the freedom to adopt stricter provisions than those set down in the text of the directive (as long as the standards of protection and time limits captured in the directive were not violated). By consequence, there exists considerable variety among the national laws that implement

the Clinical Trials Directive. Obviously, differences in domestic requirements between EU member states must be taken into account when conducting a trial in a specific EU member state. The Clinical Trials Directive specifically addresses the issue of involving minors in research in Article 4 (Table 3).

Table 2: Oviedo Convention - Article 17

Article 17: Protection of persons not able to consent to research
1. Research on a person without the capacity to consent as stipulated in Article 5 may be undertaken only if all the following conditions are met: i. the conditions laid down in Article 16, sub-paragraphs i to iv, are fulfilled; ii. the results of the research have the potential to produce real and direct benefit to his or her health; iii. research of comparable effectiveness cannot be carried out on individuals capable of giving consent; iv. the necessary authorization provided for under Article 6 has been given specifically and in writing; and v. the person concerned does not object.
2. Exceptionally and under the protective conditions prescribed by law, where the research has not the potential to produce results of direct benefit to the health of the person concerned, such research may be authorized subject to the conditions laid down in paragraph 1, sub-paragraphs i, iii, iv and v above, and to the following additional conditions: i. the research has the aim of contributing, through significant improvement in the scientific understanding of the individual's condition, disease or disorder, to the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons in the same age category or afflicted with the same disease or disorder or having the same condition; ii. the research entails only minimal risk and minimal burden for the individual concerned.

Table 3: Clinical Trials Directive – Article 4

Article 4: Clinical trials on minors
In addition to any other relevant restriction, a clinical trial on minors may be undertaken only if: a. the informed consent of the parents or legal representative has been obtained; consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor; b. the minor has received information according to its capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits; c. the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principal investigator; d. no incentives or financial inducements are given except compensation; e. some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods; additionally, such research should either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors; f. the corresponding scientific guidelines of the Agency have been followed; g. clinical trials have been designed to minimize pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress have to be specially defined and constantly monitored; h. the Ethics Committee, with pediatric expertise or after taking advice in clinical, ethical and psychosocial problems in the field of pediatrics, has endorsed the protocol; and i. the interests of the patient always prevail over those of science and society.

Third, Regulation (EC) No. 1901/2006 (further, the Pediatric Regulation) requires that clinical trials in minors be planned and conducted for all new products entering the market.[10] In this respect, sponsors must make a pediatric investigation plan after phase 1 trials in adults have been completed (in certain cases, waivers are possible). In return for the efforts to plan and conduct trials in minors, the Pediatric Regulation offers considerable rewards in the form of a prolongation of market exclusivity. The Pediatric Regulation also arranged the establishment of a pediatric committee within the European Medicines Agency that is (among other tasks) primarily responsible for the scientific assessment and agreement of pediatric investigation plans and for the system of waivers and deferrals thereof. In contrast to the European Convention and the European Directive, the Pediatric Regulation is exclusively dedicated to clinical research in minors.

DIVERSITY AND INCONSISTENCY OF THE CURRENT REGULATION

Unfortunately, the legal frameworks that govern pediatric clinical research in the EU contain contradictory provisions and lack internal consistency in several matters. With regard to non-beneficial research, for example, Article 17.2 of the Oviedo Convention stipulates that in the absence of a direct benefit to the individual research participant, a minor can be involved in research only if the study entails minimal risks and minimal burdens, while Article 4e of the Clinical Trials Directive simply requires 'some direct benefit' to the research subject or a related group of beneficiaries. This indicates that the Oviedo Convention endorses a more restrictive policy than the Clinical Trials Directive and implies that early stage drug development may be compromised in member states that have signed and ratified the Oviedo Convention. Also with regard to the right of a minor to veto participation in clinical research, contradictory provisions exist: Article 4c of the Clinical Trials Directive stipulates that the (principal) investigator must consider the explicit wish of a minor to refuse or discontinue participation (given that the minor is capable of assessing information and forming an opinion), whereas Article 17.1v of the Oviedo Convention states that minors cannot be involved in a study when they object to research participation. Thus, the Oviedo Convention grants minors a more extensive decision-making capacity than the Clinical Trials Directive does.

In addition to these contradictory provisions, the European legal framework contains numerous contingencies that require extensive interpretation. It is not clear, for example, what must be understood to be an acceptable risk–benefit ratio, what it means to 'consider' the explicit dissent of a minor, how the capacity of minors to make decisions can be assessed, or why the Clinical Trials Directive refers to minor research participants as 'patients' and links benefits to the 'group of patients'. The fact that many terms are not

clearly defined is likely to negatively affect the implementation of the European legal framework and creates the need for accurate guidance and support.

At the level of domestic regulation, requirements for the inclusion of minors in clinical research (e.g., age criteria) vary from country to country, which obviously has profound implications for the conduct of multinational trials.[11] The differences in interpretation and assessment of the acceptability of risks among European member states have important consequences. For example, trial protocols can be rejected in one member state because the risks or burdens exceed the applicable minimal risk and minimal burden thresholds, but still take place in other European member states, where these thresholds are not adopted into national law. Obviously, this may be very frustrating for researchers and minor patients and their parents who are committed to the trial. It also might concentrate certain types of non-beneficial research in a selected number of EU member states, while successful trials will result in drug licenses that cover all EU member states. This generates important justice-related issues. The premise that risks and burdens call for a proportionate counterpart, by preference in the form of a direct benefit to the research subject, challenges the involvement of minors in phase 1 research or the use of healthy controls in pediatric clinical trials. There is considerable controversy over the fact that some risks and burdens would not need any compensation and that mere altruism can have a place in clinical research.

ETHICAL ISSUES IN PEDIATRIC CLINICAL RESEARCH

The extensive body of legal regulation that has been developed over the past 15 years has not reduced the need for sound ethical reflection. In this chapter, we will discuss two major ethical concerns in pediatric clinical research: the acceptability of research risks and the informed consent process.

ACCEPTABILITY OF RESEARCH RISKS

Clinical trials entail risks and burdens. Minors are a vulnerable population, and one should be vigilant to expose vulnerable subjects to risks and burdens. Therefore, procedures have been made to review the acceptability of risks and burdens in pediatric clinical trials, in which research ethics committees play a prominent role. The main rationale behind the assessment of research risks is that such risks call for compensation. This rationale is made operational in the principle of proportionality, according to which risks can be justified by a proportionate counterpart, for example in the form of a direct benefit to the research subject. Against this background, therapeutic research (research that is likely to generate a direct benefit for the subject involved) is often distinguished

from non-therapeutic research (research that is not likely to generate a direct benefit for the subject involved). While proportionality can be regarded as a general principle, exceptions are possible. Very small risks and burdens (often defined as 'minimal risks' and 'minimal burdens') for example can be deemed acceptable without a proportionate compensation in the form of a direct benefit to the research subject.

In practice, deciding upon risks is a precarious enterprise. First, it is hard to measure benefit, risk, and burden and to assess their proportionality in a reliable way. Although risks may be determined using objective criteria or other systems for risk evaluation,[12] such criteria do not account for the subjective personal experience of risks, burdens, and benefits of research subjects, which may be closely related to their condition, disease, and personal experience.

Second, also the review of risks and burdens by ethics committees is not a mechanical or fully objective procedure. Indeed, the deliberation of one and the same protocol by different ethics committees may have significantly different outcomes. Several factors, such as differences in the composition of ethics committees (which varies from country to country) or differences in the methods and procedures (e.g., for assessing risks), may nourish diversity in outcome. For example, in many European countries, non-beneficial research is subjected to a stringent minimal-risk- and minimal-burden threshold, while in others, no explicit distinction between therapeutic and non-therapeutic research is made by law, and proportionality between risks and benefits is not linked to specific risk thresholds.

INFORMED CONSENT FOR PEDIATRIC CLINICAL RESEARCH

The doctrine of informed consent has been widely used to serve two functions. Legally, informed consent settles the relationship between the researchers and the subjects participating in the research. Ethically, informed consent serves as an operational implementation of the principle of respect for persons. As such, informed consent is to protect research subjects from deception, coercion, and abuse.

In its original design, the doctrine of informed consent has been grafted on the paradigmatic research subject of the competent adult. As such, valid decisions to participate in research must in principle be made voluntarily and by legally competent adults, after being duly informed on the nature, significance, implications, and risks and burdens of the research. For several reasons, this paradigm has serious workability problems when applied to the setting of pediatric clinical research. First, due to age restrictions, most minors are not capable of granting legally valid consent, as they may not have reached the age of medical majority (or have not been emancipated, e.g., by marriage).[13]

Second, the capacity to understand and assess information is often still underdeveloped in minor research subjects. As a result, minors may lack the competence necessary to make rational decisions and it may be difficult to inform minors duly. Third, parents enjoy considerable discretion in the way they raise their children and all the decisions that this entails. Against this background, parents are almost always involved in decisions to enroll a minor in a clinical trial, even when the minor is mature enough to make decisions on his or her own.

The involvement of a competent adult acting as a surrogate/ proxy decision-maker is thus most often required to enroll a minor in a clinical trial. Obviously, such involvement of a proxy does not preclude minors from playing an active role in decisions about clinical trial participation. Quite the reverse, if parental consent is to be held to the same ethical standard as informed consent provided by a competent adult, the child who is participating in research must somehow be involved in the decision-making process. Several decision-making strategies, including: 1) Dual consent (by the minor and the proxy decision-maker); 2) Consent by the proxy and assent (affirmative agreement of a minor to participate in research) by the minor; 3) Respect for the dissent of the child, therefore aim at encouraging shared decision-making and a fair differentiation of decision authority between the proxy decision-maker and the minor research subject.

VULNERABILITIES IN THE INFORMED CONSENT PROCESS

Informed consent, proxy consent, assent, and dissent are simple in design. In practice, however, (proxy) informed consent, informed assent, and dissent are complex and precarious processes, in which all involved face important obstacles.

First, informed consent is delicate because understanding what it means to participate in research appears hard to realize in practice. For example, research shows that parents sometimes do not remember having consented to enroll their child in a clinical trial.[14-16] Also the understanding of information and recalling what one has consented to are difficult. In this respect, Chappuy and colleagues have described an apparent discrepancy between the evaluation of the adequacy of information by parents, and the actual understanding and recalling of this information by these parents.[16] Parents also tend to overestimate their understanding in comparison to an assessors' estimation of parental understanding.[17] In addition, specific elements, such as random allocation and potential risks, are difficult to understand for parents. The parental understanding of the concept of random assignment, for example, has been shown to be doubtful,[18 19] and in a study done by Ballard and colleagues, only 5% of the parents who understood the study understood the potential risks.[14] The poor understanding of information applies to the consent as well as to the assent process.[20 21]

Second, informed consent presupposes a distinction between research and therapy. In pediatrics, however, research does not necessarily start where therapy ends. This is particularly true for the setting of pediatric oncology, where nearly all patients are receiving their treatments in the context of a trial. But also in other settings, several factors may blur the theoretically rigid distinctions between therapy and research. For interventional studies, for example, it may not suffice for parents to be informed about the trial, the risks, and the benefits according to the specificities described in the study protocol. Rather, they may want to know why it would be worthwhile for their child to participate in this trial, taking the medical history and current treatment regimen into account. As such, trials may enter the therapeutic realm. In addition, minors and their parents often find it difficult to understand and keep in mind the difference between research and therapy, which may induce 'therapeutic misconception' in the informed consent process.[22] Therefore, when research is framed in a therapeutic context, it is of key importance that research is also distinguished from therapy. In this respect, it is particularly important to communicate for example what the patient can expect after the trial has been terminated.

Third, the considerable differentiation in expertise, tasks, and responsibilities among minors, their parents, and clinicians constitutes asymmetric relationships that complicate decisions on clinical trial participation.[23] This asymmetry creates a dependency of minors and their parents upon each other and upon clinicians to provide, explain, and frame information, which raises serious ethical concerns about conflicts of interests, uncritical loyalty towards physicians, and information bias.[24-27] Nonetheless, all of these issues can be addressed adequately and need not be a hurdle to the establishment of relationships of mutual trust between all individuals involved in the decision.[28 29]

Fourth, one should be vigilant that informed consent does not become mere 'documented consent'. For several reasons, the signature of a document by no means guarantees a duly informed, well-considered, rational decision. First, the fact that informed consent is granted by competent persons does not imply that competences are actually used to take a stance towards a study protocol. Rationality is not necessarily the golden standard of all important decisions we make in life, and other factors (particularly tacit elements like hope, trust, or dependency) may shape decisions to grant informed consent. Several studies indicate issues that work against rational decision-making, such as inadequacies in understanding the research,[16-18 20 30] and emotional distress.[31] Second, Pinxten suggested that consent discussions can be well-considered and rational decisions, but might be a priori decisions as well, representing and confirming a positive (or negative) stance towards research that parents already had before recruitment.[32] Third, time constraints and the urgency of the situation may influence the consent process, for

example in emergency settings, or when inclusion in the protocol must be completed shortly after the diagnosis of a serious disease.

DISCUSSION AND CONCLUSION

Dealing with the ethical issues in pediatric clinical research is complex and delicate. Now that a growing body of ethical reflection and legal regulation aims to guide the ethical conduct of clinical trials in Europe for more than 10 years, it is important to reflect on how the available ethical and legal frameworks affect actual practice. For example, do the current ethical and legal frameworks adequately respond to the needs of the different stakeholders involved in the actual conduct of pediatric clinical research? And (how) are available guidelines implemented in practice? When addressing these questions, several considerations should be taken into account.

First, it must be emphasized that ethics, the law, and ethics committees do not establish ethical research conduct as such. Researchers and other health care professionals play a key role in the practical realization of ethical research conduct. The evolution of newer ways of data acquisition such as opportunistic sampling, dry blood spot technology, and the development of biobanks renders new challenges as well. Ethical requirements and legal regulations need to be interpreted and applied in practice, taking into account the heterogeneity of the pediatric population and the large diversity of research projects.

Second, one should be vigilant not to confuse the operational implementation of ethical principles, with the successful approach of ethical concerns as such. For example, obtaining signed informed consent does not automatically imply respect for persons.

Third, one should always keep in mind that it is all about the minor. In this respect, minors should not only get opportunities to participate in decisions concerning their health and/or participation in clinical research, they should also be given the freedom to take or leave these opportunities as they wish. For example, respect for minors may be fostered by maximizing their participation in the informed consent process (taking their understanding and maturity into account). Still, one should also consider the wish of a minor not to take part in the informed consent process, even if the minor concerned is sufficiently mature and capable of understanding what the trial is about. According to the current ethical and regulatory frameworks, however, this may not always be fully possible in practice, for example when assent or dual consent is explicitly required.

Finally, the challenge ahead is to foster ethical conduct in all involved. The mere existence of ethical reflection and legal regulation, by no means, implies a successful translation to practice. In addition, it would be unreasonable to expect from minors and their parents to just own the skills and know-how that are required to make well–considered decisions on participation in a clinical trial. However, at present, easily accessible support for minors and their parents in deciding on research participation is still largely lacking. The same holds for the challenging tasks that researchers or other medical practitioners face in pediatric clinical trials. Therefore, efforts should be made to employ the vast and unexplored potential of empowering all involved for the advancement of ethical conduct in pediatric clinical research.

ADDENDUM

The article, on which this chapter is based, was published in 2013. At that time the new European Clinical Trials Regulation was being drafted. On April 2nd 2014 the European Parliament approved the new Clinical Trials Regulation (Regulation No. 536/2014).[33] As soon as it comes into force, expectedly in 2020, this regulation will repeal the Clinical Trials Directive (Directive 2001/20/EC)[9] discussed in this chapter. The goal of the new Regulation is to simplify and harmonize the scientific and ethical review of clinical trials in the EU. In contrast to the current directive, in which EU member states are bound to implement the requirements from the directive into their national laws, the upcoming regulation has direct binding legal force in all EU member states.

Regarding pediatric clinical research, the new Regulation differs from the Directive in several respects. Some differences concern small details, while others are more substantial. For pediatric clinical research the main differences are related to the risk and burden thresholds in research without a potential direct benefit and the informed consent process.

Concerning the informed consent process for example, the regulation now states that a child who reaches the age of legal competence during a trial explicitly needs to consent before he can continue to participate (art 32:3 Clinical Trials Regulation). Another example, also relevant for pediatric clinical research, relates to new rules for informed consent in emergency situations. In contrast to the current regulation, article 35 of the Regulation now arranges conditions for the acceptability of deferred consent in emergency situations.

The main change concerning risk and burden thresholds in pediatric clinical research without a potential direct benefit can be found in article 32 of the new Regulation (table 4), which is the counterpart of article 4 in the Clinical Trials Directive. As previously discussed in this chapter, the current Clinical Trials Directive does not provide limits regarding the acceptable levels of risk and burden for pediatric research without a prospect of direct benefit; it doesn't even distinguish between pediatric research with or without a prospect of direct benefit (art 4 Clinical Trials Directive). By contrast, the new Regulation does make this distinction and sets limits to risk and burden in pediatric research without a prospect of direct benefit. It states that research with no direct benefit for the participating minor should have some benefit for the populations represented by the minor (group-relatedness) and may pose only minimal risk and burden to the minor in comparison with standard treatment of the minor's condition (art 32:1:g:ii Clinical Trials Regulation).

Table 4: Clinical Trials Regulation – Article 32

Article 32: Clinical trials on minors
1. A clinical trial on minors may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met: a. the informed consent of their legally designated representative has been obtained; b. the minors have received the information referred to in Article 29(2) in a way adapted to their age and mental maturity and from investigators or members of the investigating team who are trained or experienced in working with children; c. the explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in Article 29(2) to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator; d. no incentives or financial inducements are given to the subject or his or her legally designated representative except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial; e. the clinical trial is intended to investigate treatments for a medical condition that only occurs in minors or the clinical trial is essential with respect to minors to validate data obtained in clinical trials on persons able to give informed consent or by other research methods; f. the clinical trial either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors; g. there are scientific grounds for expecting that participation in the clinical trial will produce: i. a direct benefit for the minor concerned outweighing the risks and burdens involved; or ii. some benefit for the population represented by the minor concerned and such a clinical trial will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor's condition.
2. The minor shall take part in the informed consent procedure in a way adapted to his or her age and mental maturity.
3. If during a clinical trial the minor reaches the age of legal competence to give informed consent as defined in the law of the Member State concerned, his or her express informed consent shall be obtained before that subject can continue to participate in the clinical trial.

Due to the directly binding nature of the upcoming regulation to all EU member states the Dutch Medical Research (Human Subjects) Act (WMO) had to be adapted and aligned

with the upcoming Regulation.[34] Before March 1st 2017, the WMO held more restrictive risk and burden thresholds for pediatric clinical research without a prospect of direct benefit (former art 4:1 WMO) Currently, the adapted WMO holds the same thresholds as the upcoming regulation (new art 3:1:d WMO). In practice, this means that there has been a shift in the Netherlands towards allowing non-therapeutic research with more risk and burden to be offered to children and their parents than before. The old Dutch standard imposed a limit of minimal risk and burden, but the new puts the threshold at minimal risk and burden compared to standard treatment. How this comparator is going to be used is inevitably a topic of discussion. What if the standard is very burdensome and risky, does that mean these children can be exposed to similar high risks and burden, for non-therapeutic research purposes?

In relation to the new Clinical Trials Regulation the European Commission expert group on clinical trials revised in 2017 the 'Ethical considerations for clinical trials on medicinal products conducted with minors'.[35] To draft this revision a working group lead by the Dutch Ministry of Health, Welfare and Sports was established.[iii] The main objective of this revision was to align the document with the upcoming Clinical Trials Regulation and with the latest scientific and ethical insights regarding research with children. The revised document is meant for all parties involved in research with children, including research professionals, RECs, other regulatory authorities and potential participants and their families. It gives guidance on various ethical aspects of pediatric clinical research from birth up to the age of legal competence to provide informed consent. This guidance addresses among others: the informed consent process, risk thresholds, and required expertise for trial assessment. For example, based on new empirical and ethical insights elaborate changes have been made pertaining to the involvement of children in the decision-making process. The document also discusses new insights into how to minimize risk and burden for children participating in research.

iii I was a member of this working group. Insights from research presented in this thesis were implemented in the revision. They relate to taking into account motivations of parents and children not only in the recruitment and informed consent process but also during the design of the research, the importance of focusing on (logistical) burden and methods of minimizing that burden.

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CHAPTER 3

Pediatric clinical research in the PICU: Ethical challenges and solutions

Niina Kleiber*, Krista Tromp*, Mirjam G Mooij, Suzanne van de Vathorst, Dick Tibboel, Saskia N de Wildt.

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*[*shared first authorship]*

ABSTRACT

Critical illness and treatment modalities change pharmacokinetics and pharmacodynamics of medications used in critically ill children, in addition to age-related changes in drug disposition and effect. Hence, to ensure effective and safe drug therapy, research in this population is urgently needed. However, conducting research in the vulnerable population of the pediatric intensive care unit (PICU) presents with ethical challenges. This chapter addresses the main ethical issues specific to drug research in these critically ill children and proposes several solutions.

The extraordinary environment of the PICU raises specific challenges to the design and conduct of research. The need for proxy consent of parents (or legal guardians) and the stress-inducing physical environment may threaten informed consent. The informed consent process is challenging because emergency research reduces or even eliminates the time to seek consent. Moreover, parental anxiety may impede adequate understanding and generate misconceptions. Alternative forms of consent have been developed taking into account the unpredictable reality of the acute critical care environment.

As with any research in children, the burden and risk should be minimized. Recent developments in sample collection and analysis as well pharmacokinetic analysis should be considered in the design of studies.

Despite the difficulties inherent to drug research in critically ill children, methods are available to conduct ethically sound research resulting in relevant and generalizable data. This should motivate the PICU community to commit to drug research to ultimately provide the right drug at the right dose for every individual child.

INTRODUCTION

Drug research in children balances between the advancement of knowledge – and consequently improvement in clinical care – and protection of this vulnerable population susceptible to harm and exploitation. Children are relatively incapable of protecting their own interests and therefore need additional protection as recognized in many international ethical and legal documents concerning research with humans.[1-4] Specific provisions for minors, for example relating to the informed consent process and the acceptability of burden and risk have recently been reviewed by our group.[5] These provisions pose challenges to research in children. Failing to conduct clinical trials in minors turns children into '*therapeutic orphans*' because the level of protection is not balanced with the need of generating knowledge to improve care.[6]

THE NEED FOR DRUG RESEARCH IN CHILDREN

We need to be aware that every medication used in clinical practice that has not been studied in clinical trials can be considered an experiment. Clinical drug trials in children are essential because data on effectiveness and safety often cannot reliably be derived from data in adults. Major changes in pharmacokinetics (PK) and pharmacodynamics (PD) occur with increasing age due to changes in body composition, ontogeny of drug metabolism and transport and renal function.[7] The relative lack of knowledge on drug disposition can lead to treatment failure[8 9] and adverse events as serious as fatalities.[10 11] It is known that extrapolation from adult data has caused harm in the past. For example, a lack of knowledge on ontogeny of enzymes responsible for conjugation caused grey baby syndrome in neonates treated with doses of chloramphenicol derived from adult studies.[12 13] Similarly, drug choice and dosing for patients in the pediatric intensive care unit (PICU) cannot always be derived from research in the general pediatric population because PK/PD is influenced by critical illness [e.g. inflammation, liver and renal failure)[14-17] and its treatment modalities (e.g. extra corporeal membrane oxygenation (ECMO), hypothermia, continuous renal replacement therapy).[18-20]

Some drugs (such as vasoactive and sedative drugs) are almost exclusively used in critically ill children, and therefore can only be researched in these patients. However, a large proportion of drugs used in pediatric practice has not been systematically tested in the pediatric population. To stimulate pediatric drug research the Best Pharmaceuticals for Children Act in the US and a similar directive in Europe offered incentives to pharmaceutical companies to generate data in children.[21 22] Regrettably, fewer than 50% of these studies and 26% of those focusing on safety were published in peer-reviewed journals. Moreover, studies on safe and efficient drugs were more likely to be published than studies resulting in negative labelling change, putting children at risk of inefficient

or unsafe prescriptions.[23] Although these stimulating measures generated some useful safety and prescribing information in children, they did not result in the expected reduction of off-label use.[24 25] Estimates of off-label use in the pediatric population still range from 10-65%.[26] In the PICU, even up to 70% of drugs are unlicensed or off-label, which reflects the lack of knowledge on drug efficacy and safety in the PICU population.[27-29]

CHALLENGES OF DRUG RESEARCH IN THE PICU

The previous paragraph has made clear that drug research in the PICU is essential. But research in this population of critically ill children is precarious and raises specific ethical challenges. These challenges may be specific to culture and legislation of each individual country; this chapter focuses mainly on research in high income countries. The ethical dilemma of conducting research in the PICU is recognized by pediatric intensivists themselves; in a survey of 415 pediatric intensivists, over 95% found randomized controlled trials (RCTs) on potentially life-saving therapies ethically acceptable, but at the same time almost all were in ethical conflict with these studies.[30] The specific challenges faced by researchers in the PICU are, first, the extraordinary physical environment of the PICU that presents challenges to the design and conduct of research and its ability to generate useful results. Second, the children themselves may be too young to consent or incapable of it due to acute illness and sedation. Then, parents or surrogates are responsible for the decision to involve their child in research, with consequences for the informed consent process, notably under the stressful conditions of the admission. Last, patients in the PICU already undergo many painful and invasive procedures as part of clinical care. Therefore, additional burden and risk of research procedures must be minimized.

Improving care of the critically ill child implies generating reliable knowledge with research widely endorsed by caregivers and families. This chapter addresses the main ethical issues specific to drug research in the PICU and proposes several solutions.

OPTIMAL STUDY DESIGN AND CONDUCT IN THE PICU

Research subjects included in research of poor quality are exposed to risk and burden without benefit, neither for themselves nor for others. Therefore, only methodologically sound research that can generate new results should be proposed to possible research subjects. This requirement was already laid down in the Nuremberg Code in 1949, and consequently in all other important ethical and legal documents concerned with research with humans.[1-4] The specific study population, recruitment method, outcome measures, use of rescue medication and protocol adherence can influence the validity

of research in the critically ill child and consequently influence the usefulness of the generated results. Table 1 presents an overview of these issues.

Table 1: Challenges to quality of clinical drug studies in critically ill children

Theme	Challenge	Impact on results of trial
Study population	Heterogeneous, small patient populations and relative lack of multicenter research networks	Risk of inconclusive trials due to limited sample size
Recruitment	Risk of selective recruitment: the sickest patient may not be enrolled	Risk of bias and reduced generalizability
Outcome measure	Selection of clinical relevant outcome measures may be jeopardized by small sample sizes	Outcome may be clinically irrelevant
Rescue medication	Allowing rescue medication with the study drug in placebo arm, as not doing so may be perceived as unethical	True efficacy of study drug cannot be determined
Protocol adherence	Protocol violations due to ethical conflicts e.g. when a child's condition deteriorates and physician is biased towards the, potential life-saving, study intervention	May severely impact the validity of study results

STUDY POPULATION

Children in the PICU represent a wide age range and a broad case mix of underlying diseases and ICU diagnoses. Moreover, the critically ill child receives many drugs simultaneously and combinations differ between centers. Therefore, while studying a single drug, the interactions with co-medications and type of underlying diagnosis and care may interfere with outcomes. More than 80% of randomized controlled trials (RCT) are single-centred.[31] This reduces generalizability of the results from these trials. Data sharing and collaboration in larger international PICU research networks could overcome this limitation. Examples of pediatric critical care networks are the Canadian Critical Care Trials Group (Pediatric Interest Group) and the NICHD Collaborative Pediatric Critical Care Research Network. Europe and the other continents are lagging behind: to our knowledge international PICU networks are non-existent to date.

RECRUITMENT

An underestimated limitation to the generalizability of PICU trial outcomes could be the difficulty with recruitment. One third of RCTs in the PICU is terminated before the needed sample size is achieved, often due to recruitment problems.[31] One of the reasons for recruitment problems could be reluctance to approach potential research subjects, also known as 'gate-keeping', which attitude may be due to the clinicians' fear of excessive patient burden.[32] This usually means that the sickest patients are less likely to be included in research. To our knowledge, the study by Menon and colleagues is the only addressing barriers to the recruitment process in the PICU. This was an observational trial implying an ACTH stimulation test, blood sampling on an existing line and recruitment within 26 hours of admission. Almost 50% of 1707 eligible research subjects were not

approached due to unavailability of legal guardians, language issues, lack of agreement of treating physician or prior enrolment in another study.[33] Thus, we need to be aware of possible selection bias and its effects on generalizability of research results in the PICU. One solution to recruitment issues could be co-enrolment of patients in multiple studies.[34] Research shows that participation rates do not decline when parents are asked to have their child participate in two studies simultaneously. This is only possible, however, if it does neither effect study outcome (e.g. simultaneous inclusion in two RCTs with potential influence on outcome of the studies) nor increases patient burden and risk to unacceptable levels (e.g. additive blood sampling volume increases above safety margins).

OUTCOME MEASURES

Appropriate outcome measures in PICU research are another challenge. It is difficult to identify good outcome measures due to the combination of low prevalence of major adverse events (e.g. severe morbidity, mortality) and small sample size of many studies (median of 49 patients).[31] While the majority of trials report laboratory or physiological primary outcomes, mortality was the primary outcome measure in 2% of trials.[31] Data from a recent feasibility trial of clonidine for sedation suggest that at least 190 patients are needed to show a 1.5 day difference in days of ventilation and many more to show relevant differences for other outcomes such as length of PICU and hospital stay.[35] Laboratory or physiological outcomes should be clinically relevant, otherwise the research cannot result in improvement of patient outcome.[36] Relevant outcome measures and validated assessment tools are therefore essential. The latter is not always the case. For example, Vet and colleagues showed that two thirds of the many different sedation scores used in studies on ventilated children receiving a continuous infusion of sedatives were not validated for PICU patients.[37] Regarding the effect of a medication, it must be kept in mind that adverse effects may not become apparent until years after PICU stay. A major concern in this regard is the possible effect of sedative and analgesic medication on longer-term neurological outcome.[38] Enrolling former PICU patients in follow-up programs can broaden our knowledge on long-term outcomes. This should be encouraged, as currently very few units provide care and research beyond the ICU stay.

RESCUE MEDICATION

The use of rescue medication in a randomized trial for a potential life-saving intervention with a placebo group presents additional ethical and scientific challenges.[39] Full equipoise regarding the efficacy of the study drug contrasts with the clinician's perceived need to administer the study drug as a rescue therapy despite the inclusion of the patient in the placebo group. When rescue therapy is allowed, only 'early' versus 'late' effects can be determined when analyzing data on an intention to treat basis. More

children are needed to show a beneficial effect of the drug. As a consequence, overall more children will receive placebo and be at risk for a negative outcome, including death, provided the study drug is really effective. Holubkov and colleagues present an interesting hypothetical study, i.e. steroids for pediatric septic shock, and use sample size simulations to illustrate this challenge.[39] A solution to avoid misuse of rescue medication is to educate physicians, nurses and other staff involved in the care of research participants on the rationale and clinical equipoise in research.

PROTOCOL ADHERENCE

Protocol adherence may be jeopardized if the treating physician is biased towards the study drug and may decide to violate the study protocol when a patient's situation is deteriorating. In the survey of Morris and colleagues, discussed above, a large majority of physicians admitted that they may be biased toward the study arm on the basis of published data from uncontrolled studies.[30] Moreover, two thirds indicated that they do not fully adhere to the study protocol when the patient's condition deteriorates and parents ask for the study drug. There was a strong correlation between the occurrence of an ethical conflict and the likelihood of protocol violations, compassionate use of the study drug or alterations to the protocol. These violations are an important risk factor for bias in these studies and consequently may affect the validity of the findings. A way of avoiding protocol violation is to inform everyone involved in the care of the research subjects about the rationale for the study, the existing equipoise motivating its conduct and the potential benefits of the study.

INFORMED CONSENT PROCESS IN THE PICU

Informed consent is one of the ethical cornerstones of performing research with human subjects. It represents the implementation of the ethical principle of respect for persons. Respect for persons means that persons are treated as autonomous agents, and that persons with diminished autonomy have a right to protection.[3] Informed consent has been incorporated in many ethical and legal guidelines concerned with research with humans.[1-4 40 41] Five elements are distinguished, which are all essential for a valid consent: transmission of information; understanding of this information; no coercion by others; competence; and actual consent.[42] These requirements cannot always be met in research with children in the PICU, due to the vulnerability of the population and extraordinary surroundings. Besides that, children in the PICU generally are not able to participate in the decision as they may be too young, too ill or too heavily sedated. In these cases their parents (or legal guardians) need to consent for them, a process that is known as proxy consent.[43]

FACTORS INFLUENCING INFORMED (PROXY) CONSENT IN THE PICU

A qualitatively good consent process prepares future research subjects for the trial, is free and informed. In the PICU, quality of consent is threatened by several factors.

ANXIETY

The stressful PICU environment has great impact on parents and children. Many parents of acutely ill children suffer from acute and post-traumatic stress disorder and this often lasts for months after discharge.[44 45] Practitioners asking consent for trials in emergency situations reported that some parents are unable to focus on anything else than the health of their child and will not be able to take any decision about research, whereas others will still be receptive.[46] The most important reason for refusal to consent as spontaneously provided by parents in the PICU is anxiety or being overwhelmed.[33 47] In contrast, in a study by Thomas and colleagues parents mentioned being anxious, but said that this did not influence their decision regarding research participation.[48] These parents provided useful suggestions. For example, tell parents about ongoing trials prior to PICU admission if possible (e.g. in the case of planned surgery) and do not approach parents when their child is in the operating room, but before *or* after surgery.[48]

BURDEN OF RESEARCH

In a large study by Hulst and colleagues, 421 parents who declined informed consent to a nutritional assessment study implying additional procedures were asked for their reasons. Two-thirds wanted to avoid additional burden to their child.[49] In two multicenter studies, Menon and colleagues analyzed parents' reasons to decline informed consent. One study was an observational study involving blood sampling, the other concerned different kinds of PICU research. In both studies, the burden of blood sampling was a major reason for declining participation.[33 47] A small qualitative interview study was conducted by Thomas and colleagues among parents who accepted or declined consent in an undefined PICU trial. The interviews identified added pain, discomfort and additional diagnostic testing as factors discouraging participation.[48] Overall, it would seem that limiting the burden of research procedures is essential to increase participation. This is further elaborated on in the next paragraph about burden and risk in pediatric research.

ILLNESS SEVERITY

Interestingly, severity of illness does not seem to influence consent rates in the PICU. Two studies done in the PICU could not identify a difference in severity of illness between children of consenting and non-consenting parents.[33 49] Still it should be borne in mind that the life-threatening nature of illness in the PICU can make parents more susceptible to the idea that the trial might convey a therapeutic benefit, when this is very unlikely.[50]

UNDERSTANDING

Parents reach a good understanding of their child's health condition within 24 hours after admission in PICU,[51] but this need not be true for research participation. Studies in the neonatal intensive care unit (NICU) suggest that the conditions for a valid consent are often unmet.[52 53] Understanding and recalling of information is difficult for parents in a research context and they also overestimate their understanding.[54 55] Written information and posters are identified by parents in the PICU as useful information tools in the informed consent process.[48 56]

ALTERNATIVE FORMS OF INFORMED CONSENT

The life-threatening and acute nature of illness in the PICU puts great pressure on the validity and process of informed consent. It is not always possible to achieve written informed (proxy) consent before start of the study in emergency settings. Alternative consent processes should balance the respect for the decision of future research participants and the benefit trial participation might bring them. Two different alternative consent processes are available to deal with these time constraints: a waiver of consent or deferred consent.

WAIVER OF CONSENT

A waiver of consent, also known as exemption from informed consent, means that no consent is required for inclusion of research participants in research. It is sometimes allowed for studies in life-threatening conditions for which available treatments are unproven or unsatisfactory and the study intervention needs to be applied urgently to be effective. The conditions under which a waiver (or) is acceptable vary between countries. For example in the US, additional requirements are community consultation and public disclosure.[57] They favor dialogue with the community, which is informed about the project beforehand and its results afterwards.[58] Raymond and colleagues describe an efficient way of in-hospital community consultation for a trial of vasopressin added to adrenaline in cardiac arrest in the PICU. All parents were informed about the trial through posters, written information, a website and the research team, and were offered the possibility to opt-out of the study. 80% of parents were aware of the trial and knew how to opt out. The authors suggested this approach could increase recruitment while preserving freedom of choice.[56]

DEFERRED CONSENT

Another way of dealing with the acute nature of decisions in emergency research, but still taking into consideration parental decision, is the use of deferred consent. This form of consent implies that patients are recruited without consent and that after enrolment consent is asked for use of already collected information and ongoing participation.

Just like a waiver of consent, deferred consent is an alternative in emergency situations where obtaining prior informed consent is not possible and postponing the intervention would potentially harm the child. The conditions under which deferred consent is acceptable vary between countries, too. An example of conditions can be found in the upcoming new EU regulation on clinical trials.[40]

Research suggests that parents favor deferred consent over waived consent and consider it an acceptable alternative to informed consent for emergency situations.[59 60] In a study by Woolfall and colleagues parents suggested it would be advisable for the researchers to seek advice from the bedside nurse to establish the moment when the child's condition was stable and then ask consent.[60] Practitioners with experience in asking deferred consent were generally positive about parental acceptance of this method of consent. They highlighted the importance of explaining the purpose of its use.[46] A systematic review on waiver of informed consent in pediatric resuscitation trials concluded there is a general endorsement of research in life-threatening situations, but that parental preferences for waiving of consent or deferred consent vary depending on the approach and population.[61] Opinions of children about being enrolled in studies with a waiver of consent or deferred consent have not yet been addressed in research.

Interpretation of approval of alternative forms of consent by researchers and research ethics committee (REC) members may differ. It has been shown that REC members may be less prone to accept alternative forms of consent than are researchers.[62] This may be a barrier to conduct trials with alternative forms of consent. Documenting parental acceptance of deferred consent process could provide insight into its acceptability.

Questions still remain on how to handle consent when a child dies before deferred consent from parents or proxies is asked. Problems arise with use and storage of the collected data. Excluding data from deceased patients (for whom no deferred consent was obtained) may impair validity of the results.[63 64] Still, although seeking deferred proxy consent for a deceased child can burden parents, the majority of parents wish to be informed.[59] Bereaved parents said it was important to adapt to their needs on a case-by-case basis and to allow time after the child's death.[60]

COMBINED FORMS OF CONSENT

The waiver of consent and deferred consent methods are justified only in life-threatening situations where postponing trial inclusion would harm to the research subject.

If the required conditions should not be met, full informed (proxy) consent needs to be given prior to inclusion. Practitioners have suggested that an approach taking the reality

of parents into account would be ideal.[46] Combining different forms of consent could be a useful way of adapting to the unpredictability of acute care environment. The FEAST trial, which studied the effect of fluid resuscitation on mortality, is an example of such a combination.[65] Informed consent was asked only if the child was stable enough and the parents not too distressed. Otherwise, verbal assent was sought prior to inclusion and full written consent after child's stabilization.

IMPROVEMENTS TO THE INFORMED CONSENT PROCESS

It would be worthwhile to study alternative consent approaches in pediatric intensive care, taking into account that approaches in different situations cannot be uniform. Although we should be wary about adding burden to parents (which an informed consent conversation and decision can be), parents must be given the opportunity to make a decision. The approaches to obtaining informed consent in different situations cannot be uniform. The solutions to practical problems may never be a permit for exploitation and harm of the vulnerable population at the PICU.

Getting informed consent is not a one time achievement: informed consent is a continuous process, especially in the PICU. After improvements in health or decrease of sedation, children can regain the capacity to consent or assent; and they are entitled to do so after reaching legal age of consent. They should then be informed about the study they were involved in and their assent or consent should be sought when feasible – usually when the acute phase of the disease is over or after transfer to the ward. It is advisable to consider this re-consent process in the design of the study because the research team needs to plan for the resources needed to allow this important follow-up. There are no studies on this re-consent process in critically ill children.

To our knowledge the amount of empirical research on preferences and motivations of parents and children to participate in drug research in the PICU is small. These preferences have been assessed more extensively in other pediatric populations, but data from the PICU are lacking. It would be relevant to study factors that shape the decision to consent or dissent to drug research in the PICU– for example with a focus on altruism, hope and loyalty. Having this information would enable us to better tailor the process of recruitment and informed consent to the needs of the parents (or legal guardians) and children.

BURDEN AND RISK OF DRUG RESEARCH IN THE PICU

According to the principle of proportionality, risk and burden of research participation should be balanced against the possible benefit of the trial. The principle of subsidiarity entails that research can only take place if there are no other less burdensome and less risky methods of generating the same results. In other words: burden and risk for the research participant need to be minimized, irrespective of the possible benefits of the trial for the individual or society. These principles of proportionality and subsidiarity underlie important ethical guidelines concerning research with humans.[1-4] Children are vulnerable and therefore need additional protection against the risk and burden of research participation. Recent progress in drug research can decrease burden and risk for children participating in research in the PICU. Some of these new techniques are illustrated in the next paragraphs.

METHODS TO DECREASE BURDEN AND RISK BY USE OF NEW TECHNIQUES

PK studies traditionally implied collecting many 1-2 mL blood samples from a patient at scheduled intervals up to 12 times in 24 hours, which means a considerable burden to research subjects. Recent progress in sampling methods, data analysis and outcome measurement tools can decrease this burden while rational evidence-based drug regimens can still be derived. As an example, a solution to oversedation with morphine, which is often observed in neonates, was found using a three-step approach. First, PK data were collected during two RCTs.[66 67] Second, the data were analyzed with population PK, and it was found that same dosing guidelines of morphine resulted in much higher plasma concentrations in neonates than older infants.[68] Third, a new dosing guideline was created on the basis of this finding, and validated.[69] The following paragraphs detail how limited blood sampling schedules, novel drug concentration assays and data analysis methods can decrease burden and risk.

OPPORTUNISTIC OR SPARSE BLOOD SAMPLING METHODS

PICU patients usually have an arterial or venous central line from which blood can be drawn. To avoid accessing lines just for research purposes, sampling for research purposes can be combined with regular blood work. In the absence of a line, samples can be collected during routine heel pricks.[70] Opportunistic studies determine levels of the drug received as part of the patient's treatment and no study drug is given.[71] Another strategy is to measure drug concentration in blood left over from routine analysis.[70 71] Population pharmacokinetics make use of randomly collected and limited blood samples per patient. Maximum allowed amounts of blood for research purposes vary between hospitals and countries, but generally the maximum is set at 3-5% of total blood volume within 24 hours and 5-10% of total blood volume over 8 weeks.[72]

LOW VOLUME DRUG ASSAYS

High performance liquid (LC-MS) or gas (GC-MS) chromatography allows simultaneous analyses of many low concentration substances in small plasma volumes (10-100 µL) or left-overs.[70 73] This is of particular interest for studies in neonates and small children, whose total blood volume is small.[71] New emerging technologies such as digital microfluidics will further decrease the sample volume needed and may represent the future of PK studies.[74-76] If combined with sampling using micro needles sharp enough to minimize nerve contact,[77] these technologies will further decrease the burden and risk of clinical drug trials in children.

DRIED MATRIX SPOTS

Dried matrix spot analysis requires no more than a minimal volume (5-30 µL) of biological fluids (urine, plasma, blood) on blotting paper, allowing for easy and cost-effective sample processing, storage and shipping.[71 78] These samples can be used in PK studies and pharmacogenetic tests.[78-82] Dried blood spots obtained during routine new-born screening can be used for genetic (DNA) and epigenetic (DNA methylation) analysis until 30 years later if stored at -20°C, as is routinely done in some countries.[82 83]

PK-PD MODELLING TOOLS

Population PK-PD analysis using non-linear mixed effect models allows using samples derived from different dosing regimens with random timing and only few samples per patient to estimate PK parameters and the PK-PD relationship and to optimize dosing recommendations.[84] Sparse sampling is a strategy by which just 2-3 samples per individual allow deriving PK parameters from a group of 25-100 infants.[85] This enables studies in which the patient already receives the drug for clinical reasons and even the use of left-over material from regular blood work. Population PK calculates both the inter- and intra-individual variability. The effects of different covariates like age and weight are tested by delineating their effects on inter-individual variability. Particularly relevant to PICU patients, the effect of disease and its treatment can be taken into account (e.g. renal function, inflammation, ECMO).[86] PK-PD parameters in particular populations, such as patients on ECMO, can be estimated.[87] A next step is to validate the obtained PK data and the dosing guidelines derived from these data in a prospective trial performing the same sample analysis. In an efficient new dosing regimen, inter-individual variability should be greatly reduced and dose-effect relationships should remain unchanged or improve. Regrettably, this validation is rarely performed.[71 85]

MICRODOSING STUDIES

Microdosing is an elegant new method to minimize burden and risk in PK-studies in children.[88] It uses a sub therapeutic, extremely low dose of drug, known as a microdose

(e.g. 1/100th of the therapeutic dose).[89 90] Microdosing is ideal for non-therapeutic pharmacokinetic studies in critically ill children because therapeutic or adverse effects will not occur. Microdosing also enables knowledge gain on drug metabolism or excretion, using probe drugs for these specific pathways. Radioactive labelling allows detection of the extremely low dose and carries very minimal risk, because the level of radioactivity is well below international cut-offs for radiation safety.[91] It cannot be excluded, however, that parents and health care providers perceive this differently, and it is recommended therefore to underline in the informed consent process the minimal risk of microdosing.

Table 2: Examples of ethical challenges of clinical drug trials in critically ill children

Example of drug trial*	Ethical challenge**
RCT with daily sedation interruption[92]	Risk of 'gate-keeping' during recruitment and non-adherence to protocol during study for fear of accidental extubation or line removal.
RCT with corticosteroids for pediatric septic shock[39]	Potential life-saving medication: rescue medication in placebo arm may reduce validity of trial.
RCT with vasopressin add-on for cardiopulmonary resuscitation[93]	Emergency treatment leaves no time for informed consent: acceptability of deferred consent or waiver of consent.
Pharmacokinetic study with drug already prescribed to patient[70]	No potential benefit to patient. Multiple catheter accesses may increase risk of infection. Blood sample volume may compromise health, especially in small children.
Dose-finding study for new drug, e.g. Imatinib for pulmonary arterial hypertension	Risk of off-label prescription without any trial, ethical barriers may be perceived too high to perform a 'non-therapeutic trial'.
Microdosing pharmacokinetic study with radio-active labelled drug[94]	No potential benefit to patient despite safe radiation dose: 'gate-keeping' by physicians and/or nursing staff out of fear for radiation-related negative outcomes. And possible misunderstanding of minimal risk by parents.

*Examples are illustrative and based on trials and experiences of researchers in the PICU. **Ethical challenges are examples that researchers could face when performing these kinds of studies but are of course not limited to these examples.

CONCLUSION

Drug research in the PICU is essential because there is a great need of evidence-based dosing guidelines. Conducting drug research in critically ill children is a precarious enterprise because of the vulnerability of the research population and the specific circumstances in the PICU – which present specific ethical challenges. Examples of these challenges are presented in table 2.

Characteristics of the specific study population, recruitment issues, challenging outcome measures, use of rescue medication and sub-optimal protocol adherence, stand in the way of obtaining useful results. Gatekeeping does not only limit recruitment but is also an underestimated source of bias especially with acutely ill children. Collaboration

of intensive care units is bound to improve quality of research and to increase the likelihood of producing generalizable data.

Informed consent for research in the PICU implies almost invariably proxy consent by the parents or legal guardians. Documenting informed consent does not imply, however, that parents know what they signed for. Indirect evidence shows that informed consent may not be achieved in the stressful situation of the PICU due to parental anxiety and misunderstanding. The informed consent process does not stop when the consent is signed but is rather a continuous process. Continuous dialogue between researchers, parents, and children when possible, is the only way to do justice to the unpredictable and changing reality of the PICU. 'One size fits all' is not always possible for structuring informed consent in the PICU therefore alternative approaches to consent need to be developed and evaluated.

Drug research carries burden and risk for the subjects and it is only logical that we should prevent or minimize these, especially in the vulnerable population in the PICU. New techniques allow us to generate evidence with decreased burden and risk to the research subject and deserve to be widely used and systematically evaluated. The different types of studies (e.g. dose-finding studies, PK studies, RCTs) each present specific challenges. Dealing effectively with these challenges is an essential step towards evidence for dosing and drug choice in pediatric intensive care practice.

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CHAPTER 4

Motivations to participate in pediatric clinical research: A systematic review

Krista Tromp, C Michel Zwaan,
Suzanne van de Vathorst.

Motivations of children and their parents to participate in drug research: A systematic review.

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ABSTRACT

Information on motivations for research participation may enable professionals to better tailor the process of recruitment and informed consent to the perspective of parents and children. Therefore, this systematic review assesses motivating and discouraging factors for children and their parents to decide to participate in clinical drug research.

Studies were identified from searches in six databases. Two independent reviewers screened and selected relevant articles. Results were aggregated and presented by use of qualitative meta-summary.

38 studies fulfilled the selection criteria and were of sufficient quality for inclusion in the qualitative meta-summary. Most mentioned motivating factors for parents were: health benefit for child, altruism, trust in research, and relation to researcher. Most mentioned motivating factors for children were: personal health benefit, altruism and increasing comfort. Fear of risks, distrust in research, logistical aspects and disruption of daily life were mentioned most by parents as discouraging factors. Burden and disruption of daily life, feeling like a 'guinea pig' and fear of risks were most mentioned as discouraging factors by children.

Paying attention to these motivating and discouraging factors of children and their parents during the recruitment and informed consent process in drug research increases the moral and instrumental value of informed consent.

INTRODUCTION

Clinical drug research with children balances between the advancement of knowledge - and consequently possible improvement in clinical care - and the protection of a vulnerable population. On the one hand children are relatively incapable of protecting their own interest and therefore need to be protected from harm and exploitation in research.[1] On the other hand, clinical drug research is essential to generate sufficient evidence for improvements in pediatric care and drug dosing. Current estimates of off-label or unlicensed use of drugs range between 10% and 60% in the pediatric population.[2] Precisely because clinical drug research with children is a precarious enterprise, special attention needs to be given to the informed consent process.

Informed consent is one of the ethical cornerstones of human research. It represents the ethical principle of respect for persons: persons are treated as autonomous agents and persons with diminished autonomy are protected.[3] In the case of research with children, this means that their parents (or legal guardians) have to consent for them. This does not mean that children should be excluded from or ignored in the informed consent process. The United Nations Convention on the Rights of the Child states that children who are capable of forming their views have a right to express those views in any proceedings affecting the child directly.[4] Since they are the ones undergoing the research burden and risk, constructions of co-consent and assent are introduced in ethical and legal legislation to do justice to the opinion of children.[5-7]

The process of informed consent and assent in clinical research with children might be clear in theory, in practice it is not. The question remains how to design this process of information and consent/assent as to include the perspective of children and their parents. Their perspective is vital, since they have the key role in decision-making on research participation. One way of taking their perspective into account is to look at the motivations children and their parents have to endorse or decline participation in pediatric clinical research. When professionals know to which aspects of research children and their parents attach importance, they know what information is relevant for their decision. And this knowledge may enable professionals involved in research to better tailor the process of recruitment and informed consent/assent to the perspective and needs of parents (or legal guardians) and children.

To our knowledge no comprehensive systematic review exists on these motivating and discouraging factors for children and their parents to decide to participate in clinical drug research. Two narrative reviews exist on why parents enroll their child in research.[8 9] Both reviews show personal benefit and altruism as most important motivations of parents

to enroll their child in research. However, these narrative reviews are not comprehensive nor systematically handled. Also, these reviews do not consider children's motivations and are not focused on pharmacological research.

Therefore, we aimed to pool the existing empirical literature on motivations of children and their parents to consent or dissent to participation in clinical drug research. This systematic review attempts to answer the following research question: What are motivating and discouraging factors for children and their parents to decide to participate in clinical drug research?

METHODS

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statement.[10]

DATA SOURCES AND SEARCH STRATEGY

We searched for peer-reviewed English-language articles using Embase, Medline, Web of Science, Pubmed, PsycINFO and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) for empirical studies investigating the motivations (motivating and discouraging factors) of children and their parents to consent or dissent to participation in clinical drug trials. The search strategy was developed in collaboration with an information specialist of the Medical Library.

The search strategy was based on 3 concepts: 1) motivation for participation; 2) clinical drug research; 3) children and parents. The search strategy in Embase was as follows: ('refusal to participate'/de OR 'patient participation'/de OR 'parental consent'/de OR (((refus* OR decision* OR decid* OR allow* OR reason* OR motivat* OR willing* OR assent* OR consen* OR dissent* OR attitude* OR view* OR perspective* OR choos* OR choice*) NEAR/6 (participat* OR nonparticipat* OR enrol*))):ab,ti OR ((conflict/de OR 'motivation'/de OR drive/de OR 'informed consent'/de) AND (participat* OR nonparticipat* OR enrol*):ab,ti)) AND ('clinical trial (topic)'/exp OR 'pharmacological science'/exp OR 'clinical research'/de OR ((RCT* OR trial* OR scien* OR research*) NEAR/11 (participat* OR enrol*)):ab,ti OR (('science in general'/de OR research/de OR 'medical research'/de OR 'human experiment'/de) AND (pharmacology/exp OR 'drug therapy'/exp OR (drug* OR pharmaco* OR medication* OR psychopharmacolog*):ab,ti))) AND (child/exp OR newborn/exp OR adolescent/exp OR adolescence/exp OR 'child behavior'/de OR 'child parent relation'/de OR (adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl*

OR minors OR underag* OR (under NEXT/1 ag*) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*):ab,ti). Searches in the other databases were based on the Embase search terms.

Appendix 1 provides the exact search strategies in each database. We performed the initial search on March 20th 2013 and updated it on August 22th 2014.

INCLUSION AND EXCLUSION CRITERIA

Studies were included when they addressed empirical data of: 1) children and/or parents on; 2) motivations for dissent or consent; 3) to participation in clinical drug research. We excluded articles with: 1) No empirical data; 2) Participation in only other clinical research than drug research; 3) Participation in vaccination studies (this religiously debated subject might confound results); 4) Narrative reviews.

STUDY SELECTION

After identification of records from the search strategy, duplicates were removed from the retrieved records. In the screening phase, two reviewers (KT and WB) independently screened titles and abstracts of identified records for relevance to the research question. In case of discrepancy between the primary reviewers, a third reviewer (SV) decided upon inclusion for further eligibility assessment. In the eligibility phase, two reviewers (KT and WB) independently assessed full-text articles for eligibility. Again, in case of discrepancy between the primary reviewers, a third reviewer (SV) decided upon inclusion for systematic review. The PRISMA flow diagram presented in Figure 1 shows the process of study selection: identification, screening, eligibility assessment and inclusion.

DATA EXTRACTION AND STUDY QUALITY ASSESSMENT

We extracted relevant data from the articles eligible for systematic review with the use of a data extraction form. A template of this form can be found in appendix 2. The main outcome measures extracted were motivating factors and discouraging factors mentioned by children and/or their parents (or legal guardians). Study population, in- and exclusion criteria, patient characteristics, study design, and other outcome factors besides motivating and discouraging factors were also extracted. We graded the level of evidence of individual studies according to levels set by the Dutch Institute for Healthcare Improvement (CBO) (as indicated in table 1 and table 2) and critically appraised the eligible articles to determine study quality and risk of bias (according to the Critical Appraisal Skills Program (CASP) checklists).[11] Studies with a very low level of evidence (level 'D' for quantitative studies or level '-' for qualitative studies) or high risk

of bias (based on CASP checklists) were excluded from data synthesis of motivating and discouraging factors.

Table 1: Level of evidence of quantitative studies

Level of evidence*	Characteristics
A1	Systematic reviews involving at least two studies at A2 level, of which the results of separate studies are consistent
A2	Randomized comparative clinical studies of good quality (randomized, double-blind controlled trails) of sufficient size and consistency
B	Randomized clinical trials of mediocre quality, of insufficient size, or other comparative studies
C	Non-comparative studies
D	Expert opinion

* Levels according to those set by the Dutch Institute for Healthcare Improvement (CBO)

Table 2: Level of evidence of qualitative studies

Level of evidence*	Characteristics
++	Credible meta-synthesis of qualitative studies
+	Credible study
+/-	Study of which credibility is dubious
-	Study of which credibility is minimal

* Levels according to those set by the Dutch Institute for Healthcare Improvement (CBO)

DATA SYNTHESIS

We performed a qualitative meta-summary to give an overview of the motivating and discouraging factors mentioned by children and their parents. A qualitative meta-summary is a quantitatively oriented aggregation approach to research synthesis of descriptive findings from both quantitative and qualitative studies.[12] This approach of data synthesis entails treating research reports as indexes of the studies conducted, and the research findings in these reports as indexes of the experiences of the persons who participated in those studies. Therefore this approach functions well for our research question concerning motivations for participation, answered by qualitative and quantitative research. First, we extracted motivations mentioned by children or their parents from the result sections of the eligible studies regardless of how many participants endorsed the reason. Second, we created draft lists of all mentioned motivations in all studies for motivating factors and discouraging factors. Third, we grouped these motivations per theme and presented them as aggregated data. These themes of motivating and discouraging factors were not predefined, but defined by the total of extracted data.

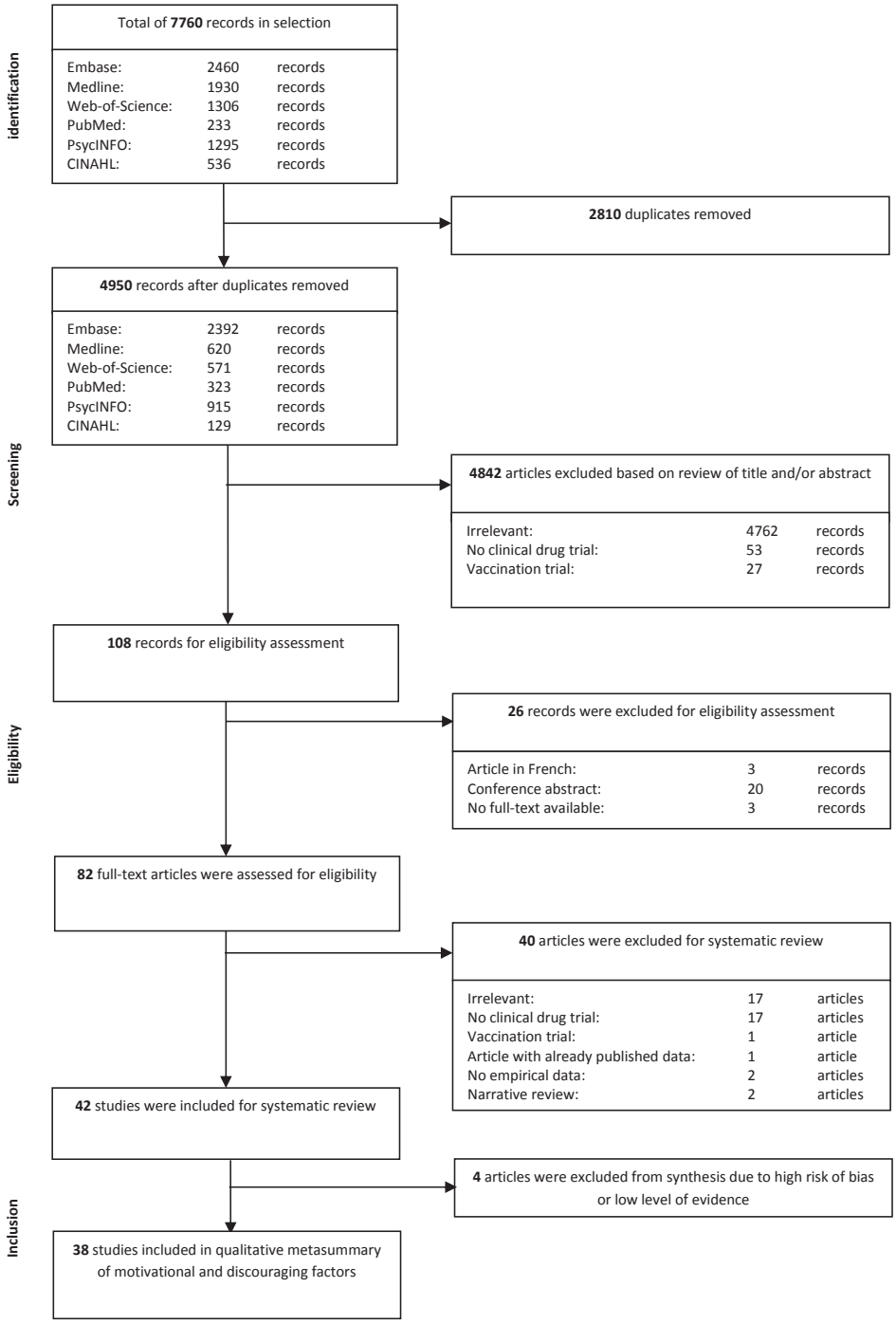

Figure 1: PRISMA flow diagram of study identification, screening, selection and inclusion

RESULTS

STUDY SELECTION

Our initial search produced 4950 titles after removing duplicates. After title and abstract screening, 108 records remained for full-text eligibility assessment. After full-text review, 42 articles could be included for data-extraction and systematic review.[13-54] Figure 1 shows in a PRISMA flow diagram the results of study identification, screening, eligibility assessment and inclusion. Extracted data from these 42 studies, including study characteristics, motivating and discouraging factors, level of evidence and critical appraisal, can be found in the evidence tables in appendix 3.

CHARACTERISTICS OF INCLUDED STUDIES FOR SYSTEMATIC REVIEW

Of the 42 articles that were included for systematic review, 26 were quantitative studies (including 15 written questionnaires, 7 verbally administered questionnaires and 4 studies analyzing registries of consent/dissent) and 16 were qualitative studies (including 10 interview studies, 2 focus group studies, 1 interview and focus group study and 3 studies with secondary analysis of interviews (of which one is a case study)). The number of research subjects involved per study ranged from 1 to 81 in the qualitative studies, and from 20 to 448 in the quantitative studies. In 37 studies parents (or caregivers/or legal guardians) were questioned about their motivations compared to 16 studies in which children themselves were questioned. The age of the children questioned ranged between 6 and 21 years. The majority of these studies included children up to 18 years of age. Three studies included children up to 21 years of age.[19 35 42] Although, in Europe, we do not consider these respondents children, these studies were included because the majority of the respondents in these 3 studies were below 18 years of age. Two studies did not define the age of their respondents [16 39]. The included studies were very diverse with regard to research population and setting (e.g. PICU/NICU setting, patients with airway diseases, with diabetes mellitus). Studies concerning oncology patients were most prevalent. Parents and children who consented to research were questioned in 39 studies, while 24 studies questioned respondents who dissented to research participation. Some studies questioned respondents about drug research in general or on a hypothetical drug study protocol (vignettes). But the majority questioned respondents in daily practice about participation in a specific drug study protocol. Most studies entailed participation in drug protocols with a prospect of direct benefit for the participant, only 5 drug protocols were considered to have no prospect of direct benefit for the participants. Table 3 shows an overview of study characteristics. The extra supplemental material provides evidence tables including these 41 studies with extracted data (*online resource 4*).

Table 3: Study characteristics of 42 included studies for systematic review

	Characteristic	No. of studies	Studies
Type of study	***Quantitative study***	*26*	*See categories below*
	Written questionnaires	15	Barakat, 2013; Berg, 2010; Buscariollo, 2012; Cain, 2005; Cherill, 2010; Hoberman, 2013; Read, 2009; Sammons, 2007; Tait, 1998; Tait, 2003; Truong, 2011; Van Stuijvenberg, 1998; Vanhelst, 2013; Wagner, 2006; Zupancic, 1997
	Verbally administered questionnaires	7	Baren, 1999; Brody, 2005; Brody, 2012; Harth, 1990; Miller, 2013; Rothmier, 2003; Wendler, 2012
	Secondary analysis of data	4	Menon, 2012; Norris, 2010; Peden, 2000; Wynn, 2010
	Qualitative study	*16*	*See categories below*
	Interviews	10	Barrera, 2005; Broome, 2003; Cartwright, 2011; Koelch, 2009; Liaschenko, 2001; MacNeill, 2013; Masiye, 2008; Patterson, 2014; Pletsch, 2001; Pletsch, 2001(2); Woodgate, 2010
	Focus groups*	3	Caldwell, 2003; Lebensburger, 2013
	Secondary analysis of data**	3	Deatrick, 2002; Hoehn, 2005; Oppenheim, 2005
Study population	**Only parents/caregivers**	26	Baren, 1999; Buscariollo, 2012; Cartwright, 2011; Caldwell, 2003; Deatrick, 2002; Harth, 1990; Hoehn, 2005; Lebensburger, 2013; Liaschenko, 2001; MacNeill, 2013; Masiye, 2008; Menon, 2012; Oppenheim, 2005; Pletsch, 2001(2); Pletsch, 2001; Rothmier, 2003; Sammons, 2007; Tait, 1998; Truong, 2011; Tait, 2003; Van Stuijvenberg, 1998; Vanhelst, 2013; Woodgate, 2010; Zupancic, 1997; Wynn, 2010; Hoberman, 2013
	Only children	5	Broome, 2003; Cain, 2005; Cherill, 2010; Koelch, 2009; Miller, 2013
	Both	11	Barakat, 2013; Barrera, 2005; Berg, 2010; Brody, 2005; Brody, 2012; Norris, 2010; Patterson, 2014; Peden, 2000; Read, 2009; Wagner, 2006; Wendler, 2012
Setting	**Oncology**	11	Barrera, 2005; Berg, 2010; Broome, 2003; Deatrick, 2002; Liaschenko, 2001; Miller, 2013; Oppenheim, 2005; Pletsch, 2001; Read, 2009; Truong, 2011; Woodgate, 2010
	Diabetes mellitus	5	Broome, 2003; Buscariollo, 2012; Cain, 2005; Pletsch, 2001(2); Pletsch, 2001
	Airway diseases	7	Barakat, 2013; Brody, 2005; Brody, 2012; Harth, 1990; MacNeill, 2013; Rothmier, 2003; Sammons, 2007
	Sickle cell disease	4	Barakat, 2013; Lebensburger, 2013; Patterson, 2014; Wynn, 2010
	PICU / NICU	4	Cartwright, 2011; Hoehn, 2005; Menon, 2012; Zupancic, 1997
	Sick and healthy children (not specified)	4	Caldwell, 2003; Cherill, 2010; Vanhelst, 2013; Wendler, 2012
	Anesthetics	3	Peden, 2000; Tait, 1998; Tait, 2003
	Emergency department	2	Baren, 1999; Van Stuijvenberg, 1998;
	Psychopharmacology	2	Koelch, 2009; Wagner, 2006
	Other***	3	Masiye, 2008; Norris, 2010; Hoberman, 2013;

Table 3: Study characteristics of 42 included studies for systematic review (*continued*)

	Characteristic	No. of studies	Studies
Type of drug research	**Real life drug study protocol**	33	Barrera, 2005; Berg, 2010; Broome, 2003; Cain, 2005; Cartwright, 2011; Deatrick, 2002; MacNeill, 2013; Harth, 1990; Hoberman, 2013; Hoehn, 2005; Koelch, 2009; Liaschenko, 2001; Masiye, 2008; Menon, 2012; Miller, 2013; Norris, 2010; Oppenheim, 2005; Peden, 2000; Pletsch, 2001; Pletsch, 2001(2); Read, 2009; Rothmier, 2003; Sammons, 2007; Tait, 1998; Tait, 2003; Truong, 2011; Van Stuijvenberg, 1998; Vanhelst, 2013; Wagner, 2006; Wendler, 2012; Woodgate, 2010; Wynn, 2010; Zupancic, 1997
	Drug research in general	4	Sammons, 2007; Tait, 1998; Tait, 2003; Van Stuijvenberg, 1998
	Hypothetical drug study protocol	5	Baren, 1999; Brody, 2005; Brody, 2012; Lebensburger, 2013; Patterson, 2014
Prospect of direct benefit	**Only studies with prospect of direct benefit**	22	Baren, 1999; Brody, 2012; Cain, 2005; Cartwright, 2011; Harth, 1990; Hoberman, 2013; Hoehn, 2005; Koelch, 2009; MacNeill, 2013; Masiye, 2008; Norris, 2010; Patterson, 2014; Peden, 2000; Pletsch, 2001(2); Rothmier, 2003; Sammons, 2007; Tait, 1998; Tait, 2003; Van Stuijvenberg, 1998; Wagner, 2006; Wynn, 2010; Zupancic, 1997
	Only studies with no prospect of direct benefit	5	Barrera, 2005; Berg, 2010; Deatrick, 2002; Miller, 2013; Oppenheim, 2005
	Both	7	Broome, 2003; Liaschenko, 2001; Menon, 2012; Pletsch, 2001; Truong, 2011; Vanhelst, 2013; Wendler, 2012
	Not specified	8	Barakat, 2013; Brody, 2005; Buscariollo, 2012; Caldwell, 2003; Cherill, 2010; Lebensburger, 2013; Read, 2009; Woodgate, 2010
Consenters or non-consenters	**Only non-consenters**	3	Peden, 2000; Norris, 2010; Menon, 2012
	Only consenters	18	Broome, 2003; Cain, 2005; Cartwright, 2011; Deatrick, 2002; Liaschenko, 2001; Masiye, 2008; Miller, 2013; Oppenheim, 2005; Pletsch, 2001; Pletsch, 2001(2); Rothmier, 2003; MacNeill, 2013; Truong, 2011; Van Stuijvenberg, 1998; Vanhelst, 2013; Wagner, 2006; Wendler, 2012; Woodgate, 2010;
	Both	21	Barakat, 2013; Baren, 1999; Barrera, 2005; Berg, 2010; Brody, 2005; Brody, 2012; Buscariollo, 2012; Caldwell, 2003; Cherill, 2010; Harth, 1990; Hoberman, 2013; Hoehn, 2005; Koelch, 2009; Lebensburger, 2013; Read, 2009; Sammons, 2007; Tait, 1998; Tait, 2003; Patterson, 2014; Wynn, 2010; Zupancic, 1997

PICU Pediatric Intensive Care Unit; **NICU** Neonatal Intensive Care Unit
* Study of Caldwell included also personal interviews; ** Study of Oppenheim is a case study; *** anorexia nervosa, malaria, vesico-ureteral reflux

STUDY QUALITY AND RISK OF BIAS

The evidence tables in the extra supplemental material show level of evidence (based on classification in tables 1 and 2) and critical appraisal (including risk of bias) for individual studies. Four studies were of insufficient quality and were excluded from the qualitative meta-summary due to very low level of evidence (level 'D' or '-') and high risk of bias. We excluded one qualitative study because the credibility was minimal (level of evidence

'-'): the presented data did not answer their research question and essential parts of the data were not presented (population consisted of patients with diabetes mellitus and cancer, but data from cancer patients were missing in the article). [19] We excluded three quantitative studies due to high risk of bias: no separate analysis of adult research subjects and children [16]; represented data did not support article conclusions [14]; and inclusion of a very specific study population (patients with Anorexia Nervosa) in which treatment and research motivations cannot be looked at separately [36]. After these four exclusions due to insufficient quality, 38 studies remained for data synthesis (qualitative meta-summary) of motivating and discouraging factors.[13 15 17 18 20-35 37-54]

QUALITATIVE META-SUMMARY OF MOTIVATING FACTORS

Of the 38 articles eligible for qualitative meta-summary 33 studies included motivating factors mentioned by parents to endorse research participation of their child. Ten studies included motivating factors mentioned by children themselves. The extracted motivating factors mentioned by parents and children in the individual studies can be found in the evidence table in the supplemental information. Table 4 and 5 give an overview of the motivating factors for parents and children. Individual health benefit, altruism (including helping others and contributing to science), a general trust in research and the relation to researchers are mentioned by parents in the highest number of studies. Other common motivating factors mentioned by parents to endorse research participation of their child include: more contact with the medical team, benefit for parents themselves, a sense of minimal burden for their child, the opportunity of financial reimbursement, feelings of having no other option, and influence of family and friends. For children themselves the most frequently mentioned factor favoring research participation include personal health benefit, altruism and increasing comfort by participation. Other motivating factors mentioned in multiple studies by children are the relation to the researcher, influence of family and friends, a financial reimbursement, increasing their knowledge about their disease and a sense of curiosity. In one study children also mentioned the feeling of having no other option available.

Table 4: Meta-summary of motivating factors mentioned by parents for participation of their child in clinical drug research

Motivating factor	No. of studies (total = 33)	Individual studies
Personal health benefit for child*	31	Barakat, 2013; Baren, 1999; Barrera, 2005; Brody, 2005; Brody, 2012; Buscariollo, 2012; Caldwell, 2003; Cartwright, 2011; Deatrick, 2002; Harth, 1990; Hoberman, 2013; Hoehn, 2005; Lebensburger, 2013; Liaschenko, 2001; MacNeill, 2013; Masiye, 2008; Oppenheim, 2005; Patterson, 2014; Pletsch, 2001; Pletsch, 2001(2); Read, 2009; Sammons, 2007; Tait, 1998; Tait, 2003; Truong, 2011; Van Stuijvenberg, 1998; Vanhelst, 2013; Wagner, 2006; Woodgate, 2010; Wynn, 2010; Zupancic, 1997
Altruism**	26	Baren, 1999; Barrera, 2005; Buscariollo, 2012; Caldwell, 2003; Cartwright, 2011; Deatrick, 2002; Harth, 1990; Hoberman, 2013; Hoehn, 2005; Liaschenko, 2001; MacNeill, 2013; Patterson, 2014; Pletsch, 2001; Pletsch, 2001(2); Read, 2009; Rothmier, 2003; Sammons, 2007; Tait, 1998; Tait, 2003; Truong, 2011; Van Stuijvenberg, 1998; Vanhelst, 2013; Wendler, 2012; Woodgate, 2010; Wynn, 2010; Zupancic, 1997
Trust in safety of research	12	Barakat, 2013; Buscariollo, 2012; Cartwright, 2011; Harth, 1990; Hoberman, 2013; Hoehn, 2005; MacNeill, 2013; Patterson, 2014; Tait, 1998; Truong, 2011; Vanhelst, 2013; Zupancic, 1997
Relation to researcher	12	Buscariollo, 2012; Caldwell, 2003; Harth, 1990; Hoberman, 2013; Masiye, 2008; Read, 2009; Sammons, 2007; Tait, 1998; Tait, 2003; Truong, 2011; Woodgate, 2010; Van Stuijvenberg, 1998
More contact with medical team	8	Buscariollo, 2012; Caldwell, 2003; Harth, 1990; Lebensburger, 2013; MacNeill, 2013; Masiye, 2008; Wynn, 2010; Woodgate, 2010
Benefit for parents themselves	5	Harth, 1990; Oppenheim, 2005; Rothmier, 2003; Wagner, 2006; Van Stuijvenberg, 1998;
Minimal burden for child	4	Patterson, 2014; Pletsch, 2001(2); Read, 2009; Woodgate, 2010
Financial reimbursement	5	Brody, 2012; Buscariollo, 2012; Harth, 1990; Masiye, 2008; Wagner, 2006
Felt as only option***	4	Cartwright, 2011; Deatrick, 2002; Liaschenko, 2001; Oppenheim, 2005
Influence of family and friends	3	Buscariollo, 2012; Harth, 1990; Read, 2009

* Factor mentioned in studies with and without prospect of direct benefit; ** In 3 studies specifically defined as no motivating factor; *** All studies were in oncology setting

Table 5: Meta-summary of motivating factors mentioned by children for participation in clinical drug research

Motivating factor	No. of studies (total = 10)	Individual studies
Personal health benefit*	8	Barrera, 2005; Brody, 2005; Brody, 2012; Cain, 2005; Miller, 2013; Patterson, 2014; Read, 2009; Wagner, 2006
Altruism	6	Cain, 2005; Miller, 2013; Patterson, 2014; Read, 2009; Wagner, 2006; Wendler, 2012
Increasing comfort	4	Cain, 2005; Koelch, 2009; Miller, 2013; Read, 2009
Relation to researcher	3	Miller, 2013; Read, 2009; Wagner, 2006
Influence of family and friends	3	Cain, 2005; Read, 2009; Wagner, 2006
Financial reimbursement	3	Brody, 2005; Brody, 2012; Wagner, 2006
Increasing knowledge	2	Cain, 2005; Wagner, 2006
Curiosity	2	Cain, 2005; Koelch, 2009
Felt as only option	1	Miller, 2013

* Factor mentioned in studies with and without prospect of direct benefit

QUALITATIVE META-SUMMARY OF DISCOURAGING FACTORS

Of the 38 articles eligible for qualitative meta-summary 24 studies included discouraging factors mentioned by parents for research participation of their child. Six studies included discouraging factors mentioned by children themselves. These include motivations mentioned by respondents who dissented to research participation, but also discouraging factors mentioned by respondents who did participate but considered these factors as negatively influencing their decision. The extracted discouraging factors mentioned by parents and children in the individual studies can be found in the evidence table in the extra supplemental material. Table 6 and 7 give an overview of the discouraging factors for parents and children. Fear of potential risks, a general distrust in research, logistical aspects and disruption of daily life and fear of burden for their child are mentioned by parents in the highest number of studies. Other common discouraging factors mentioned in multiple studies by parents for research participation of their child include: decision considered to be too stressful, a fear of randomization, no prospect of direct benefit for their child, financial constraints and a discomfort with being a proxy. Discouraging factors incidentally mentioned by parents are for example a discord between guardians, religious constraints or privacy issues. For children themselves the most frequently mentioned factors discouraging research participation include fear of burden for themselves and disruption of their daily life, feeling like a 'guinea pig' and a fear of risks. Other discouraging factors incidentally mentioned by children are the prospect of no direct benefit, no understanding of the study, preference for one arm and the decision considered to be too stressful.

Table 6: Meta-summary of discouraging factors mentioned by parents for participation of their child in clinical drug research

Discouraging factor	No. of studies (total = 24)	Individual studies
Fear of risks	14	Baren, 1999; Brody, 2005; Brody, 2012; Buscariollo, 2012; Caldwell, 2003; Harth, 1990; Hoehn, 2005; Lebensburger, 2013; MacNeill, 2013; Patterson, 2014; Pletsch, 2001(2); Read, 2009; Tait, 1998; Tait, 2003;
Distrust in research ('guinea pig')	11	Baren, 1999; Caldwell, 2003; Harth, 1990; Hoehn, 2005; Lebensburger, 2013; Menon, 2012; Peden, 2000; Read, 2009; Sammons, 2007; Tait, 1998; Wynn, 2010
Logistics / disruption of daily life*	11	Baren, 1999; Brody, 2005; Caldwell, 2003; Patterson, 2014; Harth, 1990; Lebensburger, 2013; Peden, 2000; Pletsch, 2001; Read, 2009; Tait, 1998; Wynn, 2010
Burden for child	9	Barrera, 2005; Brody, 2005; Buscariollo, 2012; Menon, 2012; Oppenheim, 2005; Peden, 2000; Pletsch, 2001(2); Read, 2009; Woodgate, 2010
Decision too stressful	7	Hoberman, 2013; Lebensburger, 2013; Menon, 2012; Pletsch, 2001; Read, 2009; Sammons, 2007; Tait, 1998
Fear of randomization	6	Caldwell, 2003; Lebensburger, 2013; MacNeill, 2013; Sammons, 2007; Tait, 1998; Wynn, 2010
No direct benefit for child**	5	Baren, 1999; Barrera, 2005; MacNeill, 2013; Read, 2009; Wynn, 2010
Financial constraints	5	Baren, 1999; Buscariollo, 2012; Harth, 1990; Tait, 1998; Wynn, 2010
Discomfort with proxy consent	2	Buscariollo, 2012; Caldwell, 2003

* For child *and* rest of family; ** Of which 3 are defined as studies with no prospect of direct benefit

Table 7: Meta-summary of discouraging factors mentioned by children for participation in clinical drug research

Discouraging factor	No. of studies (total = 6)	Individual studies
Burden / disruption of daily life	4	Brody, 2005; Koelch, 2009; Read, 2009; Patterson, 2014
Feeling like a 'guinea pig'	3	Koelch, 2009; Peden, 2000; Read, 2009
Fear of risks	3	Brody, 2005; Brody, 2012; Patterson, 2014
Decision too stressful	1	Read, 2009
No understanding	1	Read, 2009
No direct benefit	1	Read, 2009
Preference for one arm	1	Peden, 2000

DISCUSSION

This systematic review shows that the most frequently mentioned motivating factors for parents to endorse their child's participation in clinical drug research are: health benefit for their child, altruism, a trust in research, and their relation to the researcher. Most

frequently mentioned motivating factors for children to participate are: personal health benefit, altruism and increasing comfort. Fear of risks, distrust in research, logistical aspects and disruption of daily life are mentioned most frequently as discouraging factors to endorse participation of their child by parents. Burden and disruption of daily life, feeling like a 'guinea pig' and fear of risks were most frequently mentioned as discouraging factors by children.

One of the most important ethical criteria on which a research ethics committee (REC) should evaluate a research protocol, is whether the objective outweighs the risk and burden to the research subjects: called a consideration of proportionality. In other words: a REC assesses the predictable risk and burden to the research subjects in comparison to the foreseeable benefit to them and to other individuals or groups affected by the investigated condition.[6] Our review shows that this proportionality is also considered by parents and children in their own individual decision about research participation; personal health benefit and altruism are the most frequently mentioned motivating factors and risk and burden are frequently mentioned as discouraging factors. In 7 studies the weighing of these factors (proportionality) is even specifically mentioned by parents.[13 31 38 40 41 46 55] In 2 studies children mention explicit this proportionate weighing.[29 38]

BURDEN OF PARTICIPATION

The results also show that it is not only burden for the *participating child* that influences the decision, but also burden for *parents themselves and the rest of their family*. Professionals involved in pediatric research need to be aware that when a child participates in research, a lot of the burden falls on the shoulders of parents: e.g. they need to be present at the hospital; they are often the ones filling in the diaries. This burden may negatively affect the decision of parents to let their child participate in research. That is also true for logistical aspects and disruption of the lives of the whole family. Parents are the ones absent from work and they need to make sure that other family members are looked after when their child participates in research. Parents mention for example '*the inconveniences of trial participation*'[55] or '*too many visits*'[53] as reasons for dissent.

GENERAL TRUST AND MISTRUST IN RESEARCH

Issues of general trust in research or general mistrust (often explained with wordings as 'guinea pig') influence the decision of parents and children greatly. These issues of trust and mistrust might indicate that their decision is not a weighing of factors but an a priori decision. This idea of an a priori decision was also suggested a few years ago by Pinxten in his thesis.[56] The general trust of children and their parents in research needs to be protected by careful evaluation of study protocols by a REC beforehand. A proper

evaluation system beforehand ensures that the studies offered to parents and children are of such quality that their trust in research is well-founded.

PERSONAL HEALTH BENEFIT

Personal health benefit is one of the most important motivators for parents and children themselves to participate in clinical drug research. This is of course not problematic when the study has therapeutic objectives, but is problematic when no prospect of direct benefit exists.

In all 3 studies with no prospect of direct benefit (all oncology phase 1 studies) where parents were questioned, possible health benefit for their child was a motivating factor.[15 25 37] In the study of Deatrick et al. most parents saw their child's participation in the trial as *'a means of providing treatment to prolong life, though an uncertain treatment'*.[25] In the study of Barrera et al. families main motivator for enrolling in phase 1 trials was *'hope for a cure or prolongation of the child's life and their belief that participating would ensure continuity of care'*.[15] Since the objective of these phase 1 studies is safety assessment and not effectiveness, and because of the fading boundary between research and care, therapeutic misconception is a clear danger in these studies.[57] Adequate information on the rationale of the study is therefore essential. Professionals involved in clinical research need to be aware that the line between hope and reality is thin. As illustrated by an interviewed mother from the study from Oppenheim: *'…the study was proposed as an alternative, and we accepted it to avoid the operation and to gain more time, even a week, but not really believing that it could cure F'*.[37]

Children are also vulnerable to therapeutic misconception, as shown in two studies with no prospect of direct benefit in which children themselves mention therapeutic benefit as an important motivating factor.[15 35]

ALTRUISM

Helping others or contributing to science is an important motivation for parents to endorse participation in clinical drug research. However, 3 studies concluded that altruism was explicitly not a factor in the decision of parents.[13 37 50] Altruistic motivations might be overestimated in this review. These could be socially desirable answers. Remarkable is the finding of Truong et al., that parents with a child in a phase 3 study mention altruistic motivations more often than parents with a child in phase 1 studies.[47]

Helping others and contributing to science were also mentioned frequently by children as a motivation for participation in research. For example, more than 80% of the questioned children in the study of Wendler et al. indicated that finding better treatments

for others was important to their decision to enroll.[51] Two studies that showed altruistic motivations in children questioned children starting at an age of 6 years old. This might indicate that children can be altruistic at a much younger age than currently suggested.[58] Unfortunately, the studies addressing altruism had very wide age ranges (6-18 years) and no stratified analyses for age groups. It would be interesting to look deeper into the role of altruistic motivations of children in pediatric research.

RELATION TO RESEARCHER

Parents and children mention their relation to the researcher quite often as a factor influencing their decision to participate. This should not be a problem if they ask him/her for advice or feel safe with him/her. But it is problematic when parents and children use words as *'I felt pressure'*[42] or even *'They told me to'*[50]. This means that parents and children may feel less free when asked to participate. The effect of this relationship on their decision needs to be considered even more carefully when the roles of researcher and treating physician converge in one, which is often the case in pediatrics.[59]

MORE CONTACT WITH MEDICAL TEAM

Parents mentioned quite often more contact with the medical team as a favoring factor for endorsing research participation. For example, in the study by Masiye et al., some participants felt that if they would refuse to participate in the study, their child might not receive attention from the healthcare workers whenever they would visit the hospital again.[33] And some parents in Caldwell's stated that their child would be better monitored when he/she would be in the trial.[55]This suggests that parents think their child is better looked after or treated when in research. Parents need to be aware that (non-)participation in research does not affect their regular treatment. In our opinion, a patient should not be dependent on research to get the attention he/she wishes for in a treatment setting.

FELT AS ONLY OPTION

Striking is the observation that parents sometimes endorse participation because it feels for them as if they do not have an option.[23 25 31 35 42] This can be a problematic factor, when there are other options available of which parents are not sufficiently aware of. But in certain hospital settings (for example oncology setting) participation in research is indeed the only option parents and children have opposed to palliative care. Furthermore, some children and parents can only accept the child's upcoming death when they have tried all available options. One parent illustrated this clearly in a study by Deatrick et al.: '*There wasn't really a choice in my mind because if I choose to not do anything then I would have been choosing to let her go and I'm not ready for that.*'[25]

NO DIRECT BENEFIT FOR CHILD

Surprisingly, this review shows parents can refuse participation because they do not expect benefit for their child. It is striking that this is mentioned in three randomized phase 3 studies (where a prospect of benefit exists).[14 32 53] A possible explanation could be that parents have a preference for the experimental intervention arm (compared to standard or placebo arm) and are suspicious of the randomization since it does not guarantee them access to the experimental intervention arm. This is illustrated in the study by Baren et al. in which parents mention fear of receiving less than optimal treatment in the study as a discouraging factor for participation.[14]

LIMITATIONS AND STRENGTHS OF THIS REVIEW

This systematic review gives a comprehensive overview of motivating and discouraging factors for children and their parents to consent to clinical drug research. Since we aimed to give an overview of all the available empirical literature on this topic, there is a large variety in drug trials, settings and populations of the studies. This heterogeneity in studies might complicate the interpretation of the pooled data, but we feel it is essential to pool these heterogeneous results, since it reflects the diverse practice of pediatric drug trials.

Because of challenges in the search strings, we limited our research question to participation in pharmacological research. Therefore it is uncertain whether we can extrapolate these results to other medical research (including observational research and other interventional research).

We reported in the qualitative meta-summary the number of studies citing a specific factor. The number of articles reporting a specific factor may not represent the importance of this factor to the research participants. Besides that, given the wide range in the number of research participants per study, an increasing number of studies citing a factor does not necessarily reflect more parents or children mentioning this factor. However, qualitative meta-summary is still the best way to pool this kind of data from qualitative and quantitative empirical studies. To get more insight in the motivations of parents and children qualitative research is of essential value and a large portion of the data in this review comes from qualitative data. Therefore, this way of pooling the data does justice to the diversity in qualitative and quantitative research available for answering our research question. By including qualitative and quantitative research the strengths of both types of research are combined; in depth results and possibility of unanticipated motivations from qualitative research, and large sample sizes and standardization from quantitative research.

CONCLUSION

It is essential that professionals during the recruitment and informed consent/assent process pay attention to the motivating and discouraging factors children and their parents have for participation in clinical drug research When professionals know more about the motivations of parents and children to endorse or decline participation in clinical drug research, professionals know which aspects of research parents and children attach importance to and what information is of relevance for their decision. This information can then be used by professionals in the informed consent materials and conversations. When children and their parents are being informed about the aspects of research to which they attach importance, they may reach a decision more consistent with their own values. Therefore, the attention to these motivating and discouraging factors makes the *informed consent/assent* of parents and children more *informed*, which thus increases the *moral* value of informed consent/assent.

Besides leading to an increase in the *moral v*alue of informed consent, paying attention to the motivations of children and their parents for participation in clinical drug research can also be of *instrumental* value. By adapting the study protocol, the recruitment and the informed consent process to the needs and wishes of children and their parents, participation rates will probably increase (and dropout rates can decrease). For example, by diminishing logistical barriers (which this review shows, are mentioned often by parents as negatively influencing their decision) at the setup of the study, parents and children will probably be more inclined to participate. Therefore, adapting the research protocol, recruitment and informed consent process to the needs of children and their parents may lead to *more* informed consents.

This systematic review gives a comprehensive overview of the available empirical data on motivating and discouraging factors for parents and children to consent/assent to clinical drug research. But it also shows us that specific populations are underrepresented in this field of research. Further research is needed in diverse populations and research fields (for example healthy children, children with chronic disease such as cystic fibrosis, and critically ill children). This future research should specifically focus on the factors that shape the decision of children themselves, since research with children on this topic is scarce. Although children cannot consent by themselves, they can assent and we shouldn't forget to listen to them. They are the ones bearing the burden and risk during participation in clinical drug research, and possible beneficiaries of the research.

APPENDICES

APPENDIX 1

Search strings per database: page 188

APPENDIX 2

Data extraction form: page 190

APPENDIX 3

Evidence tables: page 191

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CHAPTER 5

What motivates children and their parents to participate in pediatric clinical research? An interview study

Krista Tromp, Els van der Wiel,
Inekee van der Vaart, Monique van Dijk,
Suzanne van de Vathorst.

Burden weighs more than risk: Why children and their parents decide to participate in clinical research? Results from a qualitative interview study *[submitted]*

ABSTRACT

Knowing why parents and children want to participate in pediatric clinical research, teaches us what they attach importance to, what information they base their decision on and which information they need to receive in the recruitment and informed consent process to be able to make a proper decision. In this qualitative semi-structured interview study, we explored minors' and their parents' motivations, views and expectations during the process of recruitment and informed consent for pediatric clinical research.

We interviewed children and their parents who had been asked to participate in clinical research and had had an informed consent conversation (N=34). Interviews were analyzed using thematic analysis.

Children and their parents attach more importance to burden than to risk when they need to decide about participation in clinical research. The anticipated burden of participating is most frequently mentioned as motivating or discouraging for their decision to participate. However they have a very broad notion of burden, with an emphasis on logistical burden. They outsource their concerns about risk by trusting the research staff and their physicians. Their altruistic motivations are mostly reciprocity-based.

The design of pediatric clinical research and especially the recruitment and informed consent process can be ameliorated by the findings of our research regarding the motivating and discouraging factors. This way, research will be better in line with the preference of children and parents, and children and their parents will be better equipped to make a decision about participation.

INTRODUCTION

On the one hand, we need children to participate in clinical research to advance scientific knowledge and develop new - much needed - treatment options for children. On the other hand we want to protect children against the harms from research, because they are a vulnerable and dependent population.[1]

For decades scientists, ethicists, philosophers, physicians, members of research ethics committees and other healthcare professionals write about and discuss this precarious balance between protection and advancement of knowledge.[2-5] But how do children and their parents, as key decision-makers in pediatric clinical research, experience this balance themselves? Is it a trade-off for them? Do they also weigh the harms against the benefits when they need to decide about participation in clinical research? Or are other factors just as important to them in their decision?

Why would you expose your child to the burden and risk of clinical research without the least expectation of a direct health benefit? Why would you as a child want to go to the hospital solely for research procedures, it being a place where you might already have negative experiences? Why would you undergo a bunch of procedures without knowing it will be of any help to you? Thinking about these questions makes us wonder why someone would let his/her child participate at all. Still, we do know research with children is needed, so we do offer it to them and they do participate. There are probably other factors at hand in their decisions to participate than just striking a balance between protection against harm and advancing knowledge. For example Hoberman and colleagues and Vanhelst and colleagues showed that the child's health status also is an important factor in research decision-making by parents.[6 7] The study by Hoberman also showed that parents with positive perceptions of the research team are more inclined to participate.[7] And other studies showed that for many parents not participating didn't even present itself as an option.[8]

Results from a systematic review on motivations of parents and children to consent or dissent to clinical research showed that most research on this topic is done in the oncology setting, and that other fields of clinical research are underrepresented.[9] This review also revealed that the majority of the empirical research done in this field is of a quantitative nature, while qualitative research can generate much more important and essential information to further this debate.[10] Qualitative empirical research gives better insights into research subjects' motives and attitudes, an indispensable element of normative work in medical ethics.[11] Knowing why parents and children want to participate in pediatric clinical research, teaches us what they attach importance to, what information they base their decision on and which information they need to receive in the recruit-

ment and informed consent process for pediatric research to be able to make a proper decision. It helps us with the ethically sound inclusion of children in research and can improve both the instrumental and moral value of informed consent/assent in pediatric research. It gives us the chance to: a) communicate more decision-oriented information during the recruitment and informed consent process, creating more *informed* consents/assents; and b) adapt the research design, recruitment and informed consent process to their needs and wishes, creating probably *more* informed consents/assents.

Therefore, the main objective of this qualitative interview study was to explore minors' and their parents' motivations, views and expectations during the process of recruitment and informed consent for pediatric clinical research. Secondary objectives were: 1) To assess motivating and discouraging factors that shape the decision to consent or dissent to participation in pediatric clinical research; 2) To assess their views on the recruitment and informed consent process; 3) To assess their attitude in the decision-making process; 4) To assess their expectations of participation in pediatric clinical research.

METHODS

This study is reported in accordance with the consolidated criteria for reporting qualitative research (COREQ).[12]

STUDY SETTING AND POPULATION

The study population consisted of children and their parents who had been asked to participate in clinical research and had had an informed consent conversation with a health-care professional. Between March 2014 and July 2016 participants were recruited from three departments of Erasmus MC – Sophia Children's Hospital: the department of Pediatric Intensive Care, Pediatric Oncology, Pediatric Pulmonology (division: Cystic Fibrosis).

Due to the qualitative nature of the study no sample size calculation was performed. Enrolment of participants ended when theoretical saturation was reached for answering the main research question and no new concepts emerged.[13]

To do justice to the variety of clinical research and to ensure a wide range of perspectives, purposive sampling was used for the selection of the study population.[14] Sampling consisted of children of diverse ages and mothers and fathers, who had been asked to participate in clinical drug trials (including phase I, II, III and IV; and pharmacokinetic/pharmacodynamic studies), intervention studies other than drugs (including medical devices) and observational studies.

Drawing comparisons between participants, diseases, and research types was not a central study aim nor is it possible with this type of qualitative data.[15 16]

INTERVIEWS

KT conducted semi-structured interviews with all parents and children face-to-face in the hospital, at home or by telephone, according to the family's preference. Six themes were addressed in the interviews: Why did you decide (not) to participate?; motivating and discouraging factors for this decision; views about the recruitment and informed consent process (including provision and content of the information); attitudes in the decision-making process; and expectations of participation.

CODING AND ANALYSIS

The interviews were audio taped and transcribed verbatim. Interviews were analyzed using thematic analysis. Through systematic objective coding, we identified and labelled themes, in order to elucidate relevant concepts and thus to interpret motivations, views and expectations of children and parents during the process of recruitment and informed consent in pediatric clinical research. We coded and analyzed the data using QSR International's NVivo 11 qualitative data analysis Software.

KT initially coded all interviews. SvdV coded all interviews as a second researcher. Disagreements were settled by consensus. Initial coding tree was based on the interview guide and included: 1) Main reason for participating in specific clinical research study; 2) Motivating factors; 3) Discouraging factors; 4) Views about recruitment and informed consent process (including information material); 5) Attitudes in the decision-making process; 6) Expectations for participation in the research. Initial coding for motivating and discouraging factors was based on results from a previously executed systematic review on motivations for parents and children to participate in clinical research.[9] During the process of coding and analysis this initial tree was adapted and elaborated based on the data from the interviews. Interview coding and analysis continued until no new codes, concepts, or patterns emerged.

RESULTS

STUDY POPULATION

Between March 2014 and July 2016 34 participants of 21 families participated in this interview study. We interviewed 4 children about their own decision and 30 parents (11 fathers, 18 mothers, one adult sister) about the proxy decision for participation of their child. Participants were equally distributed amongst the three departments and

educational level of the parents was diverse. Some families had consented and some had declined to participate in the proposed pediatric clinical study. Table 1 presents an overview of the participant characteristics.

Table 1: Participant characteristics

	Characteristic	No. of participants
Family role	Father	11
	Mother	18
	Sister*	1
	Child	4
Disease of child	Cancer **	11
	Cystic Fibrosis	10
	Craniosynostosis	6
	Esophageal reflux	3
	Rare genetic condition	2
	Necrotizing enterocolitis	2
Education level parents	Secondary school	2
	Intermediate vocational education	11
	Higher vocational education	7
	University	6
	Unknown	4
Age parents	Median age [range]	34 [18-70] years of age
Age of their children	Median age [range]	3 [0-17] years of age
Age interviewed children*	Median age [range]	15 [11-17] years of age

* 1 adult sister joined the interview, she is regarded a parent in the analyses; ** including acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), lymphoma; *** not all children were interviewed, because they were too young or did not want to be interviewed

MAIN MOTIVATOR TO CONSENT OR DISSENT

All parents and children were asked why they decided to consent or dissent to the proposed clinical study.

One mother decided not to let her child participate in the proposed clinical research study. And another mother agreed with her child (boy, 17 year of age) not to consent to participation in the proposed clinical research study. Both children did participate in research in the past. Their main reason for not participating in the proposed study was concern with the expected burden of the study (table 2).

Table 2: Example burden as reason for dissent

Participant	Quote
Child 201 *(age 17)*	*If it doesn't work, it doesn't work, that's what they said…I am not a pill swallower. I've tried, but it really did not work. Twice it was successful and then they said: "You have to wait another day." And then I thought: "I'm not going to take pills for another day" ... Then I said: "No." Then it stopped.*

Children and parents who had consented to participation in the proposed clinical study, were asked what their main reason for participation was. Table 3 gives an overview of these main reasons for consent. The expected minimal or no burden of participation for the child was the most frequently mentioned main motivator. Altruistic motivations (not defined, helping science or helping other/future patients) and a personal benefit for the child were also mentioned frequently. Other main reasons included among others: a general trust in research and researchers and trust in the safety of research. Some participants mentioned a combination of two or more reasons for participation.

Table 3: Why did you decide to participate? Examples of main reasons for participating

Main reason for participating*	Quote
Minimal or no burden for child	*... understood from everything that she is not bothered by it herself and I think that is the most important thing. If she were bothered by it, I would not have done it.* (mother 122)
Altruism **- Helping future or other patients** **- Helping science**	*Yes, that was to see what helps best for later, for the future. And that's why I participated, it can help people later. For me it does not really matter that much, they said, but I think yes if I can help people, try. ... Yes, when I was one years old, I also had cancer, I also helped a lot of people. That's what I'm gonna try again now.* (child 201, age 17)
Health benefit for child	*We think it is important that a solution is sought of course for his illness. That medication comes that improves his quality of life and of course stretches his life.* (father 053)
No risks associated with participating	*Yes the same applies to me. If it is risk-free for him, I think it's okay.* (father 243)
General trust in research **- Trust in researchers** **- Safe otherwise wouldn't be offered**	*I have all the confidence in this study. I had ... I think it's one and a half, two years ago, that [physician x] started talking about it. And I also viewed his explanation on YouTube a couple of times and I just really had all confidence. And I asked him, because at that moment we could not start because the study did not start yet, I said what would you do? And then he said to start immediately, he said. And I just had every confidence in it.* (mother 042)
Possibility to stop participation	*But then it turned out, yes I do not know about studies and stuff, I thought yes when you join then you are obliged [to continue (red)], but then it turned out that you could stop at any moment, if you did not like it anymore. So that is actually the reason that I thought I'll do it.* (mother 062)
Curiosity	*Curiosity, well what will come from it. Yes how it develops further.* (father 123)
Combination of reasons	*Because I think it is important that research can be done so that other people in the future can benefit from it. And also, they said at least, if in adults, the drug also tackles a broader spectrum of fungi t, so this medication also seems better to me.... Yes that that medication works better than the standard medication.* (child 131, age 16)

* Answer to the open question: "Why did you decide to participate in this clinical study?" or "Why did you let your child participate in this clinical study?"

MOTIVATING AND DISCOURAGING FACTORS

When asked to elucidate their decision, interviewees revealed that most of the times their decision was a result of weighing several motivating and discouraging factors (table 4). An illustrative overview of these motivating and discouraging factors is shown in figure 1.

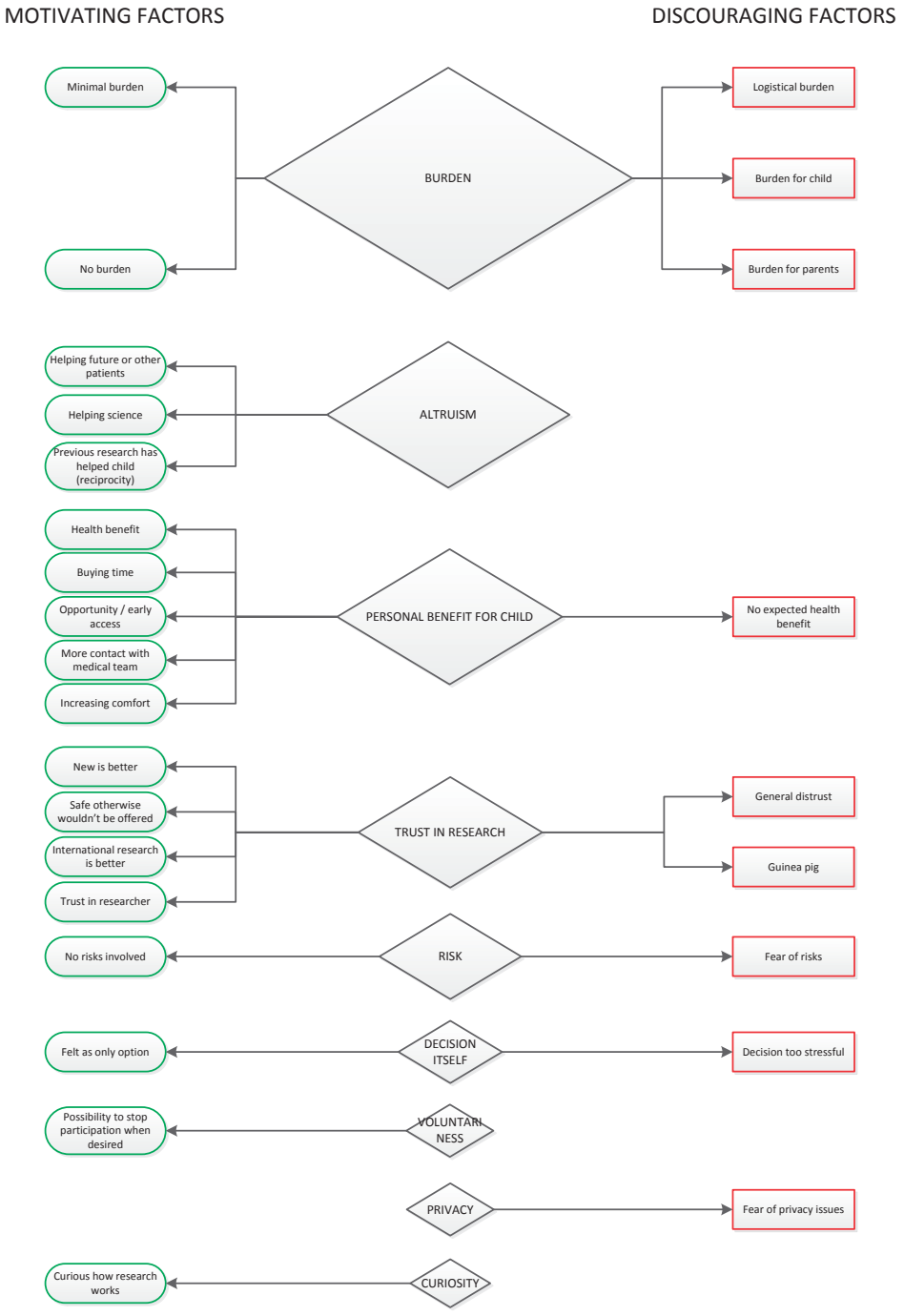

Figure 1: Overview of motivating and discouraging factors
Diamond shapes show the factors influencing participation (reason); size of the diamond shape illustrates importance of mentioned factors. Red squared boxes indicate discouraging factors; Green rounded boxes indicate motivating factors.

Burden was mentioned by almost all participants as having an influence on their decision (table 4). This included minimal and no burden as a motivating factor and too much expected burden as discouraging factor. Fear of expected burden was not only limited to the burden of study procedures on the child, but included also the way in which their child's participation would burden the parents (e.g. filling in questionnaires) and the logistical burden of being in clinical research (e.g. travel arrangements).

Table 4: Examples of motivating and discouraging factors

Participant	Quote
Weighing of factors	
Mother 222	*Yes, we have already participated in several studies. And I often have something like, if it doesn't burden them and cannot do any damage, then I think: "Yes, you do not do this research for nothing, so it probably has positive effects for children who come after them or at least there is information that others can use." And yes, then I do not mind.*
Burden	
Mother 112	*Yes of course it must be interesting, how often do we need to go to the hospital and that is to be planned with my husband's job and that's pretty much it. We do not live nearby… I mean to the hospital once more that does not matter. But if you are continuously…then it is not interesting for us: No.*
Child 151 *(age 15)*	*I first thought about it, because they said what you would need to do and that you had to go to the hospital more often. I thought: "I really don't want that, I do not want to go to the hospital more often and I do not want to do more than what I already do, with school and stuff." So at first I said: "No, I do not want it."*
Personal benefit	
Father 053	*It was a promising study, what the doctors thought very promising. So we thought something like: "When we participate in that study, there is a follow-up study, then he actually is ahead, before the medication comes on the market."*
Child 151 *(age 15)*	*And yeah, if I can continue with it and it helps better than nebulizing, that would be easier of course. Because then I can go on with it in one go, it's less work, I like that better. Yeah, it is not every single time a device, charging the device, and all that kind of things.*
Altruism	
Mother 242	*For me it is a basic value, why I am also a blood donor and organ donor, things that I find important. If you can help someone with that, I actually think you should do that if it is possible.*
Mother 072	*Yes, I think that is the ultimate goal, of course, to help your own child and other children. That is, what I think is the overarching ... not so much that it is not burdensome, but of course you do it for science and for the future.*
Mother 132	*I think the biggest reason is, yes you see from all sides that this study is necessary, that there is so much possible and it is of course beautiful that there is so much. Yes a lot of study is needed for that. And yes, you yourself think if you can help a hand somewhere; if you see how much they do here for your child, what is mega important; and if you can help a little something with it. Then you do that. Then you want to do that.*
Child 131 *(age 16)*	*Because I think it is important that research can be done, so that other people in the future can benefit ... Yes ... without ... If no research could take place, in that way they would never evolve in healthcare. So then, like in the old days, it would have been, at least not that long ago ... now it's a lot nicer to be here.*
Trust and distrust	
Mother 242	*No actually not. Out of curiosity I would inquire about the usefulness, the necessity. But I assume that what they come up with and where budget is made available for, that that is necessary. So it does not matter to me.*
Father 173	*But if she would act as a guinea pig, yes, I would have my doubts about it.*

Expected personal benefit for the child encompassed not only direct personal health benefit (e.g. possible cure), but also an increase of comfort (e.g. less medication), buying time, the opportunity to get early access to new drugs, and more contact with the medical team (table 4).

Altruism was frequently mentioned as a reason for participation (table 4). Parents let their child participate, not only to help patients in the future or to further science, but also because they acknowledged that in the past children had participated in research of which their child might have benefitted now. Children themselves also mentioned altruistic reasons.

Parents and children also mentioned a general trust in research or the contrary, distrust in research, as a reason influencing their decision (table 4). Distrust included mentioning of words like "guinea pig' or experimenting. Trust in research showed in terms like: I trust my doctor, it is safe otherwise it wouldn't be offered and since it is an international and multicenter study, new medication is better.

Other reasons parents and children mentioned were related to the risks of participating, the decision itself, the voluntary nature of participating, and privacy issues.

VIEWS ON RECRUITMENT AND INFORMED CONSENT CONVERSATION

Parents and children made explicit that they want to be asked for participation in clinical research, even in stressful situations with little time to decide (e.g. at the intensive care unit). They gave suggestions on how to approach them in those situations and advised to inform all personnel, research and healthcare personnel, about the study and include them in the organization (table 5).

ATTITUDE IN THE DECISION-MAKING PROCESS

Parents discuss the clinical study with each other when possible and this deliberation is considered relevant and important to them. They hardly mentioned discussing the study with other people except their child, partner or healthcare / research professionals.

Parents do discuss the study with their child and feel the child's opinion is very important. Most of them mentioned incorporating their child's opinion in their decision or following the child's wish, also when the child is not legally competent to consent. The older the child, the more importance they attach to their child's opinion (table 5).

Table 5: Examples views on recruitment and informed consent conversation, attitude in the decision-making process, and expectations

Participant	Quote
Views on recruitment and informed consent conversation	
Mother 182	*Just in two sentences: "I do research and this is what I need from [name child], but I understand the situation, that it is too much. But I want to ask if you want to think about it and then I leave some more information behind and then I'll be back tomorrow." But do not talk for minutes about your little research. No, because that really doesn't interest you, when you are in the ICU. No, of course not, why would you care, it's about your child getting better, not what kind of research is being done here... Yes, I mean they are walking around here at the ICU, so you can come, but just ask the nurse of [name child]: "How is [name child] doing? Is it okay? And do you think I can approach the parents for research?"*
Father 042	*I think it works well, I think they are very professional. Our contact moments are very good. If we have questions we can ask them, we get good and comprehensive answers.*
Attitude in the decision-making process	
Mother 182	*Yes, we do ask each other whether we are doing this or not? I'm not going to decide by myself.*
Mother 062	*I remember that I had [research nurse a or b] on the phone, at least one of those two. And I said: "Oh well I do not know." Then she said: Well, then I just say that you will not participate." Then I thought: "Oh yeah, that's a possibility too." Then I was hesitating again, so that's how it went.*
Mother 022	*And that is actually the age of [child, age 4] now. Then we would like to talk about it with [child]. About, yes they have to draw blood for research, do you want that? Yes, for us his opinion means a lot, especially because he has a chronic illness.*
Child 171 *(age 11)*	*Yeah, I thought: "They are older and more knowledgeable about things. So, yeah, you just do it and I'll go along."*
Child 151 *(age 15)*	*Yeah, yeah. Then, of course, your parents will push you a little bit: "Join in ... ".Yeah, but that's part of it, I guess. If I said no, they would have been fine with it too. Yeah, in the end I have to do it myself, so they can say: "Yes, do it." But if I do not feel like it, I will definitely not do it every time.*
Expectations	
Mother 174	*I do not think so. We have signed a contract. Yes, he cannot stop, we will not stop. Yes, then I think it's over.*
Father 152	*But there isn't actually. There is no risk; at least it has all been tested in advance. So it has already been tested on adults. Well if you are not hypersensitive to that drug, then why would you not do that? I see no reason for that.*

EXPECTATIONS

Almost all parents and children were interviewed before their participation in the clinical research study had started or just at the beginning of the clinical research study. When deciding about participation they had certain expectations about their participation in the research, which were made explicit by them in the interview. Some of these expectations were surprising. Most parents and children consented on the assumption that participation in the clinical research study would not burden but benefit them in one-way or another. One parent expected her child to benefit from participation in an observational study. Several parents expected their child to be checked up more regularly in the study by the medical team. One family assumed being randomized to the standard treatment, meant not participating in the research at all. A frequently en-

countered assumption was related to the expected safety of pediatric clinical research. Multiple parents assumed research participation to be without any risks, because the drug was already used safe and effective in adults. One family had assumptions about the (in)voluntary nature of the study; they talked about signing a contract and were not aware of the right to withdraw from research (table 5).

DISCUSSION

BURDEN WEIGHS MORE THAN RISK IN THE DECISION

Our interview study shows that children and their parents attach more importance to burden than to risk when they need to decide about participation in pediatric clinical research. The anticipated burden of participating is most frequently mentioned as motivating or discouraging for their decision to participate (or let their child participate). This focus on burden is not only related to the burden of specific research procedures for the child, but entails also the logistical burden of participating in research for both child and parents. This includes time spent in the hospital for research purposes, missing school or workdays due to participation and missing out on leisure time. When a child is a research participant, it is easy to forget parents are not only proxy *consenters* but proxy *participants* as well: a child often depends on his/her parents to travel to the hospital, parents need to fill in questionnaires or help with diaries and parents need to collect samples for research purposes. These are efforts they are willing to make for care, but not always for research.

In designing and reviewing pediatric clinical research, and in the recruitment and informed consent process, this type of logistical burden for both child and parents should be given attention. Furthermore, since it is a main factor influencing their decision, minimizing this burden is crucial. A systematic review about discontinued clinical trials showed that burden for participants is one of the major reasons for recruitment failure.[17] Therefore paying more attention to these types of burden during the design of the study will also contribute to the success of clinical research.

TRUST IN RESEARCH

Although parents and children do not frequently mention risks as a factor influencing their decision, their focus on burden does not mean risk does not matter to them. On the basis of these interviews we conclude parents and children outsource their concerns about risk. They have a great deal of trust in research, research staff and physicians and do not expect high risk research or bad quality research to be offered to them.

This shows how important ethics governance systems and the prior-review role of research ethics committees are. Despite the ongoing criticism on the ethical review system, including accounts of overprotection,[18 19] our study shows potential participants expect research to be checked and reviewed beforehand and only safe and sound research to be offered to them, making ethical review an essential step in the process.

RECIPROCITY IS KEY IN ALTRUISTIC REASONING

Parents we interviewed quite often referred to helping other or future children and science as important considerations in their decision. There is much debate in literature whether you can call this altruistic reasoning, given that parents are not research participants themselves.[20] But taking in consideration our findings on burden, you can argue that parents also partly self-sacrifice when their child participates, an essential element of altruism. Therefore we characterize these considerations of children and parents as altruistic reasoning.

Striking was that parents and children not only point to the future in their altruistic reasoning, but also reason backwards. Parents and children do not only focus on future patients, but also consider children who participated in the past. They now benefit, because in the past children participated in research. Luchtenberg and colleagues also recognized this backward reasoning in their interviews with children about research participation and introduced the term 'reciprocity' to characterize this type of altruism.[21] The results from our interviews accentuate this reciprocity-based altruistic reasoning in parents and children who are asked for clinical research.

PARENTS AND CHILDREN WANT TO BE ASKED, GATEKEEPING NOT DESIRABLE

Our interviews show that parents and children want to be asked for clinical research, even in difficult and stressful situations. However research professionals do not always approach all eligible patients for participation in a research study for various reasons (e.g. protection from burden, prejudiced anticipation on their dissent), a practice called 'gatekeeping'. An undesirable practice, as several other authors remarked in previous articles.[22-24] Results from this interview study endorse this disapproval of individual gatekeeping by professionals, with respect for persons as the most important argument: parents and children want to be asked for research participation, and then decide themselves.

SUGGESTIONS FOR IMPROVEMENT IN THE INFORMED CONSENT AND RECRUITMENT PROCESS

The interviewed children and parents showed a large deal of trust in their treating physician. Previous research also showed that this trust is central to the willingness to

participate in research.[25 26] But we need to be aware that this trust can become problematic and jeopardize the voluntariness of research participation.[26-28] Parents introduced a possible solution for this problem in our interviews and advised to let their treating physician introduce the study in just a couple of sentences and subsequently let the research nurse or researcher explain the study in more detail and do the informed consent procedure. This process would strike the right balance of trust in your own physician and being able to make an independent free decision.

Another issue parents addressed in the interviews, and we observed ourselves, was the fact that not all personnel with whom parents were in contact with in the hospital knew about a study, resulting in insufficient or even incorrect information. Therefore, it is essential that everyone at the work floor knows about the clinical trial.

A third issue addressed by parents was their desire to receive information about the aggregate results at the end of the clinical research study. This is not yet, very common in research practice. We therefore advice research professionals to develop a policy at the start of the study for return of results, e.g. keep an update on a website, and ask all participants during the informed consent process if they want to be updated.

MISCONCEPTIONS BRING A RESPONSIBILITY FOR THE RESEARCHER

We were confronted with multiple misconceptions when asked about their expectations of research participation. These included difficulties with understanding the research-care distinction, the research design, the voluntary nature of participation, and risks associated with pediatric clinical research. These misconceptions can lead to participation in clinical research based on false assumptions. Therefore prevention of these misconceptions brings a responsibility to research professionals to inform parents and children correctly, be alert for these misconceptions and stay in contact during the study period.

STUDY STRENGTHS AND LIMITATIONS

This qualitative interview study contributes to better acknowledgement of the importance of knowing the reasons why one might or might not want to participate in research.[29] The recently revised Common Rule states mere comprehension and understanding of given information is not sufficient, the given information needs to be relevant for the decision.[30] In order to design the informed consent process in a way that matches these needs of the participants, qualitative research into the motivations of people to participate in research is essential. Because we interviewed parents and children with cancer and other diseases, this study adds new perspectives and variety to the body of empirical research into the motivations for pediatric research participation.

Unfortunately, only a limited number of participants who dissented to research participation was interviewed. Probably, people who dissent to a specific clinical study also dissent to participation in this interview study. Our study would have benefitted from inclusion of more dissenting families, to do justice to the variety of decisions. This type of qualitative research does not give insights in the distribution of motivations; therefore quantification of motivations is not possible with this data.

CONCLUSION

Parents and children want to be approached for participation in clinical research, and burden is the most important factor in their decision. In general, the motivating and discouraging factors influencing the decision of children and their parents are in line with discussions in research ethics committees. Our interviews revealed parents and children however have a much broader notion of burden, for example they attach importance to logistical burden, and that this is crucial in their decision on participation.

The design of pediatric clinical studies and especially the recruitment and informed consent in pediatric research can be ameliorated by the findings of our research regarding the motivating and discouraging factors. This way studies will be better in line with the preference of children and parents, and parents and children will be better equipped to make a decision about participation.

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CHAPTER 6

Parents' perspectives on pediatric clinical research: A focus group study with laypeople

Krista Tromp, Suzanne van de Vathorst.

Parents' perspectives on decisions to participate in pediatric clinical research: Results from a focus group study with laypeople
[submitted]

ABSTRACT

Knowing why parents decide to consent or dissent to participation of their child in pediatric clinical research is essential to further the ethical debate concerning pediatric research. We performed this qualitative focus group study with 16 parents from the Dutch general public to explore their perspectives on decisions to participate in pediatric clinical research.

Group discussion revealed: Parents conflate clinical research and clinical care; they do not grasp the trajectory of pediatric drug development; their protectiveness matches current research guidelines; and benefit for their child is the most important factor in their decision.

Research professionals should be aware of the knowledge gap of parents, the pitfalls of jargon, and unintended false expectations.

INTRODUCTION

'Are you allowed to do that, test drugs on children?' That's the response we quite often received from friends and family at social gatherings when we tell them about our research on how to test new drugs on children in an ethically responsible way. Funnily, we hardly encountered such reactions during our research into the decision-making of parents and children concerning their participation in clinical research. Could it be that a lot of the children and parents questioned in previous studies were actually '*proto-professionalized',* leading to a skewed view, and that we do not have a good idea of how laypeople view the dilemmas concerning participation of children in clinical research?

The views from parents not recruited through hospitals, but from the general public are very much underrepresented in the literature. Most research in motivations and decision-making in pediatric research is done with (parents of) hospitalized sick children.[1] The perspectives of parents from the general public might differ from parents of hospitalized sick children due to not being familiar with clinical research and not having to cope with a sick child. Our hypothesis is that this selection created a bias in the literature.

Knowing why parents decide to consent or dissent to participation of their child in pediatric clinical research is essential to further the ethical debate but especially the practices concerning pediatric research. The goal of informed consent for clinical research should be for potential research participants to make an informed decision, not simply for them to opt in to research participation.[2] In practice the informed consent process often fails to achieve that objective, e.g. because people misunderstand information or receive irrelevant information.[3-7] More insight in the decision-making of parents enables us to tailor pediatric clinical research and the accompanying recruitment and informed-consent processes to their needs and perspectives. This includes the needs and perspectives of 'first timers' in a hospital, who have little experience in research and hospitalization but can be confronted with offers for participation of their child in clinical research. It is therefore important to add their 'laypeople' perspectives to the body of evidence.

Of course these perspectives cannot be taken at face value but should be used to inform normative deliberation on this topic.[8] As a first step they should be incorporated in a reflective equilibrium.[9 10] Reflected upon they may further the ethical debate concerning pediatric research. A valuable method to gain access to these perspectives is a focus-group study. A focus group does not only create the opportunity to collect perspectives, but also to deepen them.[11] Parents will not only interact with us as researchers, but also with each other. This makes them question others' ánd their own intuitions, creating

a dynamic development of their perspectives. Surprisingly, even though these advantages have been acknowledged in the literature, focus group research into parents' perspectives on pediatric clinical research is scarce. A systematic review about motivations of minors and their children to participate in clinical research identified only two focus group studies [1]. Lebensburger and colleagues identified with their focus groups common barriers and facilitators in pediatric Sickle Cell Disease trials.[12] And Caldwell and colleagues showed with their focus groups that educating parents about trials, improving communication, increasing incentives while decreasing inconveniences, and providing decision aids for parents may increase parents' willingness to let their child participate in trials.[13]

We designed and performed this qualitative focus group study with parents from the Dutch general public to explore their perspectives on decisions to participate in pediatric clinical research. We assessed their intuitions concerning pediatric research, their motivations to endorse or refuse their child's participation in clinical research and which factors would influence their decision.

METHOD

This study is reported in accordance with the consolidated criteria for reporting qualitative research (COREQ).[14]

This qualitative focus group study was deemed exempt from ethics approval by the research ethics committee of Erasmus Medical Center (protocol number: MEC-2016-060). Written informed consent was obtained from all participants before start of the focus groups. All in accordance to Dutch legislation for medical research with humans.

POPULATION

The study population consisted of 16 parents from the Dutch general public. Participants needed to have at least one child below the age of 12 years old and speak Dutch. To ensure a wide range of perspectives, purposive sampling was used by including a variety of parents concerning family composition, educational level and age of their children. Participants were recruited from the general public with assistance from 'CG Selecties' a bureau specialized in recruitment of participants for marketing research. This approach enabled us to recruit laypeople from the general public with minimal foreknowledge and experience in hospitals and medical research.

FOCUS GROUPS

The two focus groups were held at Erasmus Medical Center in July 2016 and lasted up to 120 minutes. One researcher (SvdV) moderated the discussions; One researcher (KT) took notes and aided in the discussions when required. Interaction and discussion between the participants was allowed and encouraged. But the researchers interfered when the debate strayed away from the purpose of the focus group or saturation was reached.

Informed consent was obtained from the participants before start of the focus group. This included permission to audio-record the focus groups to be transcribed later. To ensure confidentiality only participants and the two researchers were in the room, and confidentiality of the discussions was discussed and agreed upon by all participants.

The two focus groups were divided in three parts:

PART 1: INTRODUCTORY ROUND

In part 1 participants were asked to introduce themselves by use of several key questions. 1) Who are you? Who are your children? Do you or your children have hospital experience? Do you or your children have experience with clinical research experience?. Answers to these questions were also collected at the end of the focus groups by use of a written questionnaire (supplementary file 1)

PART 2: INTUITIONS

Part 2 consisted of a facilitated group discussion to explore intuitions concerning medical research. Discussion centered around three key themes: 1) clinical research; 2) pediatric clinical research; 3) specific knowledge. Table 1 lists the key questions used in the discussion.

Table 1: key questions – part 2

Key questions – part 2
1. Clinical research with humans:
a. What do you think about then?
b. What kind of research?
c. Would you participate?
2. Clinical research with children:
a. What do you think about then?
b. What kind of research?
c. Would you let your child participate?
3. Specific knowledge:
a. Off label use of pediatric drugs
b. Sick vs. healthy children
c. Research vs. care

PART 3: VIGNETTE DISCUSSION

To identify relevant factors influencing parents' decisions we used a vignette method in part 3. Two vignettes presented two hypothetical research protocols. Participants were asked which factors would influence their decision to participate in these two studies. With post-its they identified motivating and discouraging factors, followed by a group discussion about these factors. Table 2 and table 3 present the discussed vignettes.

Table 2: Vignette A

Clinical drug trial (phase 1/2)
The goal is to investigate the safety and efficacy of a cancer drug. The product has already been tested on animals, it was found safe in that study. Subsequently it was tested in adults, and for them it was found to be safe and working. Now the researchers want to investigate the drug in children.
- The study lasts a total of 8 weeks. - Your child needs to take the medicine twice a day (by mouth) after a meal. - Your child may not drink carbonated drinks during the study period. - At 0, 4 and 8 weeks your child must come to the hospital for monitoring. - During these visits, your child will have: - a physical examination - a blood sample taken - At these moments, you and your child will also be asked to complete a questionnaire.

Table 3: Vignette B

Observational cohort study
By collecting data in different ways, research is carried out into the development and growth of children, into the development of diseases and behavioral problems. The research thus makes an important contribution to health and care for all children in the Netherlands.
- The study lasts a total of 5 years. - You and your child must visit the hospital every year for examination. This visit takes about 4 hours each time. - During these visits, the following examinations are carried out on your child: - Physical examination (blood pressure, hearing, vision) - Lung function test - Electrocardiogram (ECG) - X-rays of the teeth - Urine sample - Blood sample (1 tube of blood) - Bike test (exercise test) - Echo of the abdomen - MRI scan to look at the brain and the heart - IQ test - Questionnaire (about health, feelings and school) - We also ask you as parents to fill in two questionnaires (health, lifestyle, important events). We also take your blood sample (1 tube of blood).

CODING AND ANALYSIS

The focus groups were audio taped and consequently transcribed verbatim by an independent person. Focus groups were analyzed using thematic analysis. Through systematic objective coding, we identified and labelled themes, in order to elucidate relevant concepts. KT initially coded the focus groups. SvdV coded the focus groups as a second researcher. Disagreements were settled by consensus. Initial coding tree was based on the focus group guide and included: 1) Intuitions clinical research; 2) Intuitions clinical research with children; 3) Knowledge clinical research with children; 4) Motivating factors vignette A; 5) Discouraging factors vignette A; 6) Motivating factors vignette B; 7) Discouraging factors vignette B. During the process of coding and analysis this initial tree was adapted and elaborated based on the data generated from the focus groups. Interview coding and analysis continued until no new codes, concepts, or patterns emerged. We coded and analyzed the qualitative data using QSR International's NVivo 11 qualitative data analysis software.

RESULTS

STUDY POPULATION

A total of 16 parents participated in in two focus groups. 9 participants in one focus group and 7 participants in the other. Age, gender, educational level, and number and age of their children were very diverse in the population. Some parents had experience as a research participant in clinical research themselves, but the majority had no experience with clinical research, neither personally nor with one of their children. Some parents had a chronically ill child (e.g. eczema, asthma) and some had experience with hospitalization of their children. Table 4 presents an overview of participant characteristics.

Table 4: Participant characteristics

	Characteristic	No. of participants
Gender	Father	9
	Mother	7
Educational level	Secondary school	2
	Intermediate vocational education	5
	Higher vocational education	7
	University	2
Median age [range]	Median age [range]	39.5 [32-53] years of age
Number of children	Median number [range]	2 [1-5] children
Age of children	Median age [range]	7 [0-18] years of age

Table 4: Participant characteristics (*continued*)

	Characteristic	No. of participants
Approached for clinical research	Yes	5
	No	11
Clinical research participant themselves	Yes	5
	No	11
Child approached for clinical research	Yes	3
	No	13
Child clinical research participant	Yes	3
	No	13
Child hospitalized	Yes	6
	No	10
Child with chronic illness	Yes	3
	No	13

INTUITIONS: RESEARCH IN GENERAL

Parents' intuitions about research with humans included reference to the importance of doing research:

> *"I think it's really important that it happens, because you have to know the effect on people; you can keep testing on mice for a very long time, but in the end you can only know when you actually check things, check on people."*

> *"So yes, it never stops, healthcare, there will always have to be research."*

Feelings of distrust, associations with animal research and 'guinea pigs' and financial incentives for participation were also common first reactions:

> *"No, personally I think it does, a lot happens that we do not know of."*

> *"Do you know how far reaching the power of the pharmaceutical industry is? They buy entire countries; they cause the collapse of economies."*

> *"I see it right in front of me, these mice and those swollen heads, that's a picture I get right in front of me, so I would be careful"*

> *"At first I think of studies that you can earn a lot of money with, then I think: the more money, the more danger."*

Parents in the focus groups associated 'research' with a broad range of activities. They started talking not only about clinical drug trials, but also about clinical testing (e.g. an MRI scan, CT scan), new operating techniques, screening programs, IQ tests, behavioral tests and vaccinations:

> *"Yes, or cancer research, that can also be preventive, like the research on cervical cancer, that is also in your own interest to see if you have something."*

> *"A few years ago vaccination was announced, that everyone had to vaccinate against ..."*

INTUITIONS: RESEARCH WITH CHILDREN

Their first reactions concerning research specifically with children revealed that their knowledge about this topic was limited and that it was hard for them to grasp the trajectory of clinical research and drug development. As some parents stated:

> *"... I would not know how a company, a hospital or an agency, a medicine magnate will approach my daughters like 'You want to participate in research?'. Never heard about it too."*

> *"I think that no medication is given to children ... I think it will be tested on adults and if it is in an advanced stage ... I do not think that drugs will be tested on children just like that."*

Another parent grasped and expressed the dilemma of drug development and off-label drug use in children very well:

> *"Yes, I think it's ambivalent, because on the one hand, if my child gets a medicine that has never been tested, I think that's bad. But on the other hand, I also find it very bad when my child ... that he will test that medicine."*

The consensus in the group was that parents are more protective of their child than of themselves. As one father explained:

> *"That was also the reason why I just said: the children ... I would more easily participate myself than allow them to participate in research. I myself am responsible for my own situation; I can judge for myself what is happening. And I do not want to place that responsibility with my daughter who cannot defend herself. I think that's really a point. Imagine that I make a wrong deci-*

sion and I destroy her life, then I am responsible for it. And I just do not want that on my conscience. So that would be an important reason for me to say no, I'm not going to do that fuss with my daughter, only when she wants to herself, then she is allowed to decide herself, but I will not start it."

Parents were reluctant to let their child participate in clinical research, and expressed a lack of trust, and fear of risk and burden:

"My first impression is that my children are not allowed to participate in medical research. It may be important, but I do not want to expose my children to it. But my first thought goes to a kind of drug research. But perhaps that can be broader, if it is only weighing and measuring, then I may judge differently. But the first impression is: No."

"No, but I think with people it [red: research] is important, and in children as well, but to a certain level because children themselves cannot say what they want or not, because they cannot see and judge what the consequences are."

"Look, if they take a little blood, I think it's fine… if you are fully pumped with a new drug: Yeah, that's different."

During the group discussion parents mentioned a variety of reasons for letting their child participate in clinical research. Expected benefit from participation for their child was mentioned by almost all parents as the main reason for having their child participate in clinical research. A lot of the discussion in the group about reasons for participation circled around the concepts of familiarity, knowing the disease first hand, and proximity, having a relative/neighbor with a disease. Both concepts played an important role in their future decisions:

"I can imagine if my niece gets seriously ill, that I would also like to let my children participate in a study."

"Yes, but also in general, you are a little bit more supportive of the research when there is something of a link with a child you know."

VIGNETTE DISCUSSION

The vignette discussion centered around the questions: 'Would you let your child participate?' and 'What factors would influence your decision?'. Table 5 and 6 present an overview of the mentioned motivating and discouraging factors for both vignettes,

illustrated with quotes from the group discussion. In response to both vignettes the parents most frequently mentioned factors related to expected benefit and burden for their child. Their notion of benefit did not only entail direct health benefit (e.g. finding a cure), but also entailed getting a check-up for their child. In the context of vignette B parents in both focus groups referred to a periodic MOT-test for cars. Interestingly, the mentioning of a periodic check-up as an important reason for participating created a discussion in both focus groups about the return of individual research results. Most parents assumed that they would learn the results of all the tests during participation, while this was not mentioned in the vignette.

"... so only if you get results right away, otherwise I would never do it."

The discussion also revealed factors that parents mentioned would be relevant for their decision but were unknown in the proposed vignettes. These included for vignette A: age of their child (referring to their ability to execute research procedures and to their decisional capacity), health status of their child and alternative treatment options, and for vignette B: consent of their child, financial compensation, logistical aspects, and privacy-guarantees.

Table 5: Would you let your child participate and what factors would influence your decision? (Responses to vignettes: Motivating factors)

Motivating Factor	Quote Vignette A: clinical drug trial	Quote Vignette B: observational cohort study
Altruism		
Helping other children	*"I would like to participate because you can help other children, I wrote that down."*	*"But when I look at my son again, he would really like to do this, so he can help other people. That is his responsibility."*
Helping science	*"Yes, to actually mean something to science that is good."*	*"Well, if science benefits from this, then that is always a reason."*
Benefit for child		
Treatment / last resort	*"Then you come back to the point where we just were. Look if you hear that, I think you would seize everything to save your child."*	[not mentioned]
Checkup of child	*"I like that there is, for example, a periodic check-up, I think that's a nice thing. And I like it that it is a factual check."*	*"At first what [participant x] said, like a regular MOT test actually , that you can see closely how the development of your child goes ... Then you know right away if they are completely healthy, you have had everything."*
Educational / interesting for child	[not mentioned]	*"…my daughter would really like this…she would find that very interesting, I'm sure."*

Table 5: Would you let your child participate and what factors would influence your decision? (Responses to vignettes: Motivating factors) (*continued*)

Motivating Factor	Quote Vignette A: clinical drug trial	Quote Vignette B: observational cohort study
Minimal risks		
Is safe (tested on animals/ adults	*"Because it is a test and it is safe on adults and cancer is of course bad enough, so I almost think how bad can it be."*	[not mentioned]
No adverse events	Not mentioned	*"And it does not affect [his] health. While with those other pills or whatever, medical research, or medication, then of course that could be the case."*
Minimal burden		
Burden is low	[not mentioned]	*"Okay, they have to spend a few hours once a year. But yeah they are just a little bothered by it."*
Short study period	*"Well I found eight weeks a short period of time... Would it be you have to do something for six months, I would find that too much."*	[not mentioned]
Curiosity		
Self-interest of parents	[not mentioned]	*"I like to participate because I find it interesting to follow the developments in this way."*

Table 6: Would you let your child participate and what factors would influence your decision? (Responses to vignettes: Discouraging factors)

Discouraging factor	Quote Vignette A: clinical drug trial	Quote Vignette B: observational cohort study
Burden		
Burden for child too high	*"Swallowing by mouth is difficult for my child …I think a hospital admission is a bit much."*	*"X-rays of the teeth, well we go to the dentist twice a year, that could just as easily be requested from the dentist. And blood sample and an ultrasound and that MRI scan... yes that's a bit scary, that makes me think about it. If that is not the case. If, for example, it had been just one of those tests, only a blood sample, I would say well okay, that is still limited. But all those tests together I find it drastic."*
Too many restrictions	*"Well anyway, those drinks they aren't allowed. And I miss the explanation why carbonated drinks aren't allowed to be drunk, I would absolutely want to know."*	[not mentioned]
Study period too long	[not mentioned]	*"I think it's too much to state it like that. And I just think it takes a long time. It's five years, the research lasts four hours."*

Table 6: Would you let your child participate and what factors would influence your decision? (Responses to vignettes: Discouraging factors) (*continued*)

Discouraging factor	Quote Vignette A: clinical drug trial	Quote Vignette B: observational cohort study
Risks		
Fear of risks / adverse events	*"I drop out with the word cancer, the fact that it's drugs against cancer. For me, that means a heavy drug. And I do not want a heavy drug in my children... Or if there is too much risk, I think that's more precise."*	*"Those x-rays, they are equal to so much radiation. And if your child is healthy ... you just said it yourself: if you have a child that maybe is not healthy then you might do it, but now: No."*
Consequences unknown	*"It does not say anything about the consequences."*	[not mentioned]
Not enough check ups	*"In this case, I found that there were few control moments, because quite a lot can happen in four weeks. And especially when it comes to oral medication, I think I would feel safer if the child would drop by every week to see how things are going and what the effects are."*	[not mentioned]
Study design		
Questionable study reliability	*"And last, answering a questionnaire with the child… I have my thoughts about that: I think what will that be?"*	*"What I had written as negative: The purpose of research. It only concerns research on disease causes and behavioral problems. But the link between behavioral problems and an MRI scan, I do not see that. …We live in a very prosperous country, and these diseases in children are they very common? Is that why you want to do research? Isn't there a goal behind it, shall I say?"*

DISCUSSION

PARENTS CONFLATE CLINICAL RESEARCH AND CLINICAL CARE

Our focus group study revealed that parents have various interpretations of the term 'research' and not everyone understands the difference between research and care. This difference however does matter to them and influences their decision. Responsible research professionals should focus on this difference during the recruitment and informed consent process for pediatric clinical research.

In medical practice the word 'research' is used in very different contexts. Especially in Dutch, the native language of the participants in the focus groups, 'research' (in Dutch: 'onderzoek') has multiple homonyms. Dutch people do not only use this word to address clinical research, but also use the word for specific clinical tests (e.g. MRI/CT/blood tests) and for screening purposes. Therefore, it is not surprising that parents have very diverse

associations with the term 'research' and that they conflate these different contexts. This conflation can create a therapeutic misconception.[15 16] This becomes problematic when unjustified therapeutic optimism influences parents' decisions to have their child participate in clinical research. A recent study by Janssen and colleagues showed that decliners of study participation had significantly fewer therapeutic misconceptions than consenters.[17] Discussion in our focus groups showed that the difference between research and care, when understood correctly, does matter to parents and that they make different decisions concerning research and clinical care. Although some authors argue we do not have to focus on the fundamental difference between research and care or even try to avoid the therapeutic misconception,[18] our findings emphasize the importance of disentangling research and clinical care to potential research participants and their parents. Therefore, it is crucial that health care and research professionals explain this difference to parents (and their children) during the recruitment and informed consent process, and start this discussion with explaining what 'research' actually means and avoid the pitfalls of jargon.

PARENTS DO NOT GRASP THE TRAJECTORY OF PEDIATRIC DRUG DEVELOPMENT

The discussion in the focus groups revealed that most parents do not grasp the trajectory of pediatric drug development. For parents to be able to make an informed decision about their child's participation in clinical research, they must understand to what they consent or dissent. Our study indicates there is a knowledge gap between starting level of the information in informed consent documents and the basic knowledge of parents about what clinical research and drug development entails.

Context is crucial; for detailed information on a specific trial (e.g. goal, burden, risk) to stick, knowledge about the whole research enterprise is essential. However, empirical research in this field of comprehension mainly been focused on the understanding of specific elements of informed consent documents and improvement of these documents.[19 20] This could explain why single interventions to improve informed consent documents are not consistently effective.[21 22] Initiatives to improve parents' understanding should therefore not only focus on interventions for the informed consent documents for specific trials but also on interventions to improve this knowledge gap. For example, before giving information about a specific trial, give short, but comprehensible information about clinical research and drug development in general.

PARENTS PROTECTIVENESS MATCHES CURRENT RESEARCH GUIDELINES

Parents in our focus group were more protective of their children than of themselves, and stated it is better to test drugs on adults than on children. They value their child's opinion in the decision to participate. Current guidelines concerning informed consent/assent and burden and risk thresholds in pediatric research are in line with these parental intuitions.

In important legal and ethical guidelines (e.g. CIOMS guideline, Declaration of Helsinki, EU Clinical Trials Regulation) additional measures are taken for the protection of minors.[23-25] For example, all three documents: 1) State that research with children cannot be carried out if it can be carried out with less vulnerable subjects. This matches parents' statements that it is better to test drugs on adults than on children; 2) Set limits to acceptable risk for pediatric research without a direct benefit, matching the greater protectiveness that parents have for their children than for themselves; and 3) Value the opinion of the child by requiring assent of the child for participation, matching the importance parents attach to their child's choice.[23-25]

BENEFIT FOR THEIR CHILD IS THE MOST IMPORTANT FACTOR IN THEIR DECISION

Discussion in the focus groups revealed benefit for their child to be the main motivator of parents to endorse participation of their child in clinical research. Interestingly, parents use a much broader definition of benefit than direct health benefit, e.g. being regularly checked up also constitutes a benefit for them. However this can only be a benefit when they are informed about the results of the check-up, so a proper return of results policy is necessary in these cases. The discussion in our focus groups showed that people expect the individual test results to be returned back to them and see no return of result as a good result (my child is healthy). Such a return of results policy is not always at hand. To the contrary, in practice, tests with a research objective are done and evaluated most of the time without a clinical look, and are sometimes not even evaluated during the trial but afterwards.

As expected benefit plays an important factor in the decision-making of parents to participate in research, we should ask what counts as benefit. Research can only be acceptable when the risk-benefit ratio is positive. A lot has been written and discussed about the risk and burden in that equation for pediatric research,[26 27] but much less research focused on the other side of that equation, benefit.[28] The parents in this focus group study, next to a direct health benefit for their child, also considered being checked up regularly and, for example, an educational benefit for their child, as benefits for their children. Staphorst and colleagues found similar results concerning benefit in their interview study with children.[29] These children also had a much broader notion of benefit than direct health benefit. Staphorst and colleagues argued, based on these results, that next to direct health benefit other specific forms of benefit (learning, altruism and fun) could also be justifiably qualified benefits of research participation. But they also argued that 'getting extra attention from healthcare staff' isn't one of those justifiable benefits that could be used in the risk-benefit analysis.[29 30] We completely agree. Patients (including parents and children) should not be dependent on research to get the attention they wish for in clinical practice.[1] It can be considered an undue inducement for

research participation. That parents do state it as an important reason for participation is therefore problematic and deserves attention.

STUDY LIMITATIONS

This study has some limitations that deserve mentioning. Unfortunately, the study consisted of just 2 focus groups with a total of 16 participants. Ideally, more participants should have been included to make the results more robust. On the other hand, data saturation was reached within both focus groups. The focus group sample was diverse in many aspects (e.g. age, gender, educational level) and people with different ethnic backgrounds participated, but ethnicity of the participants was not registered. Therefore, this aspect could not be taken into consideration, while it can be a relevant aspect in empirical research into research participation.[31]

CONCLUSION

Despite its limitations this focus group study makes two important contributions to the tailoring of pediatric research to the perspective of parents. First, it makes clear that parents have various interpretations of the term 'research' and do not always understand the difference between research and care. But this difference does matter to them and does influence their decision. During recruitment and informed consent for pediatric clinical research this difference should therefore be explicitly discussed. Secondly, the main motivator for parents to endorse participation of their child in research is expected benefit for their child. Their definition of benefit however is much broader than direct health benefit as commonly discussed in research ethics committees. For parents being regularly checked up is a benefit as well. This implies research professionals need to present a proper return of results policy.

On the whole, research professionals should be aware of the knowledge gap of parents concerning drug development and clinical research, the pitfalls of jargon, and unintended false expectations.

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CHAPTER 7

Gatekeeping in pediatric clinical research: An undesirable practice

Krista Tromp, Suzanne van de Vathorst.

Gatekeeping by professionals in recruitment of pediatric research participants: Indeed an undesirable practice.
Am J Bioeth. 2015;15(11):30-32

ABSTRACT

Professionals should not be reluctant to ask young people to participate in clinical trials; overly doing so is known in the literature as gatekeeping (not approaching all eligible research participants).

Our research into participation in pediatric clinical trials identified reasons why professionals engage in gatekeeping; these are e.g. protection of child and prejudice beliefs about the choice the child will make.

Although gatekeeping might be understandable, we argue it is not desirable because of the negative implications this practice entails (e.g. denies children a choice, might introduce inclusion bias and introduces unfair distribution of risk and benefit).

We call upon pediatric health care and research professionals to be aware of the many negative implications of their reluctance and in principle to refrain from the problematic practice of gatekeeping.

PREAMBLE

The article, on which this chapter was based, was an open peer commentary on a target article by Luchtenberg and colleagues in The American Journal of Bioethics.[1] Although this chapter is a commentary it can be read and understood without reading that specific target article.

Luchtenberg and colleagues interviewed 25 young people aged 10 to 23 years of age who were invited to take part in clinical trials. They had a similar goal as we had for our interview study: to understand the experiences and motivations of people participating in pediatric clinical research. There is a difference also: we mainly interviewed parents, whereas they interviewed adolescents. They found that personal benefit and helping others were the main motivators for the adolescents, and that these factors were more complicated than they expected. Similar to our results, discussed in chapter 5, they also found the altruistic motives of participants to be reciprocity-based.

Another important similar finding they showed was the fact that the interviewed adolescents wanted to be asked to participate in clinical research and they concluded their article with the statement that research professionals should not be reluctant to ask young people to participate in clinical trials. We agree with that statement. In this commentary, we elucidate our views about gatekeeping by professionals in pediatric clinical research.

INTRODUCTION

Luchtenberg and colleagues bring their interesting article to a close with the concluding statement that professionals should not be reluctant to ask young people to participate in clinical trials. They substantiated this recommendation with results from their interview study with young people about their experiences with and motivations for participation in clinical trials. The young people they interviewed welcomed the opportunity to contribute to medical research and wanted to learn from it. Unfortunately though, the interviewed young people also mentioned that they had wanted to take part in clinical trials before, but had not always been offered a chance to contribute.[1]

We recognize this reluctance of professionals to ask children, and consequently their parents, to participate in clinical trials. Being overly reluctant is a practice known as gatekeeping. Definitions of gatekeeping in a research context differ in the literature. For instance, Hudson and colleagues define gatekeeping as the process by which people's

capacity to be invited into a research project, or to make an informed decision regarding research participation, is inhibited by others.[2] The definition of Sharkey and colleagues focuses on the health care professional who prevents the researchers access to eligible patients for research recruitment.[3] These definitions have in common that eligible subjects are not approached to participate in research. Therefore, we define gatekeeping by professionals in a research context as follows: having implicit in- and exclusion criteria that lead to not approaching all *eligible research participants*. This gatekeeping by individual professionals adds a third layer to the assessment of acceptability of pediatric research (the protective measures in legislation concerning research with children being the first layer and evaluation of the protocol by a research ethics committee (REC) the second).

During our own empirical research concerning participation of minors (and their parents) in clinical research this practice of gatekeeping kept cropping up. We have encountered it ourselves: we were dependent on other professionals to approach their patients (children and their parents) for participation in our interview study, and noticed eligible children and their parents were selectively approached. The issue also rose in discussions, focus groups and personal talks we had with other researchers, physicians and (research) nurses about participation of children in clinical research.

In this commentary we want to share some of the reasons these professionals mentioned to justify their gatekeeping behavior. These reasons show why gatekeeping can be an understandable practice. Moreover, we want to point out that there are negative implications and argue that, however understandable, it is not a desirable practice.

REASONS FOR GATEKEEPING

So, why are professionals reluctant to approach children and their parents for participation in clinical trials? In all probability the core of their justification lies in the fact that children are a vulnerable population susceptible to harm and exploitation in research and need to be protected. For this reason precisely, ethical and legal documents concerning research with humans, such as the Declaration of Helsinki, set specific protective measures for children in research.[4] However individual professionals might feel they need to be more protective than the legislation and/or REC prescribe.

The explicit intention to protect the child from burden and risk associated with trial participation is a reason we were frequently given by professionals for not approaching eligible children (and their parents). This reluctance to burden patients can result in not

approaching the sickest children, and lead to inclusion of a non-representative study population.

Furthermore, sometimes professionals think the informed consent procedure itself is too burdensome for certain eligible children and their parents. They decide not to approach children and their parents to protect them from the burden of being asked.

A third reason we encountered is that professionals sometimes refrain from approaching certain eligible children and their parents in order to protect the researcher. For example: a clinician does not approach an eligible child that has shown non-compliance with a prescribed drug before, in order to protect the researcher from the possibility of drop-out.

Prejudiced beliefs of professionals about the choice children and their parents will make regarding trial participation can be considered yet another reason for gatekeeping behavior. This may happen, for example, if in the past parents did not consent to participation of their child in a similar study, and the research nurse therefore assumes they do not want to participate in this new study and refrains from approaching them.

It can also be the case that the health care professional responsible for recruitment (e.g. the treating physician) does not support the rationale or methods of the study and therefore decides not to approach his/her patients eligible for the study.

Finally, practical concerns can influence reluctance of professionals to approach eligible research subjects. Especially when the professionals responsible for recruitment are not involved in the research project themselves (e.g. lack of time or resources to approach eligible children).

NEGATIVE IMPLICATIONS OF GATEKEEPING

Although gatekeeping is understandable in pediatric research, it is not desirable because of the negative implications this practice entails. Luchtenberg and colleagues already addressed an important one: it denies children the opportunity to contribute to medical research.[1] However, gatekeeping has many more negative implications.

First of all, gatekeeping by professionals involved in pediatric research denies parents (and children who have the capacity to co-consent or assent) a choice. Thereby, gatekeeping in recruitment for research violates the principle of respect for persons.[3]

In pediatric clinical trials, respect for persons is operationalized by the informed proxy consent of parents for the participation of their child and when possible the co-consent or assent of the child itself.[4] In general children's right to express their views is arranged in the United Nations Convention on the Rights of the Child.[5] It is therefore problematic that the young people interviewed in the target article stated they had not been offered the chance to participate. Essentially, with gatekeeping, it is the professional who makes the choice (one of non-participation), not the child and his/her parents, which is a paternalistic practice.

Second, by not approaching eligible children and their parents with an offer for participation in the trial, professionals could deny children a possible beneficial treatment. This argument is not applicable to so called non-therapeutic research (e.g. observational studies and phase 1-drug trials). However professionals need to be aware that there are studies from which children may directly benefit (e.g. randomization in intervention arm of phase III drug trial); and by withholding the opportunity to participate from children and their parents, they might withhold a beneficial intervention.

Third, gatekeeping practices of professionals decrease inclusion rates in trials. This can become problematic when this decrease means that the needed sample size is not achieved. This endangers the scientific and social value of the study. A large international review study showed that one third of randomized controlled trials in the Pediatric Intensive Care Unit (PICU) is terminated before the needed sample size is achieved, often due to recruitment problems.[6] We suggested in a previous article that these recruitment problems in the PICU could be caused by gatekeeping of professionals.[7]

Fourth, gatekeeping does not only *decrease* inclusion, it can also cause *selective* inclusion. The selective approaching of eligible children introduces bias. This selective approach can create a non-representative study population, which endangers the generalizability of the results. A recent study by Crocker et al. showed that this threat is not hypothetical at all. They found evidence of gatekeeping behavior (they call it selective invitation practices) that can bias research findings in pediatric palliative care research.[8] The effects of gatekeeping bias on the representativeness of the study population are more difficult to assess than other biases. For instance: non-response bias can be assessed by comparing responders with non-responders. But with bias due to gatekeeping this is generally not possible as the eligible patients who are not approached, are not known.

Finally, gatekeeping by professionals involved in research could create an unfair distribution of burden, risk and benefit among children and thereby violates the principle of justice.[3]

GATEKEEPING IS AN UNDESIRABLE PRACTICE

Although gatekeeping might be understandable in the context of pediatric clinical research, there are also negative implications. Gatekeeping should therefore be avoided. Luchtenberg and colleagues already concluded their target article with the statement that professionals should not be reluctant in approaching young people for participation in research.[1] They base their recommendation on their finding that children welcome the opportunity to contribute to medical research.

We presented some additional arguments to support their recommendation. To control gatekeeping practices in pediatric clinical research, it is of crucial importance that professionals involved in the recruitment process are aware of their behavior and the negative implications of their gatekeeping.

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CHAPTER 8

The role of trust in pediatric clinical research

Krista Tromp, Suzanne van de Vathorst.

Patients' trust as fundament for research ethics boards.
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ABSTRACT

Trust plays a fundamental role in patients' willingness to participate in research.

Some authors have suggested that empirical findings related to trust challenge the current model of research ethics, 'because that model is primarily focused on supporting individual autonomy.' We disagree. To the contrary, we argue that patients' trust confirms the rationale and necessity for the current model of research ethics. We argue the current model consists of more than informed consent, as the consent can only be asked for after a review process by a research ethics committee.

We substantiate this statement with results from interviews we did with parents and children about their willingness to participate in research.

PREAMBLE

The article on which this chapter was based was an open peer commentary on a target article by Kraft and colleagues in The American Journal of Bioethics.[1] Although this chapter is a commentary it can be read and understood without reading the target article.

Kraft and colleagues presented results from their focus group study about biobank research with ethnically diverse people. They focused specifically on how to build long-term trusting relationships with participants. They discussed four points of consideration: 1) addressing the history and the role of trust; 2) tackling concerns about potential group harm; 3) addressing cultural values and communication barriers; and 4) integrating patient values and expectations in oversight and governance structures.

In this commentary we corroborated their empirical findings on trust, as we found similar results in our interview study. However, we drew different conclusions from these results. They state that their findings concerning patients' trust challenge the current model of research ethics; we think it rather underlines its importance.

INTRODUCTION

Kraft and colleagues make a convincing plea for the importance of trustworthiness and trusting relationships between patient-participants and research professionals in medical research in their interesting article.[1] We do however not agree with the authors that their findings concerning patients' trust challenge the current model of research ethics, 'because that model is primarily focused on supporting individual autonomy', to the contrary, we think it underbuilds the current research system.

Although Kraft and colleagues specifically researched trust in biobank research among ethnically and culturally diverse groups, we also found trust to be of major importance in an average Dutch population who were asked for participation in a clinical trial.

We interviewed parents and their children about their willingness to participate in clinical research, after observing informed consent conversations between them and research professionals. We wanted to know: what motivated them to participate, and what influenced their decision? Trust was one of the main issues that was put forward by them as an influencing factor. In this commentary we want to share our results and corroborate the results presented by Kraft and colleagues. But we also want to point out that we draw partially different conclusions from these results.

TYPES OF TRUST INFLUENCING PARTICIPATION

In our own empirical research we asked over 30 parents and children what motivated them to consent or dissent to the clinical trial proposed to them. Together with anticipated burden and altruistic reasons, trust was mentioned by them as one of the most important factors influencing their decision and willingness to participate. We therefore completely agree with Kraft and colleagues that trusting relationships are very important in medical research.

Kraft and colleagues identified the trustworthiness of physicians, researchers, health care system, government and corporate institutions as important condition for ethnically and culturally diverse participants' willingness to participate in precision medicine research. Even though our own research was in a very different population and setting (Dutch parents and children asked for participation in a clinical trial), we identified identical types of personal trust and institutional trustworthiness influencing their decision.

PERSONAL TRUST

As the authors address, we also found a type of personal trust, directly linked to the researcher. For many (chronically ill) patients, a personal relation with the researcher influences their decision to participate (table 1).

Table 1: Example personal trust

Participant	Quote
Mother *(age 52)*	*I just trusted his judgment. I asked him: 'what would you do in my place?' He then answered 'start immediately'. I just completely trusted that answer.*

For a potential participant to actually trust the researcher, it means that they believe that the researcher has designed and will conduct the research in their best interest. In a way they 'surrender' their health to the research professional.[2] This sense of trust is closely linked to the doctor-patient relationship, and therefore not entirely without moral problems. Patient-participants do not always distinguish the separate roles of their treating physician and research professionals. Their treating physician should act in the best interest of the patient, but for research professionals other interests are also at stake. Although a research professional will always need to minimize burden and risk and avoid harm to the participants, that does not mean that participation is always in the best interest of the patient. This physician- and research-role can conflate in practice and then potential participants' trust is not always based on correct assumptions. It is the responsibility of the researcher to make this distinction clear, so that the personal trust participants have in them is legitimate.

INSTITUTIONAL TRUST

Second, our potential participants' willingness was also influenced by institutional trustworthiness. For example, for some respondents, the fact that a study was done with international collaboration or an academic hospital, enhanced their trust (table 2).

Table 2: Example institutional trust

Participant	Quote
Father *(age 48)*	*That the study was done internationally played a big role, so yes, then you already have faith in it. If it were a study of just the [x]-hospital, their own in-hospital research, that would be a different picture.*

For this type of trust it is not so much the personality of the individual researcher that influences the decision of the potential participant, but the characteristics of the institute in itself (e.g. international collaboration is better, academic hospital is better).

TRUST IN RESEARCH IN GENERAL

We also found that potential participants' trust can be linked to a trust in research in general. We quite frequently encountered a positive stance towards research and an optimism regarding the possible benefits: 'what is being investigated is new, and what is new, is better' (table 3).

Table 3: Example trust in research in general

Participant	Quote
Boy *(age 16)*	*They're, of course, not going to do something they think does nothing. A lot of people believe that this is better*

We consider this form of therapeutic optimism (or maybe even therapeutic misconception, since research should be based on clinical equipoise), as an expression of trust in research. Potential participants can believe that research means progress and conclude from that, that new/experimental is always better. This type of therapeutic optimism and the link to trust is also identified and emphasized by other authors.[3] It is crucial that research professionals are realistic about the rationale of the study and its anticipated benefits and do not to take advantage of this type of trust.

TRUST IN OVERARCHING SYSTEM

The last type of trust we identified, also in line with the authors' results, is trust in the overarching system. Our respondents told us that they expect that immoral and unsafe research would not be allowed and offered to them, and that any research that is allowed in an academic hospitals such as ours, must therefore be safe (table 4).

Table 4: Example trust in overarching system

Participant	Quote
Father *(age 48)*	*Of course, there are some risks attached, but even so, once they're testing on humans a lot of steps have been made towards this point, so it'll be safe*

You could say that by this type of trust they outsource their concerns about risks. They assume the research that is offered to them is adequate and safe, otherwise it wouldn't be offered to them; and they expect that processes are in place that protect them.[4] This trust in an overarching system, a type of institutional trust as Kraft and colleagues call it, shows the importance of the ethical review system and the 'filtering' role of research ethics committees (RECs).

FILTERING ROLE OF THE RESEARCH ETHICS COMMITTEE

As presented above, we found in our own research results parallel to those by Kraft and colleagues. Our conclusions differ, however. They state that their results challenge the current model of research ethics, *'because the current model of research ethics…focuses primarily on supporting individual autonomy'*.[1] We conclude the opposite: The trust that patient-participants have in the overarching system actually confirms the rationale and necessity for the current model of research ethics and the importance of RECs.

Consensus exists about the primary role of RECs to protect participants, whilst not standing in the way of advancing science. However, according to some, there is a threat of RECs being overprotective and acting as a gatekeeper to filter research.[5-7] Several authors have argued that this 'filtering' role gives RECs the inappropriate capacity to prevent research from being conducted, since participants, as long as they are competent, are best placed to decide on what are appropriate risks when deciding whether to take part in research.[8] We argue, based on the results presented above, that this filtering is a legitimate and even fundamental task of a REC.

In order to deserve the trust that patients have in the system (allowing only morally and medically acceptable research), the 'filtering' role of a REC is crucial. A REC needs to make a decision whether a specific research protocol is scientifically and ethically adequate before it can be proposed to potential participants. This filtering task is moreover laid down in important ethical and legal rules and legislation, like the Common Rule and the Declaration of Helsinki.[9 10] Our research shows potential participants assume that this filtering has taken place; they rely on the filtering by the REC. In this way they outsource a part of their decision-making process to the REC.

CONCLUSION

We therefore do not agree with the authors that autonomy seems to be the only important element in research ethics, nor that it should be. Of course, respecting autonomy, by making sure every potential participant has given informed consent, is a cornerstone for research ethics, but it is not the whole building. Kraft and colleagues' results, combined with the results we just presented, concerning patients' trust emphasize this.

Informed consent can only be given after a REC has evaluated the protocol and executed their legitimate filtering role. The large influence that patients' trust has on the decision of potential participants emphasizes the necessity of this prior review of a REC and its filtering task.

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CHAPTER 9

General discussion

This thesis aims to contribute to the optimal inclusion of children in pediatric clinical research, in such a way that we can further clinical research to advance scientific knowledge and develop much-needed treatment options for children while protecting children against harms from research.

In this chapter, I combine the main findings of the preceding chapters into a normative framework to assist research professionals when including children in clinical research. This framework aims to tailor the process of recruitment and informed consent to the perspective and the needs of children and their parents, who have the key role in decisions regarding research participation. I will conclude this chapter with some developments in clinical research that necessitate new research efforts, policy changes and new ethical guidance.

Before formulating this framework, I need to explain the steps in the research enterprise before children can participate in research.

GATES IN THE RESEARCH ENTERPRISE

Before a research proposal reaches potential participants (and their parents), other ethical decisions related to the research have been made on which the potential research participants and their parents have no influence. Only then potential participants and their parents make a decision about participation. I call those decisions, 'gates' in the research enterprise. These decisions concern 1) protective measures in legislation; 2) research design; 3) medical-ethical review; 4) recruitment by the professional; and 5) informed consent by the potential research participant. Figure 1 shows an illustrative overview of these gates.

GATE 1: PROTECTIVE MEASURES IN LEGISLATION

Protective measures start with the fact that society has laid down specific requirements for clinical research, especially for research involving children, in law and legislation. The rationale behind these requirements is that there is a consensus about the fact that not all research with children is ethically acceptable. These requirements are related to, e.g., informed consent/assent, dissent and refusal during research and risk and burden thresholds. Related to these risk and burden thresholds, most countries, including the Netherlands, have restrictions on pediatric clinical research without a prospect of direct benefit.

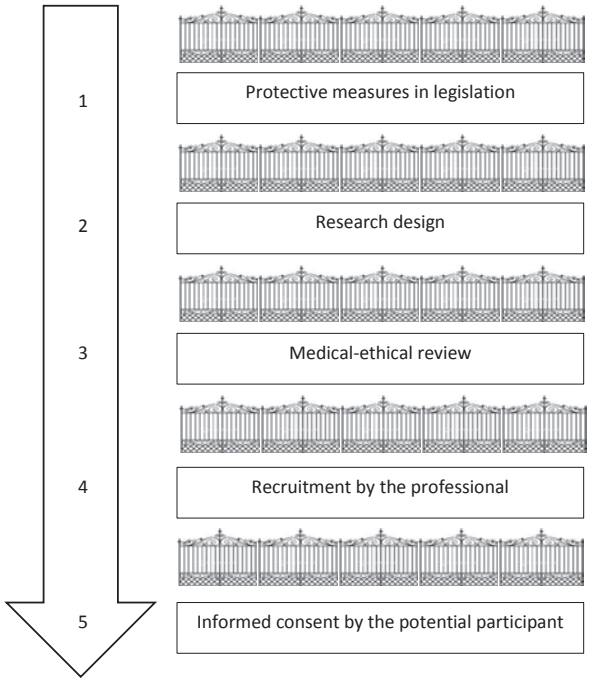

Figure 1: Overview of the gates in the research enterprise

As discussed in chapter 2, restrictions on research without a prospect of direct benefit vary between legal frameworks. Chapter 2 compares these specific requirements for pediatric clinical research in the European Clinical Trials Directive and the European Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine (further Oviedo Convention). In the addendum of chapter 2 I have added information regarding the upcoming European Clinical Trials Regulation that will replace the Directive. The common core of the upcoming EU Clinical Trials Regulation, the Oviedo Convention and also the Dutch WMO, is that certain limits are set to pediatric clinical research without a direct benefit to the child participating.[1-3] Some pediatric clinical research is not allowed at all or is required to adhere to specific risk and burden thresholds. This implies that even if researchers want to design these types of clinical research and even if children and their parents want to participate, legislation prohibits these studies. These studies are simply not allowed and may not be offered to potential participants. There is, of course, an ongoing discussion about these restrictive policies.[4 5] Based on results presented in this thesis, there are arguments either way. On the one hand, the empirical finding presented in chapter 5 that parents and children want to be asked for research participation even in difficult and stressful circumstances, could be used to argue that all research should be offered to children and their parents. No risk and burden thresholds or filtering should be in place

beforehand, making additional risk thresholds in legislation unnecessary. On the other hand, the empirical finding presented in chapter 5 that parents and children expect only safe-and-sound research to be offered to them, could emphasize the necessity of these additional risk thresholds in legislation. However, whether these specific restrictions concerning risk and burden thresholds are justified is beyond the scope of this thesis. I took these legal and ethical requirements as fixed points. Nonetheless, it is important to note that these legislated restrictions create a first gate before children and parents can say yes or no to research.

GATE 2: RESEARCH DESIGN

A 'gate' that is quite often forgotten as being an ethical gate and having influence on who participates in the research is the design of the research by the research professional. Decisions made by research professionals in the design of the research influence the participation of children and their parents. The selection of the study population prescribes whether a child *can* participate, while for example, the choice of research procedures influences whether a child *wants* to participate.

The selection of the population is made explicit by the inclusion and exclusion criteria in a research protocol. The criteria need to be specific enough so that the research will generate valid results and that people who should be protected against harm are excluded but wide enough so that results from the trial will be generalizable to clinical practice and that people who could benefit from participation gain the chance to be in the trial. It is important that research professionals find a balance between their inclusion and exclusion criteria so that the right children are included in the trial.

Furthermore, the study design chosen by research professionals also directly influences the willingness of children and parents to participate in research. As we showed in chapters 4 and 5, burden is one of the most important factors for children and their parents, influencing their decision to participate. Research professionals therefore need to look critically at the design of their study and assess from the start how they can minimize the burden on participants. In chapter 3, we made some concrete suggestions for lowering the burden of specific procedures in clinical drug research by using new techniques. Techniques such as low-volume drug assays, dried matrix spots and PK-PD modeling tools decrease the amount and intensity of blood sampling from children. The empirical research into the motivations of children and their parents described in chapters 4 and 5 also showed that the focus of children and their parents on burden is not exclusively related to the burden of specific research procedures for the child but entails much more. The logistical burden of participating in a trial for both children and parents greatly influences their decision. This includes time spent in the hospital

for trial purposes, missing school or workdays due to participation and missing out on leisure time. Additionally, when a child is asked to participate in research, it is easy to forget that parents are not only proxy consenters but also proxy participants. A child often depends on his/her parents to travel to the hospital, and parents regularly need to collect samples for research purposes. In designing pediatric clinical research, this type of logistical burden on both children and parents should be given attention and minimized. The design of the research is thus a second gate in the research enterprise before children and their parents are offered participation and can consent to research.

GATE 3: MEDICAL-ETHICAL REVIEW

After a specific research protocol is designed, in most cases (depending on local rules), it has to be reviewed by an independent research ethics committee (REC). An REC evaluates the risk-benefit ratio of the protocol and assesses whether the proposed research is ethically acceptable. In other words, an REC needs to decide whether a specific research protocol is ethically acceptable before it can be proposed to potential participants. The rationale behind this role of RECs is that one cannot offer just any research to potential participants because they do not have the tools, experience and knowledge to assess the ethical quality of the research. Therefore, in practice, we need two approvals for clinical research: approval from the REC and from the potential participant. There is currently much criticism on the role of RECs, specifically, on their protective nature and their filtering role.[6 7] Some authors such as Edwards and colleagues have argued that RECs are too paternalistic since participants are best positioned to decide themselves on what risks are appropriate when deciding whether to take part in research.[8] In chapters 5 and 8, we argued, on the contrary, that RECs and their filtering roles are legitimate and vital for an ethically acceptable research enterprise. Chapter 5 showed that children and their parents outsource their concerns about risk and that they expect research to be evaluated and reviewed beforehand so that only safe-and-sound studies be offered to them. The trust that potential participants have in research and in research professionals further emphasizes this filtering role of RECs (chapter 8).

In addition, the trust by parents and children is not served with a review process that only checks the compliance of a protocol to relevant regulations, as some authors propose to be the sole task of an REC.[9] Such trust requires an REC that expertly and thoroughly assesses the ethical acceptability of protocols, including a judgment about the scientific justification, methodological approach and competency of the research team.[10] The results in this thesis show that parents and children expect that only ethically acceptable research is offered to them. This finding shows the importance of an adequate review by an REC as an essential gate for research.

GATE 4: RECRUITMENT BY THE PROFESSIONAL

A research protocol that has been approved by an REC can start with the inclusion of participants. This inclusion is conducted by professionals. I call this process gate 4 in the research enterprise. Researchers decide (implicitly or explicitly) who they will approach for a specific research project. Explicit factors that play a role in this recruitment by the professional are the predefined in- and exclusion criteria in the research protocol. Children who do not fulfill these criteria will not be approached. As discussed in chapter 7, these factors can also be implicit. Professionals may have implicit criteria for (not) approaching potential participants (e.g. wanting to protect children from risk and burden associated with trial participation or prejudiced beliefs about their choice). This can result in gatekeeping by professionals, meaning that they do not approach all eligible research participants. In that sense, this approach creates a fourth gate in the research enterprise before parents and children can make a decision about participation. I will elaborate on the desirability of this practice later in this chapter (Step 1: Who do you approach).

GATE 5: INFORMED CONSENT BY THE POTENTIAL PARTICIPANT

After the research plan has already passed four gates, the potential research participant has the choice to give informed consent (or not) for participation in that research study after a proper informed consent process.

GATES: OBSTACLES OR NECESSARY SAFEGUARDS?

The above-described gates are pivotal in the research enterprise. When we revisit the central dilemma of clinical research with children, people who are more on the protective side would see the presented gates as necessary and useful protective safeguards for children in clinical research. Others who lean more towards the other side might see the presented gates, especially gates 1 and 3 (protective measures in legislation and medical-ethical review), as unnecessary obstacles that impede improvement and innovation in medicine or as overprotective paternalistic hurdles that withhold parents and children from having a choice about participation.

FRAMEWORK FOR RECRUITMENT AND INFORMED CONSENT

This thesis is mainly focused on the last two gates: recruitment by the professional and informed consent by the potential participants or their parents. Therefore, the second part of this chapter will go more into detail regarding these two gates. How can we ensure that these last two gates serve their purpose in pediatric clinical research? How can

we incorporate views of children and their parents into the pediatric research enterprise and specifically into these last two gates of recruitment and informed consent?

When we know why children and parents consent or dissent to research and what elements they use in their decision, we know what they attach importance to in their decision. From this data, we learn which information they want and need to make a valid informed decision. This information helps us to increase both the moral and instrumental value of informed consent in pediatric clinical research.

I propose a normative framework to support research professionals in the ethically sound inclusion of children in pediatric clinical research. This framework tailors the process of recruitment and informed consent to the perspectives and needs of children and their parents. Figure 2 shows an illustrative overview of this framework for recruitment and informed consent.

STEP 1: WHO IS ASKED

Gate 4 starts with the recruitment of potential research participants by the professional. Professionals are in the lead for approaching parents and children for their research. However, who should they ask? To state it bluntly: Everyone who is eligible.

Unfortunately, as illustrated with some examples in chapter 7, this is not the case in practice. I learned during my empirical research that professionals do not always approach all eligible potential research participants: this selection is known as *gatekeeping*. We argued that, although this practice is understandable, professionals should refrain from it since it is not ethically desirable. Arguments that undergird our point of view are both ethical and methodological and relate to respect for persons, individual beneficence, scientific and social value, introduction of bias and justice. An important empirical finding supporting this concept can be found in the fact that children and their parents actually want to be asked. The results from the interview study presented in chapter 5 show that children and their parents want to be given the chance to say yes (or no), even in stressful and difficult decisions. They explicitly stated that it was not up to the researcher to decide for them.

The general rule should be to ask everyone eligible, with specific attention to how and when. Clinical professionals can help find the right moment to approach children and their parents. This timing and coordinating can make a difference when children and their parents are approached for participation in clinical research. It is therefore important that research professionals who recruit potential participants communicate with their clinical colleagues. Nurses, in particular, have frequent contact with patients during

the day. Parents and children ask them questions when research professionals are not around. These colleagues from clinical practice should therefore also be informed about (and endorse) the study.

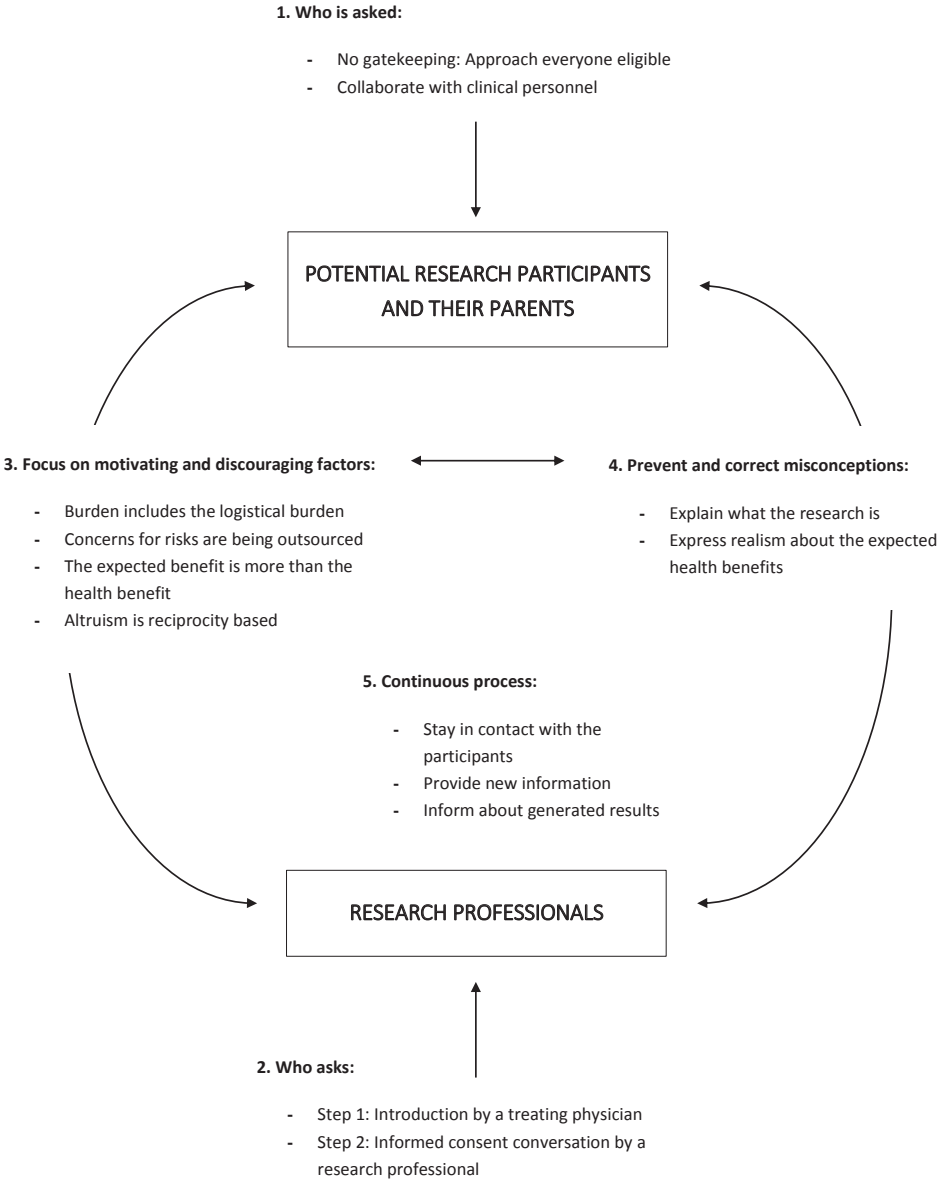

Figure 2: Overview of the framework for recruitment and informed consent

STEP 2: WHO ASKS

As discussed in step 1 ('who should be asked'), a question emerges regarding who should do the asking. Who should approach the potential research participants and their parents? In short, the answer is the research professional, preferably (when possible) a research nurse.

Chapters 4, 5 and 8 showed that trust is an important motivational factor in the decision-making process for parents and children. In chapter 8, we distinguished four types of trust: personal trust, institutional trust, trust in research in general and trust in the overarching system. In particular, personal trust, directly linked to the research professional, influences the decision to participate. Chapter 5 shows that parents and children believe that the research professional has designed and will conduct the research in their best interest. In that sense, their trust is closely linked to the doctor-patient relationship. The treating physician should act in the best interest of the patient, but for research professionals, other interests are also at stake. In practice, the physician role and researcher role can be conflated. Then, this trust is not always based on correct assumptions. Therefore, it is the responsibility of the research professional to make this distinction clear, so that the trust participants have in him/her is legitimate (chapter 8).

When possible, the roles of treating physicians and research professionals should be separate to avoid therapeutic misconception and to guarantee the voluntary nature of research participation. A recent study by Hoof and colleagues showed that physicians and research nurses in pediatrics differ in their opinion about this matter. The questioned physicians clearly indicated that informed consent is the sole responsibility of the treating physician. The research nurses, however, also saw a role for other research professionals such as themselves in the informed consent process.[11] I agree with these research nurses. It is the research professional who is ethically and legally responsible for the informed consent for a research proposal. Informed consent legally defines the rights and duties of both the research professional and the participant, not of the treating physician and of the patient.

I suggest creating a two-step recruitment and informed consent process in which these roles are distinguished: 1) introduction of the research proposal by the treating physician and 2) an informed consent conversation with the research professional. The introduction of the research by the treating physician (e.g., in a couple of sentences) shows the parents and children that their treating physician endorses the aim of the proposed research. The informed consent conversation with the research professional will make it clear to the potential participants that research is fundamentally different from clinical care and emphasizes the voluntary nature of the decision. In practice, the treating physician is sometimes also one of the researchers. Especially in these situa-

tions, it is important to use this two-step approach to clarify the distinction. Preferably, the responsibility for step 2 should lie with the research nurses. Due to their coordinating role, they have an overview of all research protocols currently being undertaken in a specific department that an individual researcher may not have. This gives research nurses the possibility to combine multiple research proposals within one informed consent conversation (when applicable) and to address the collective additional burdens and risks for the potential research participants and their parents.

STEP 3: FOCUS ON MOTIVATING AND DISCOURAGING FACTORS

Law and legislation prescribe what information a research professional needs to give to potential research participants and their parents. Then, the parents and children are able to make an informed decision. However, if the potential participants do not use the informational elements in their decision-making is the informed consent then not informed? A research professional needs to determine which factors parents and children attach importance to and which they would want to use in their decision and inform them about these aspects, thereby identifying the motivating and discouraging factors relevant to the decision.

It is essential that research professionals pay attention during the recruitment and informed consent process to the motivating and discouraging factors children and their parents have for their research participation. When professionals discover more about the motivations of parents and children to accept or decline participation in pediatric clinical research, the professionals will know which aspects of research the parents and children attach importance to and what information is relevant to their decision. This information can then be used in the informed consent materials and conversations.

IMPORTANT MOTIVATING AND DISCOURAGING FACTORS

RECs assess the expected risks and burdens for potential participants in comparison to the expected benefit to them and to other individuals or groups affected by the investigated condition, a process involving proportionality weighing. The empirical research presented in chapters 4, 5 and 6 shows that this proportionality is also considered by parents and children in their own individual decision about research participation. Benefit and altruism are important motivational factors, risk and burden are important discouraging factors, and potential participants often emphasize the weighing of these factors in their decision.

The systematic review presented in chapter 4 and the interview study presented in chapter 5 show that children and their parents attach more importance to burden than to risk when they need to decide about participation in pediatric clinical research. The

anticipated burden of participating is most frequently mentioned as motivating or discouraging for their decision to participate (or to let their child participate). As mentioned before, this focus on burden is not only related to the burden of specific research procedures imposed on the child but also entails the logistical burden of participating in research for both children and parents. Research professionals need to pay specific attention in the recruitment and informed consent process to this type of logistical burden for both children and parents.

The systematic review presented in chapter 4 showed and the focus group and interview studies presented in chapters 5 and 6 confirmed benefits for the child to be a main motivator of parents to endorse the participation of their child in pediatric clinical research. Interestingly, parents in the focus groups used a much broader definition of benefit than direct health benefit, e.g., being regularly checked up also constituted a benefit for them. However, these check-ups can only provide a benefit when the participants are informed about the results. Research professionals need to be aware of this concern and develop a proper return-of-results policy.[12 13]

The systematic review in chapter 4 and the interview study in chapter 5 show that altruism is an important reason for parents and children to participate in research. An interestingly related result from the interviews, which was not found in the included articles in the systematic reviews, is that parents and children not only consider the future in their altruistic reasoning but also reason backwards. Parents and children not only focus on future patients but also consider children who participated in the past. They now benefit because, in the past, other children participated in research. Luchtenberg and colleagues recognized this concept in their interviews with children regarding research participation and introduced the term 'reciprocity' to characterize this type of altruism.[14] The results from our interviews accentuate this reciprocity-based altruistic reasoning in parents and children who are asked to participate in clinical research. In my view, research professionals may endorse this reasoning when parents or children bring it up. It is important, however, that they do not use this reasoning as leverage in the decision-making process.

Finally, it can be very informative for research professionals to know why potential participants decide not to participate. This information can be used to perhaps adapt the current research and definitely to design future research protocols in such a way that they better fit the wishes of the research population. Therefore, I suggest registering the discouraging factors children and their parents mention when they explain why they decided not to participate. However, it should never become mandatory for parents and children to state their reasons, nor should they be pressured to state their reasons.

STEP 4: PREVENT AND CORRECT MISCONCEPTIONS

During the informed consent process, it is important to pay attention to misconceptions children and their parents may have about participation in the research. Their motivations to participate can be influenced by misconceptions, and their motivations can also expand the misconceptions they have. It is the responsibility of the research professional to prevent and correct these misconceptions.

There are no intrinsically wrong motivations for parents and children to participate in research unless they conflict with the parents' duty to care for their children. The empirical research presented in chapters 4, 5 and 6 did not uncover any such motivations conflicting with parents' duty to care. We did, however, encounter motivations of children and their parents based on incorrect information or misinterpretation of correct information. Preventing and correcting these misconceptions are the responsibility of the research professional. What can we do about these misconceptions and on which elements should a research professional focus?

Although the written informed consent material represents only one aspect of the informed consent process, it continues to serve as the primary vehicle for the disclosure of research information.[15] Additionally, a signed informed consent document is not an end in itself; it represents only the conclusion of a participant's decision-making. To achieve the goal of adequately informing a potential participant, informed consent materials, including the informed consent document itself, should be as simple and concise as possible.[16] Tait and colleagues concluded from their research that an eighth-grade reading level, improved formatting, and use of graphical elements improve the comprehensibility of informed consent materials.[17] Particularly in research involving children, examining these factors when designing information materials can make a difference due to the children's developing capacity. To address this issue in pediatric clinical research, Grootens-Wiegers and colleagues developed and tested new information materials specific for children in the Netherlands, in the mode of a comic book.[18] It is crucial that these initiatives are stimulated and implemented in practice.

I received feedback on informed consent documents multiple times from parents in my interview study: "I read the information material for children; it is more understandable than the one that is written for myself". Does this feedback mean that the material for parents is written at a too-high level? It is likely that it is. Some years ago, in a different project, we evaluated the comprehensibility and language level of informed consent documents in the Netherlands. We concluded from a reading level test of 35 informed consent documents approved by RECs in the Netherlands that the majority (n=33) were too difficult for the general public to understand.[19] It would be much better if research

professionals invested in understandable information material and pay attention to preventing and correcting misconceptions of children and parents in the informed consent process.

IMPORTANT MISCONCEPTIONS

Chapters 5 and 6 discuss misconceptions of children and their parents that were encountered in the interviews and focus groups. In general, parents (and children) conflate research and care and have difficulties grasping the trajectory of clinical drug development (chapters 5 and 6). It is therefore important for research professionals to start their informed consent conversations by explaining what research actually means.

This explanation of research is also vital to tackle misconceptions regarding the benefit someone can expect from research participation. The research presented in chapters 4, 5 and 6 demonstrated that the expected health benefit is an important reason for children and their parents to participate but that the chances of this benefit arising are also often misinterpreted. Interviewed parents and children expected health benefits, even from observational research. This expectation is much related to the idea they have of being checked up regularly in clinical research and receiving extra attention from healthcare staff. As we already argued in chapter 6, patients (including parents and children) should not be dependent on research to receive the attention they wish for in clinical practice. Therefore, it is advisable for research professionals to avoid such terminology.

In phase 1 pediatric drug research especially, misconceptions related to expected benefits should be prevented and corrected. Research professionals should try and temper the understandable hope for benefit that parents and children have by emphasizing the reality that most children do not benefit from participation in a phase 1 pediatric drug trial. Falsely reassuring communication may lead children and their parents to make decisions they might not have made otherwise.[20] Miller and colleagues showed in their observation and interview study that physicians in phase 1 pediatric research failed to mention no treatment and/or palliative care as options in 68% of the informed consent conversations. Physicians also failed to mention in 85% of the informed consent conversations that the disease was incurable.[21] Physicians should be honest and realistic and should state that most children do not respond to phase 1 pediatric trials. The reality is that phase 1 trials are not developed with the aim of benefiting the patients participating in the trial. Although some mention that this premise does not count for pediatric phase 1 research because it is built on adult data, two extensive reviews show that the opposite is true. All phase 1 pediatric oncology trials published in the periods 1990-2004 and 2004-2015 showed an objective response rate of only approximately 10% (including complete and partial responses), while the average grade 3/4 adverse

event rate was more than 1 per person.[22 23] Both reviews concluded with the statement that these findings are similar (with respect to benefit and harm) to the results of phase 1 trials in adults.

STEP 5: INFORMED CONSENT AS A CONTINUOUS PROCESS

Research professionals should consider and act upon informed consent as being a continuous and dynamic process. Obtaining a signature on an informed consent form is not the goal and endpoint of an informed consent process. Research professionals should stay in contact with the participating parents and their children regarding their decisions during the course of the research.

Although the framework ends after this step 5, the informed consent process in clinical research does not stop. It is important to realize that informed consent is not a one-time achievement but should be a continuous and dynamic process between research professionals and (potential) participants. In pediatric clinical research, the continuity of the informed consent process is even more important because of children's developing capacity.

In a recent article, Kadam depicts informed consent as an information highway in clinical research to explain study procedures, risks, benefits and participant rights.[24] I do not know if a highway is the analogy I would choose, but to continue the traffic terminology, I would rather use a round-about to illustrate the informed consent process, namely, a dynamic and continuous process before and during the research, in which (potential) participants can at any time make different choices based on new information. Informed consent in pediatric clinical research should therefore encompass a dynamic and continuing exchange of information between the research team and (potential) participants and their parents.

In practice, this means the following for research professionals: Stay in contact with your participants, including during the course of the research. Research professionals should provide participants and their parents with new information when relevant and be aware that their former decisions can change. Just as research professionals should not act upon implicit assumptions about the initial choice children and their parents will make regarding trial participation, professionals also should not act upon these assumptions during the trial. When an aspect might be relevant to the decision made by children and their parents, professionals should inform them about it. To optimally guide the process, it is important for research professionals to anticipate the continuity of the process of informed consent at the beginning of the research.

NEW DEVELOPMENTS: NEW ETHICAL GUIDANCE

New developments in medicine, clinical research, ethical oversight and technology bring new questions that request new ethical guidance. These developments are not specific to clinical research with children but present overarching themes that are also relevant for pediatric research practice. New developments also arose during the course of this research. The framework I presented and the conclusions I drew will be dependent upon and will need to be adapted to these (upcoming) developments. In this paragraph, I therefore discuss some of these developments and make suggestions regarding how guidance should proceed or what new ethical research would be needed to optimally incorporate these developments. These developments may have an effect on all five gates in the research enterprise because they necessitate changes in the protective measures in legislations, new choices in research design, adaptation of the medical-ethical review process, and different recruitment strategies; these developments will also influence the informed consent by potential participants.

DIGITAL TECHNOLOGIES IN INFORMED CONSENT

New digital technologies are emerging, and they could also be useful tools to improve the informed consent process in pediatric clinical research.[25-28] In particular, as informed consent is considered a continuous dynamic process, new digital technologies can support and emphasize this continuous and dynamic contact between participants and research professionals. For example, block chain technology has even been introduced by researchers to follow such types of informed consent flows in clinical research to improve the transparency and traceability of informed consent.[29]

Of course, the use of new digital decision support and informed consent tools should not completely replace the much-needed face-to-face contact between a researcher and potential participant. The use of new digital technologies in the informed consent process will probably raise the same concerns regarding the amount of information, readability and formatting as paper informed-consent documents did, but there are a couple of advantages. New digital decision support and informed consent tools: 1) can promote active participation instead of the passive participation mode of a paper consent form; 2) can possibly provide a pictorial superiority effect (a picture says more than words), especially in people with poor literacy; 3) can incorporate corrective feedback that results in real-time understanding and learning; and 4) can tailor the information to the needs of the individual participant.[15]

A systematic review performed by Grootens-Wiegers and colleagues made apparent the large readability gap between the reading level of the information material for pediatric

clinical research and the reading ability of children.[30] For example, an empirical study by Tait and colleagues showed that compared with the use of traditional modes of information dissemination, the use of digital information resulted in a significant increase in understanding by children and parents.[31] Their review also showed that interventions that were effective used a story format, multimedia or illustrations for probabilities in pediatric clinical research. These last three components lend themselves perfectly to be implemented in new digital technologies. To enhance understanding, research professionals and RECs should adopt innovative communication strategies and new digital technologies.

The implementation of these new digital technologies requires critical reflection on and perhaps even a revision of ethical and legal guidance concerning informed consent. For example, in the Netherlands, researchers are obliged to use an informed consent document template designed by the Dutch Clinical Trial Foundation (DCRF) working group commissioned by the Central Committee on Research Involving Human Subjects (CCMO). It would be worthwhile to investigate how to adapt the current templates into digital support tools so we can stimulate researchers to tailor the process of informed consent more closely to the needs of their study population.

Another way to implement new digital technologies in pediatric clinical research would be to explore the possibility and acceptability of digitally signing informed consent forms. Currently, an original autograph written on paper is needed. In the practice of clinical research, this signing of the papers can be logistically very difficult, while this prerequisite has no effect on the meaningfulness and validity of the informed consent. Especially in pediatric research, the collection of autographs of both parents and children at the same time can be logistically demanding. Could digital signing of informed consent documents by the use of DigiD be an elegant way of tackling this issue?

ALTERNATIVE FORMS OF INFORMED CONSENT

In principle, we want informed consent of potential participants before we commence research procedures. This order of consent and then participation can become compromised during research in an emergency setting. For instance, in the research practice of the PICU, it is not always possible to achieve written informed (proxy) consent before the start of the study. The following alternative consent models are being introduced to balance respect for the decision of potential participants and the benefit research participation might bring them: a waiver of consent and a deferred consent approach. These alternatives are discussed in chapter 3. As a waiver of consent means not asking for consent at all, I do not consider this a justified alternative. It does not balance any other aspects and completely eliminates the choice of potential participants and their

proxy decision-makers. However, a process of deferred consent may be an elegant solution in specific difficult circumstances.

Currently, the WMO gives minimal ethical guidance about the acceptability of deferred consent (art 6:4 WMO 1998). The WMO considers deferred consent acceptable only when it is practically impossible to obtain consent before the start of the trial and when the trial may benefit a participant in urgent need of medical treatment. Some researchers suggest using deferred consent when they consider the decision to be too stressful for parents and potential participants, even without an emergency situation. In my view, difficult circumstances, stress for parents or an expected high dissent rate are not acceptable arguments to justify the implementation of such a procedure. On the contrary, the results in chapter 5 show that parents and children want to be asked about participation, even in stressful situations. International legislation and guidance documents concerning this topic also propose other conditions that need to be met for deferred consent to be acceptable,[32] namely: limits to the acceptability of burden and risk in the trial (upcoming EU Clinical Trials Regulation); mandatory public consultation beforehand about the desirability of deferred consent (US guidance for IRBs); and mandatory public information in the department where the research is carried out, for example, through poster announcements (US guidance for IRBs).[1 33]

It may be worthwhile to assess the desirability and necessity of implementing these additional requirements in Dutch research practice. Developing a framework for deferred consent in the Netherlands should be done considering the additional measures that are used in other countries. This framework will help research professionals implement deferred consent in an ethical manner and provide RECs with much-needed tools to review these adapted informed consent models.

COMBINING RESEARCH PROTOCOLS

A new approach in clinical drug development is the creation of overarching research protocols that combine different phases of drug research, especially in pediatric research, for example, creating a study in which phase 1, 2 and 3 studies are combined in a single protocol. Researchers aim to accelerate drug development through this approach, which creates more coherence and effectiveness and reduces time and cost compared to stacking individual trials. However, it also creates an ethical concern relating to the risk-benefit ratio in such combined research.

Drug development is traditionally split in separate phases of research, with each phase having its own distinct goal, outcome measures and population. These distinctions lead to different expected benefits and risks for the different stages of research and result

in differing risk-benefit ratios for the consecutive phases of research.[34] When these different phases are combined in one protocol, it begs the question of how the overall risk-benefit assessment is created by researchers, evaluated by RECs and perceived by potential research participants in their decision-making.

The creation of one risk-benefit ratio for such a combined protocol by researchers is flawed for the following reasons. First, different subjects participate in the different phases of the specific research, and there is no overarching risk-benefit ratio for an individual participant. Second, how are researchers even able to estimate the benefit and risk in the subsequent phases before the start of the initial phases of the research? It is not possible to make those estimates when the early phase research has not been carried out and has not yet generated results that inform the expected benefit and risk. Therefore, researchers should separate the risk-benefit ratios for the different phases, even if they combine the different phases into one protocol.

RECs evaluate the ethical acceptability of research protocols and assess the risk-benefit ratio. To evaluate such a combined research protocol, it is necessary to assess the different phases of the research with their distinct risk-benefit ratios. Therefore, RECs need to have explicitly available in the protocol the risks and benefits of the separate phases and which participants participate in which phase. Only then can they evaluate the risk-benefit ratio. In practice, RECs will hopefully give provisional approval of the protocol, which includes only the first phase of the research. The expected safety and risks for participation in the consequent phases cannot be evaluated by an REC until the moment the first phase has generated results.

As already stressed before, burden and expected benefit are important factors for the decision-making process of potential research participants, which implies that their decisions will differ for the different phases. Participants will participate in a specific phase of the research and should therefore be informed about the expected benefit and risks associated with participating in that specific phase. To present the potential participants with the overall risk and benefits of the entire research would be misleading. It is necessary to create different information materials and informed consent documents for the separate phases.

The above discussion makes it clear that this new trend of combining research protocols is ethically problematic and that RECs need to be vigilant regarding the proposed combined risk-benefit assessments and informed consent documents in such protocols. Although combining protocols can accelerate the research process, separate risk-benefit

assessments and informed consent documents for the subsequent phases of a research protocol are needed, both for the REC and for the potential research participant.

CREATING READINESS COHORTS

Novel approaches are being developed to improve screening for eligibility and facilitate the recruitment of research participants. One of those developments is the creation of 'readiness cohorts' for clinical research. This approach has been mainly developed and published in research on the prevention of Alzheimer's dementia.[35 36] It is, however, not unthinkable that the development of readiness cohorts will also reach other fields of medicine, including research involving children. Because of the small population available for pediatric clinical research in orphan diseases, these readiness cohorts can be expected to become more common.

These 'readiness cohorts' link existing research cohorts, studies or patient registries with new research. The primary goal of these cohorts is to provide a well-characterized population of potential research participants for recruitment into trials, for example, to reduce recruitment time and costs. From these established 'readiness cohorts', individuals are recruited into new clinical trials. Although this development may improve research recruitment, setting up such research infrastructures obliges us to evaluate our current ethical guidance, which is currently focused on distinct individual trials. Specific attention should be given to the requirements for recontacting participants in existing research studies and for obtaining informed consent as participants move through the research process.[37]

We need to be aware that people participating in a readiness cohort might drop out at increased rates from the existing studies because this process adds a burden. Next, we need to think of guarantees to ensure access to an actual trial for people who are not part of the readiness cohort. In addition, the other way around, people participating in a readiness cohort should not be excluded from other research offers merely on the grounds that they were placed in this cohort. Both constraints would create a monopoly of these patients and influence the voluntary nature of research participation.

The longitudinal and transitional character of readiness cohorts makes it difficult to ensure that potential participants are fully informed about the scope of the research before they consent to take part. Participants in a readiness cohort do not know at the start whether they will eventually be asked to participate in a clinical trial and what that trial will entail because this information is not known beforehand. This situation creates the danger of a fish trap. One is drawn into the research project, in which it becomes increasingly difficult to return or leave the research project. This fish trap can be pre-

vented by introducing a staged consent model.[37 38] This consent model feeds relevant information, bit by bit, along a research participant's journey and asks for informed consent at every moment in which important decisions need to be made by participants. Although informed consent is always given for a specific stage of the research project, information about the 'totality of the project' also needs to be always and explicitly part of the informed consent process. It is important that researchers and RECs are aware of the distinct ethical challenges that are related to this new development of 'readiness cohorts'.[iv]

LEARNING HEALTHCARE SYSTEM

We are moving gradually into a new era of clinical research and the research ethics related to it. In 2007, Emanuel and Grady elaborated on four paradigms in clinical research and oversight. They defined four different paradigms in research: 1) research paternalism; 2) regulatory protectionism; 3) participant access; and 4) collaborative partnership.[39] These paradigms follow each other, with several elements of previous paradigms still being present. I believe we are slowly stepping into a new, fifth paradigm with the implementation of 'Learning Healthcare Systems'.[40] A learning healthcare system combines care and research and originates from high-scale reuse of health data and the inclusion of patient perspectives into care models.[41] In the field of pediatrics, the learning healthcare system is also being explored. Pediatric oncology, where research and care are highly intertwined, is mentioned as an example of a learning healthcare system.[42]

Advocates of learning healthcare systems want to achieve additional and direct effects of research on clinical care and more clinical perspectives in research. Although I support this goal, I wonder whether a learning healthcare system can achieve this goal in a morally acceptable way. A learning healthcare system is characterized by the intertwinement of clinical care and research. This intertwinement imposes the need to find a new collaboration between traditional research ethics and clinical ethics.[43 44] Brody and Miller state that it is crucial that we retain the distinction between research and clinical care, and I agree.[45] The following important elements differ between clinical care and research: 1) patient - research participants; 2) individual - population; 3) request for help - hypothesis testing; 4) treatment - generalizable knowledge. The results from this thesis show how important the distinction between research and clinical care is for potential research participants and how difficult it is for them to grasp the concept of research. The danger of this new paradigm is that we lose the ethical guidance and the

iv This paragraph is partly based on an article I wrote with colleagues from the European Prevention of Alzheimer's Disease (EPAD) consortium (Milne R, Bunnik E, Tromp K, Bemelmans S, Badger S, et al. Ethical issues in the development of readiness cohorts in alzheimer's disease research. J Prev Alzheimers Dis 2017;4(2):125-13).

sensitivity that were developed for clinical research and its oversight and that we return to a situation of less transparency and more reliance on individual trust. This new paradigm requires new ethical thinking based on empirical research, specifically focused on the research-care intertwinement before we can introduce it in a way that we advance science but still provide adequate protection.

CONCLUSION

With this thesis, I aimed to contribute to the optimal inclusion of children in pediatric clinical research in such a way that we can further clinical research to advance scientific knowledge and develop much-needed treatment options for children while protecting children against harm from research. I combined the main findings of my research into a normative framework for research professionals to include children in pediatric clinical research. This framework tailors the process of recruitment and informed consent to the perspective and the needs of children and their parents, who have the key role in decisions regarding research participation. I focused mainly on the motivations children and their parents have to participate in clinical research. With this approach, research professionals can increase the moral and instrumental value of informed consent in pediatric clinical research: more *informed* consent and probably *more* informed consent.

In this way, we can support children and their parents, such as the mother I quoted at the beginning of this thesis, in finding a balance in that difficult ethical dilemma regarding pediatric clinical research and in making an informed, meaningful and valid decision about participation in pediatric clinical research.

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CHAPTER 10

Summary / samenvatting

SUMMARY

With this thesis, I aim to contribute to the optimal inclusion of children in pediatric clinical research in such a way that we can further clinical research to advance scientific knowledge and develop much-needed treatment options for children while protecting children against harm from research.

Ethicists, researchers and physicians have extensively discussed this precarious balance between advancement and protection in pediatric research. However, how do children and their parents view this balance? Do they also weigh the possible harms against the benefits when they are approached for participation in clinical research? Or do they have other reasons and put other factors into the equation? Because children and their parents are the key decision-makers and children are ultimately the ones participating and undergoing the risk and burden of the research, it seems obvious that their views about this balance are crucial.

Why do children and parents want to participate (or not)? What are their motivations and what is important to them in their decision? What expectations do they have of participation? Answers to these questions are indispensable in order to incorporate their views into the pediatric research enterprise and tailor the process of recruitment and informed consent to their needs and perspectives. When we know why children and parents consent or dissent to research and what elements they use in their decision, we know what they attach importance to in their decision. From this data, we learn which information they want and need to make a valid informed decision. This information helps us to increase both the moral and instrumental value of informed consent in pediatric clinical research; we obtain more *informed* consent and probably *more* informed consent.

Therefore, the **main research aims** of this thesis are as follows:

1. To explore children's and their parents' motivations, views and expectations during recruitment and informed consent processes in pediatric clinical research.
    - What are their motivations to consent/assent to participation in pediatric clinical research? What factors influence their decisions?
    - What are their views on recruitment and informed consent?
    - What are their expectations of research?

2. To analyze these motivations, views and expectations and the factors that shape them from an ethical and legal perspective.

3. To develop a normative framework to support research professionals in the ethically sound inclusion of children in pediatric clinical research. This framework tailors the process of recruitment and informed consent to the perspective and the needs of children and their parents, who have the key role in decisions on research participation.

Chapter 2 sketches the European regulatory landscape for pediatric clinical research and shows how specific ethical issues regarding clinical research with children, such as informed consent/assent and risk-benefit thresholds, are incorporated into relevant legislation.

This chapter focusses on three documents: the European Convention on Human Rights and Biomedicine (also called the Oviedo Convention); Directive 2001/20/EC (also called the Clinical Trials Directive); and Regulation (EC) No. 1901/2006 (also called the Pediatric Regulation). In addition, this chapter discusses major ethical concerns in pediatric clinical research, with a focus on the acceptability of research risks and the informed consent process. In a short addendum I explain the new upcoming European Clinical Trials Regulation.

Chapter 3 gives an overview of the ethical challenges that arise when planning and conducting clinical research with a specifically vulnerable group of children, namely, critically ill children in the Pediatric intensive care unit (PICU). This chapter discusses ethical challenges concerning study design, informed consent and risk and burden and proposes several solutions to these ethical challenges.

The informed consent process at a PICU is a challenge due to the stressful environment for parent and child and the frequently occurring need to act acutely. Alternative forms of informed consent have been developed taking into account the unpredictable reality of the acute critical care environment and are discussed in this chapter. Furthermore, as with any research in children, burden and risk should be minimized also in the PICU. This chapter demonstrates recent developments in sample collection and analysis that should be considered in the design of studies in the PICU. Despite the difficulties inherent to clinical research in critically ill children, ethically sound research resulting in relevant and generalizable data is possible. This chapter states how.

Chapter 4 reviews the empirical literature concerning the motivations of children and their parents to consent or dissent to pediatric clinical drug research. This chapter provides a comprehensive overview of the motivating and discouraging factors that

influence children's and their parents' decisions to participate in pediatric clinical drug research reported in the empirical literature.

Relevant empirical studies were identified from searches in 6 databases and subsequently screened and selected for analysis. Results were aggregated and presented by use of qualitative meta-summary. 38 studies fulfilled the selection criteria and were of sufficient quality for inclusion in the qualitative meta-summary. Most frequently mentioned motivating factors for parents were: health benefit for child, altruism, trust in research, and relation to researcher. Most mentioned motivating factors for children were: personal health benefit, altruism and increasing comfort. Fear of risks, distrust in research, logistical aspects and disruption of daily life were mentioned most by parents as discouraging factors. Burden and disruption of daily life, feeling like a 'guinea pig' and fear of risks were most mentioned as discouraging factors by children.

Chapter 5 reports on a qualitative interview study aimed at gaining insight into children's and their parents' motivations, views and expectations during the process of recruitment and informed consent for pediatric clinical research. This interview study presents perspectives from three different hospital settings: children and their parents in pediatric oncology, pediatric pulmonology (subdivision: cystic fibrosis) and the PICU.

I interviewed children and their parents who had been asked to participate in clinical research and had had an informed consent conversation (N=34). Children and their parents attach more importance to burden than to risk when they need to decide about participation in clinical research. The anticipated burden of participating is most frequently mentioned as motivating or discouraging for their decision to participate. However they have a very broad notion of burden. This burden also includes traveling to the hospital and needing time off from work or school (an emphasis on logistical burden). The interviews revealed also that they outsource their concerns about risk and have a great deal of trust in their treating physicians and research professionals. They expect only safe and sound research to be offered to them. Additionally, parents and children often refer to helping other or future children and science as important considerations in their decisions. The design of pediatric clinical research and especially the recruitment and informed consent process can be ameliorated by the findings presented in this chapter. This way, research will be better in line with the preference of children and parents, and children and their parents will be better equipped to make a decision about participation.

Chapter 6 reports on a qualitative focus group study aimed to explore parents' perspectives on decisions to participate in pediatric clinical research. This focus group study was

performed with 16 parents recruited from the general public to add the intuitions and motivations of non-professionalized (non-hospitalized) parents to the body of empirical evidence.

We explored their perspectives on the (hypothetical) decisions to participate in pediatric clinical research. Group discussion revealed that: parents conflate clinical research and clinical care; they do not grasp the trajectory of pediatric drug development; current ethical guidelines are in line with their protective intuitions; and benefit for their child is the most important factor in their decision. The results presented in this chapter teach us that research professionals should be aware of the knowledge gap of parents, the pitfalls of jargon, and unintended false expectations.

Chapter 7 discusses the phenomenon of gatekeeping in the recruitment for pediatric clinical research. Gatekeeping is a practice in which research professionals have implicit inclusion and exclusion criteria that lead to not approaching all eligible research participants.

Our research into participation in pediatric clinical trials identified reasons why professionals engage in gatekeeping; these are e.g. protection of the child and prejudiced beliefs about the choice the child or parent will make. Although gatekeeping might be understandable, we argue it is not desirable because of the negative implications this practice entails (e.g. it denies children a choice, might introduce inclusion bias and introduces unfair distribution of risk and benefit). This chapter calls upon pediatric professionals to be aware of the many negative implications of their reluctance and in principle to refrain from the problematic practice of gatekeeping.

Chapter 8 discusses the different types of trust that children and their parents have in the research enterprise illustrated with empirical results from the interview study presented in chapter 5. This chapter also sketches how this trust influences their decision-making and how it emphasizes the necessity of prior review of a research ethics committee and its filtering task.

We argue in this chapter that patients' trust confirms the rationale and necessity for the current model of research ethics that consists of more than informed consent, as consent can only be asked for after a review process by a research ethics committee. We substantiate this statement with results from the interviews with parents and children about their willingness to participate in research presented in chapter 5.

Chapter 9 concludes this thesis with a general discussion in which I combine the main findings of the preceding chapters into a normative framework for research professionals to include children in an ethically sound manner in pediatric clinical research.

This chapter starts with an overview of the steps in the research enterprise before children can participate in research. Before a research proposal reaches potential participants (and their parents), other ethical decisions related to the research have been made on which the potential research participants and their parents have no influence. Only then potential participants and their parents make a decision about participation. I call those decisions, 'gates' in the research enterprise. Consecutively, I propose a framework that tailors the process of recruitment and informed consent to the perspectives and needs of children and their parents. This framework addresses five elements: 1) who is asked; 2) who asks; 3) focus on motivating and discouraging factors; 4) prevent and correct misconceptions; 5) informed consent as a continuous process. I conclude this chapter with some developments in clinical research that necessitate new research efforts, policy changes and new ethical guidance. I discuss: digital technologies in informed consent, alternative forms of informed consent, combining research protocols, creation of readiness cohorts and the implementation of learning health care systems.

SAMENVATTING

Met dit proefschrift beoog ik bij te dragen aan de optimale inclusie van kinderen in medisch-wetenschappelijk onderzoek; op een zodanige manier dat we adequate wetenschappelijke kennis genereren en de hoognodige behandelingsopties voor kinderen ontwikkelen, terwijl we tegelijkertijd ook kinderen beschermen tegen schade door hun deelname aan onderzoek.

Ethici, onderzoekers en artsen hebben al uitgebreid gediscussieerd over dit precaire evenwicht tussen vooruitgang en bescherming bij medisch-wetenschappelijk onderzoek met kinderen. Maar hoe zien kinderen en hun ouders dit evenwicht? Wegen zij ook de mogelijke nadelen af tegen de voordelen wanneer ze worden benaderd voor deelname aan onderzoek? Of hebben ze andere redenen en spelen andere factoren een rol in hun afweging? Aangezien kinderen en hun ouders een sleutelrol hebben in de beslissing en kinderen uiteindelijk degenen zijn die deelnemen aan onderzoek en het risico en de belasting van het onderzoek ondergaan, zijn hun opvattingen over dit evenwicht cruciaal.

Waarom willen kinderen en ouders meedoen (of niet)? Wat zijn hun motivaties en wat is voor hen belangrijk in de beslissing? Welke verwachtingen hebben ze van deelname? Antwoorden op deze vragen zijn onmisbaar om hun opvattingen mee te nemen in de ontwikkeling van medisch-wetenschappelijk onderzoek met kinderen. Hiermee kunnen we het proces van werving en informed consent aanpassen aan hun behoeften en perspectieven. Als we weten waarom kinderen en hun ouders toestemmen geven voor deelname aan onderzoek en welke elementen zij in hun beslissing gebruiken, weten we wat zij belangrijk vinden en wat zij nodig hebben voor een valide geïnformeerde beslissing. Deze informatie helpt ons om zowel de morele als de instrumentele waarde van informed consent in medisch-wetenschappelijk onderzoek met kinderen te vergroten. Zo komen we tot meer *geïnformëérde* toestemming en waarschijnlijk *méér* geïnformeerde toestemmingen.

De belangrijkste **doelstellingen** voor dit proefschrift zijn dan ook:

1. Het verkennen van de motivaties, opvattingen en verwachtingen van kinderen en hun ouders tijdens de werving en het informed consent proces in medisch-wetenschappelijk onderzoek met kinderen.
    - Wat zijn hun motivaties om toestemming te geven voor deelname? Welke factoren beïnvloeden hun beslissing?
    - Wat zijn hun opvattingen over de werving en het informed consent proces?
    - Wat zijn hun verwachtingen van deelname aan het onderzoek?

2. Het analyseren van deze motivaties, opvattingen en verwachtingen en de factoren die daar invloed op uitoefenen vanuit een ethisch en juridisch perspectief.

3. Een normatief kader ontwikkelen om onderzoeksprofessionals te ondersteunen bij het ethisch verantwoord includeren van kinderen in medisch-wetenschappelijk onderzoek. Dit kader laat zien hoe we het proces van werving en informed consent zo goed mogelijk kunnen laten aansluiten bij het perspectief en de behoeften van kinderen en hun ouders.

Hoofdstuk 2 schetst het Europese landschap van regelgeving voor medisch-wetenschappelijk onderzoek met kinderen en laat zien hoe specifieke ethische kwesties voor onderzoek met kinderen zijn opgenomen in deze regelgeving (zoals informed consent en de aanvaardbaarheid van risico en belasting bij onderzoeksdeelname).

Dit hoofdstuk richt zich op drie documenten: het Europees Verdrag inzake de rechten van de mens en de biogeneeskunde (ook wel het Verdrag van Oviedo genoemd); Richtlijn 2001/20/EC (ook wel de Europese Richtlijn Geneesmiddelenonderzoek genoemd); en Verordening (EG) Nr. 1901/2006 (ook wel de Pediatrische Verordening genoemd). Daarnaast behandelt dit hoofdstuk de belangrijkste ethische aspecten van medisch-wetenschappelijk onderzoek met kinderen, met een focus op de aanvaardbaarheid van onderzoeksrisico's en het informed consent proces. In een kort addendum bij dit hoofdstuk bespreek ik de nieuwe Europese Verordening Geneesmiddelenonderzoek.

Hoofdstuk 3 geeft een overzicht van de ethische uitdagingen die zich voordoen bij het opzetten en uitvoeren van medisch-wetenschappelijk onderzoek met een specifiek kwetsbare groep kinderen, namelijk kritisch zieke kinderen op een pediatrische Intensive Care (kinder-IC). Dit hoofdstuk behandelt ethische uitdagingen met betrekking tot onderzoeksdesign, informed consent en belasting en risico van deelname en suggereert verschillende oplossingen voor deze ethische uitdagingen.

Het informed consent proces op een kinder-IC is een uitdaging door de stressvolle omgeving voor ouder en kind en de vaak voorkomende noodzaak om acuut te handelen. Alternatieve vormen van informed consent zijn mogelijk waarbij rekening wordt gehouden met de onvoorspelbare realiteit van de acute zorgomgeving (bijv. deferred consent). Deze komen in dit hoofdstuk aan de orde. Bovendien moeten, net als bij al het medisch-wetenschappelijk onderzoek, belasting en risico ook bij onderzoek op de kinder-IC geminimaliseerd worden. Dit hoofdstuk beschrijft enkele innovatieve onderzoeksmethoden om dit te doen. Ondanks de moeilijkheden die inherent zijn aan

medisch-wetenschappelijk onderzoek met kritisch zieke kinderen, is ethisch verantwoord onderzoek op de kinder-IC mogelijk. Dit hoofdstuk stelt voor hoe.

Hoofdstuk 4 betreft een systematisch literatuuronderzoek over de motivaties van kinderen en hun ouders om toestemming te geven voor deelname aan pediatrisch geneesmiddelenonderzoek. Dit hoofdstuk biedt een uitgebreid overzicht van de motiverende en ontmoedigende factoren die van invloed zijn op de beslissingen van kinderen en hun ouders.

Relevante artikelen zijn verzameld uit zes databases en vervolgens gescreend en geselecteerd voor beantwoording van de onderzoeksvraag. De resultaten zijn verzameld en gepresenteerd aan de hand van een kwalitatieve metasamenvatting. 38 studies voldeden aan de selectiecriteria en waren van voldoende kwaliteit om te worden opgenomen in de kwalitatieve metasamenvatting. De meest genoemde motiverende factoren voor ouders waren: gezondheidsvoordeel voor het kind, altruïsme, vertrouwen in onderzoek en relatie tot de onderzoeker. De meest genoemde motiverende factoren voor kinderen waren: persoonlijk gezondheidsvoordeel, altruïsme en verbetering van comfort. Angst voor risico's, wantrouwen jegens onderzoek, logistieke aspecten en verstoring van het dagelijks leven werden door ouders het meest genoemd als ontmoedigende factoren. Belasting en verstoring van het dagelijks leven, het gevoel een 'proefkonijn' te zijn en angst voor risico's werden het meest genoemd als ontmoedigende factoren bij kinderen.

Hoofdstuk 5 presenteert de resultaten van een kwalitatieve interviewstudie opgezet om inzicht te krijgen in de motivaties, opvattingen en verwachtingen van kinderen en hun ouders tijdens het proces van werving en informed consent voor medisch-wetenschappelijk onderzoek met kinderen. Deze interviewstudie beschrijft perspectieven vanuit drie verschillende ziekenhuisafdelingen: kinderoncologie, kinderlongziekten (divisie: cystische fibrose) en de kinder-IC.

Ik interviewde kinderen en hun ouders die waren gevraagd om deel te nemen aan medisch-wetenschappelijk met kinderen en een informed consent gesprek hadden gehad (N = 34). De resultaten lieten zien dat kinderen en hun ouders de belasting van het onderzoek meer laten meewegen in hun beslissing over onderzoeksdeelname dan het risico. De verwachte belasting bij deelname wordt het meest genoemd als motiverend of ontmoedigend voor hun beslissing om deel te nemen. Ze hebben echter een zeer breed begrip van belasting. Kinderen en ouders verstaan veel zaken onder belasting, zoals ook het reizen naar het ziekenhuis of vrij moeten nemen van school of werk (veelal de nadruk op logistieke belasting). Uit de interviews bleek ook dat zij hun bezorgdheid over risico's 'uitbesteden' en veel vertrouwen hebben in hun hun behandelend artsen

en onderzoeksprofessionals. Zij gaan ervanuit dat ze alleen onderzoeksprotocollen voorgelegd krijgen die adequaat en veilig zijn. Tenslotte verwijzen ouders en kinderen vaak naar het helpen van andere en/of toekomstige kinderen en een bijdrage aan de wetenschap als belangrijke overwegingen bij hun beslissingen. De opzet van medisch-wetenschappelijk onderzoek met kinderen en in het bijzonder het proces van werving en informed consent is te verbeteren met behulp van de bevindingen in dit hoofdstuk. Op deze manier zullen studies meer in overeenstemming zijn met de wensen van kinderen en ouders, en zullen kinderen en hun ouders beter toegerust zijn om een beslissing te nemen over mogelijke deelname.

Hoofdstuk 6 rapporteert de resultaten van een kwalitatieve studie met focusgroepen, opgezet om de perspectieven van ouders te verkennen, als zij moeten beslissen om hun kind deel te laten nemen aan medisch-wetenschappelijk onderzoek. Deze focusgroep studie werd uitgevoerd met 16 ouders geworven uit de algemene bevolking om de intuïties en motivaties van niet-geprofessionaliseerde ouders toe te voegen aan de empirische literatuur.

We onderzochten hun perspectieven op (hypothetische) beslissingen om hun kind deel te laten nemen aan medisch-wetenschappelijk onderzoek. Uit de focusgroepen bleek dat: ouders onderzoek en zorg door elkaar halen; ze het traject van geneesmiddelenontwikkeling niet begrijpen; de huidige ethische richtlijnen in overeenstemming zijn met hun beschermende intuïties; en voordeel voor hun kind de belangrijkste factor in hun beslissing is. De resultaten die in dit hoofdstuk worden gepresenteerd, laten zien dat onderzoeksprofessionals zich bewust moeten zijn van de kenniskloof van ouders, de valkuilen van jargon en onbedoelde valse verwachtingen.

Hoofdstuk 7 bespreekt het verschijnsel *gatekeeping* bij het werven van deelnemers voor medisch wetenschappelijk onderzoek met kinderen. *Gatekeeping* is een praktijk waarbij onderzoeksprofessionals impliciete inclusie- en exclusiecriteria hanteren die leiden tot het niet benaderen van alle geschikte potentiele deelnemers.

Ons onderzoek naar deelname aan medisch-wetenschappelijk onderzoek met kinderen identificeerde redenen waarom professionals *gatekeeping* toepassen; deze zijn bijvoorbeeld bescherming van het kind en overtuigingen over de keuze die het kind of de ouder zal maken. Hoewel *gatekeeping* misschien begrijpelijk is, roept dit hoofdstuk onderzoeksprofessionals op zich bewust te zijn van de vele negatieve implicaties (bijvoorbeeld het ontnemen van een keuze, introductie van inclusiebias en oneerlijke verdeling van risico en voordeel van onderzoeksdeelname) en in principe af te zien van deze problematische praktijk.

Hoofdstuk 8 bespreekt de verschillende soorten vertrouwen die kinderen en hun ouders hebben in onderzoek, geïllustreerd met empirische resultaten van de interviewstudie gepresenteerd in hoofdstuk 6. Dit hoofdstuk schetst ook hoe dit vertrouwen van invloed is op hun besluitvorming en hoe essentieel de filtertaak en toetsing van protocollen door een medisch-ethische toetsingscommissie is.

We beargumenteren in dit hoofdstuk dat het vertrouwen van patiënten de rationale en de noodzaak bevestigt van het huidige model van onderzoeksethiek. Dat bestaat immers uit meer dan geïnformeerde toestemming: toestemming kan alleen kan worden gevraagd na een beoordelingsproces door een medisch-ethische toetsingscommissie. We onderbouwen deze verklaring met resultaten van de interviews met ouders en kinderen over hun bereidheid om deel te nemen aan onderzoek gepresenteerd in hoofdstuk 5.

Hoofdstuk 9 sluit dit proefschrift af met een algemene discussie waarin ik de belangrijkste bevindingen van de voorgaande hoofdstukken combineer tot een normatief kader voor onderzoeksprofessionals om kinderen op een ethisch verantwoorde manier te includeren in medisch-wetenschappelijk onderzoek. Dit kader laat zien hoe we het proces van werving en informed consent zo goed mogelijk kunnen laten aansluiten bij het perspectief en de behoeften van kinderen en hun ouders.

Het hoofdstuk begint met een overzicht van de stappen in de opzet van onderzoek voordat kinderen aan onderzoek kunnen deelnemen. Voordat een onderzoeksvoorstel potentiële deelnemers (en hun ouders) bereikt, zijn er andere ethische beslissingen in relatie tot het onderzoek genomen waarop de potentiële onderzoeksdeelnemers en hun ouders geen invloed hebben. Daarnaast nemen zij uiteraard ook zelf een beslissing over deelname. Ik noem die beslissingen *gates*. Vervolgens stel ik een normatief kader voor dat de werving en het informed consent proces afstemt op de perspectieven en behoeften van kinderen en hun ouders. Dit kader behandelt vijf aspecten: 1) wie wordt gevraagd; 2) wie vraagt; 3) motiverende en ontmoedigende factoren; 4) misconcepties; 5) informed consent als continu proces. Ik sluit dit hoofdstuk af met enkele ontwikkelingen in medisch-wetenschappelijk onderzoek die vragen om nieuwe onderzoeksinspanningen, beleidswijzigingen en nieuwe ethische richtlijnen. Ik bespreek: digitale technologie in informed consent, alternatieve vormen van informed consent, het combineren van onderzoeksprotocollen, het creëren van *readiness cohorts* en de implementatie van *learning healthcare systems*.

ADDENDUM

IMPLEMENTATION

RESEARCH PROJECTS

This thesis is a result of a research project funded by ZonMw: The Netherlands Organization for Health Research and Development in the program Priority Medicine for Children (grant number: 113203203). Part of this program aimed to generate more knowledge on the ethical and legal aspects of clinical drug research with children.

My research focused on the motivations of children and their parents to participate in clinical research. Five other research projects in the Netherlands were funded in this program with different focus points in pediatric clinical research which resulted in several PhD-theses:

- Research by Wendy Bos focused on risk-benefit assessments of RECs and dissent/resistance of children in pediatric clinical research.[1]
- Research by Sara Dekking focused on dependency and the research-care distinction in pediatric clinical research in oncology.[2]
- Research by Irma Hein focused on children's competence to consent to pediatric clinical research.[3]
- Research by Ronella Grootens-Wiegers focused on development of information material for children in pediatric clinical research.[4]
- Research by Mira Staphorst focused on children's experiences of burden in pediatric clinical research.[5]

IMPLEMENTATION OF RESULTS

Relevant results from our distinct research projects were implemented in (upcoming) guidelines for clinical research with children. Results from systematic reviews we performed in the research projects were implemented in the 'Guideline Criteria Research with Children' of the Dutch Association of Pediatrics. The results published in chapter 5 of this thesis are implemented in this upcoming guideline. Results from the above mentioned research projects were also implemented in the revision of the 'Ethical considerations for clinical trials on medicinal products conducted with minors' of the European Commission. The main objective of this revision was to align the document with the upcoming Clinical Trials Regulation (EU) No 536/2014 and with the latest insights on research with children. I was a member of the working group lead by the Dutch Ministry of Health, Welfare and Sports who drafted this revision. Specific results from my research project were implemented in that revision (e.g. results relating to motivations, burden and trust in research).

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3. Hein IM. Children's competence to consent to medical treatment or research [Ph.D. thesis]. University of Amsterdam, 2015.
4. Grootens-Wiegers P. Targeted informed consent: Empowering young participants in medical-scientific research [Ph.D. thesis]. Leiden University, 2016.
5. Staphorst M. Hearing the voices of the children: The views of children participating in clinical research [Ph.D. thesis]. Erasmus University Rotterdam, 2017.

APPENDIX 1

SEARCH STRINGS PER DATABASE – CHAPTER 4

Database
Embase
('refusal to participate'/de OR 'patient participation'/de OR 'parental consent'/de OR (((refus* OR decision* OR decid* OR allow* OR reason* OR motivat* OR willing* OR assent* OR consen* OR dissent* OR attitude* OR view* OR perspective* OR choos* OR choice*) NEAR/6 (participat* OR nonparticipat* OR enrol*))):ab,ti OR ((conflict/de OR 'motivation'/de OR drive/de OR 'informed consent'/de) AND (participat* OR nonparticipat* OR enrol*):ab,ti)) AND ('clinical trial (topic)'/exp OR 'pharmacological science'/exp OR 'clinical research'/de OR ((RCT* OR trial* OR scien* OR research*) NEAR/11 (participat* OR enrol*)):ab,ti OR (('science in general'/de OR research/de OR 'medical research'/de OR 'human experiment'/de) AND (pharmacology/exp OR 'drug therapy'/exp OR (drug* OR pharmaco* OR medication* OR psychopharmacolog*):ab,ti))) AND (child/exp OR newborn/exp OR adolescent/exp OR adolescence/exp OR 'child behavior'/de OR 'child parent relation'/de OR (adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 ag*) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*):ab,ti)
Medline
("refusal to participate"/ OR "patient participation"/ OR "parental consent"/ OR (((refus* OR decision* OR decid* OR allow* OR reason* OR motivat* OR willing* OR assent* OR consen* OR dissent* OR attitude* OR view* OR perspective* OR choos* OR choice*) ADJ6 (participat* OR nonparticipat* OR enrol*))).ab,ti. OR (("Conflict (Psychology)"/ OR "motivation"/ OR "drive"/ OR "Intention"/ OR exp "informed consent"/) AND (participat* OR nonparticipat* OR enrol*).ab,ti.)) AND (exp "clinical Trials as Topic "/ OR "Biomedical Research"/ OR ((RCT* OR trial* OR scien* OR research*) ADJ11 (participat* OR enrol*)).ab,ti. OR (("Science"/ OR research/ OR exp "Human Experimentation"/) AND (exp pharmacology/ OR pharmacology.xs. OR exp "drug therapy"/ OR drug therapy.xs. OR (drug* OR pharmaco* OR medication* OR psychopharmacolog*).ab,ti.))) AND (exp child/ OR exp infant/ OR adolescent/ OR exp "child behavior"/ OR exp "Parent-Child Relations"/ OR (adolescen* OR infan* OR newborn* OR (new ADJ born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under ADJ ag*) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*).ab,ti.)
Web-of-Science
TS=(((((refus* OR decision* OR decid* OR allow* OR reason* OR motivat* OR willing* OR assent* OR consen* OR dissent* OR attitude* OR view* OR perspective* OR choos* OR choice*) NEAR/6 (participat* OR nonparticipat* OR enrol*)))) AND (((RCT* OR trial* OR scien* OR research*) NEAR/11 (participat* OR enrol*))) AND ((adolescen* OR infan* OR newborn* OR new born* OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR under age* OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*)))
Pubmed
(refus*[tiab] OR decision*[tiab] OR decid*[tiab] OR allow*[tiab] OR reason*[tiab] OR motivat*[tiab] OR willing*[tiab] OR assent*[tiab] OR consen*[tiab] OR dissent*[tiab] OR attitude*[tiab] OR view*[tiab] OR perspective*[tiab] OR choos*[tiab] OR choice*[tiab]) AND (participat*[tiab] OR nonparticipat*[tiab] OR enrol*[tiab]) AND (scien*[tiab] OR research*[tiab]) AND (adolescen*[tiab] OR infan*[tiab] OR newborn*[tiab] OR new born*[tiab] OR baby[tiab] OR babies[tiab] OR neonat*[tiab] OR child*[tiab] OR kid[tiab] OR kids[tiab] OR toddler*[tiab] OR teen*[tiab] OR boy*[tiab] OR girl*[tiab] OR minors[tiab] OR underag*[tiab] OR under age*[tiab] OR juvenil*[tiab] OR youth*[tiab] OR kindergar*[tiab] OR puber*[tiab] OR pubescen*[tiab] OR prepubescen*[tiab] OR prepubert*[tiab] OR pediatric*[tiab] OR paediatric*[tiab] OR school*[tiab] OR preschool*[tiab] OR highschool*[tiab]) AND publisher[sb]

Psycinfo
("Participation"/ OR "client participation"/ OR (((refus* OR decision* OR decid* OR allow* OR reason* OR motivat* OR willing* OR assent* OR consen* OR dissent* OR attitude* OR view* OR perspective* OR choos* OR choice*) ADJ6 (participat* OR nonparticipat* OR enrol*))).ab,ti. OR ((exp "Conflict"/ OR exp "motivation"/ OR "Intention"/ OR exp "informed consent"/) AND (participat* OR nonparticipat* OR enrol*).ab,ti.)) AND ("clinical Trials"/ OR ((RCT* OR trial* OR scien* OR research*) ADJ11 (participat* OR enrol*)).ab,ti. OR (("Sciences"/ OR Experimentation/ OR) AND (exp pharmacology/ OR exp "drug therapy"/ OR (drug* OR pharmaco* OR medication* OR psychopharmacolog*).ab,ti.))) AND (100.ag. OR 200.ag. OR "Child Psychology"/ OR exp "Parent-Child Relations"/ OR (adolescen* OR infan* OR newborn* OR new ADJ born* OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR under ADJ ag* OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*).ab,ti.)
CINAHL
(MH "refusal to participate"+ OR MH "Consumer Participation"+ OR (((refus* OR decision* OR decid* OR allow* OR reason* OR motivat* OR willing* OR assent* OR consen* OR dissent* OR attitude* OR view* OR perspective* OR choos* OR choice*) N6 (participat* OR nonparticipat* OR enrol*))) OR ((MH "Conflict (Psychology)"+ OR MH "motivation" OR MH "drive" OR MH "Intention" OR MH "consent"+) AND (participat* OR nonparticipat* OR enrol*))) AND (MH "clinical Trials"+ OR ((RCT* OR trial* OR scien* OR research*) N11 (participat* OR enrol*)) OR ((MH "Science" OR MH research) AND (MH "Pharmacy and Pharmacology"+ OR MH "drug therapy"+ OR (drug* OR pharmaco* OR medication* OR psychopharmacolog*)))) AND (MH child+ OR MH "child behavior"+ OR (adolescen* OR infan* OR newborn* OR (new N1 born) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under N1 age) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*))

APPENDIX 2

DATA EXTRACTION FORM – CHAPTER 4

Study Number		
Author and year		
Type of study	□ Qualitative study: … □ Quantitative study: …	
Setting (description)		
- Moment of questioning related to decision and participation		
- Real life / hypothetical research / research in general		
- Therapeutic / non therapeutic		
- Parents and /or children		
- Separate analysis of parents and children?		
- Consenters / non-consenters		
Study for which participation is asked		
Study population		
- Number of participants		
- Inclusion criteria		
- Exclusion criteria		
- Participant characteristics		
Objective/ hypothesis		
Methods		
Motivating factors	Parents:…	Children:…
Discouraging factors	Parents:…	Children:…
Other outcome measures		
Possible confounders		
Critical appraisal (including risk of bias)*		
Level of evidence**	Quantitative study: □ A □ B □ C □ D	Qualitative study □ + + □ + □ + / - □ -

* With use of the Critical Appraisal Skills Program (CASP) checklists; ** Levels according those set by the Dutch Institute for Healthcare Improvement (CBO)

APPENDIX 3

EVIDENCE TABLES – CHAPTER 4

Author, year	
Barakat, 2013	
Study population: 103 children and 76 AYA's with Asthma or SCD and their 224 caregivers with and without prior research experience. Inclusion criteria: ability to speak and read English. Exclusion criteria: not mentioned. Characteristics: consenting and non-consenting children (8-18 years) and parents. Design: quantitative study; written questionnaires during regularly scheduled follow-up visits in clinic about research in general (including drug trials). Exploratory factor analysis to identify latent structures.	Motivating factors: patient benefit, trust in safety of research, the opportunity costs to engaging in research (parents). Discouraging factors: mistrust of research and researchers (parents). Other outcomes: proportionality, prior research exposure. Confounding: not mentioned. Level of evidence: B Critical appraisal: large sample size, adapted questionnaire for children. No open ended questions, only opinion (yes/no) asked about statements. No descriptive results of questionnaire published, only the factors in the model.
Barrera, 2005	
Study population: 227 parents of children being seen for minor traumatic injuries in 3 pediatric emergency departments. Inclusion criteria: not mentioned. Exclusion criteria: parents whose children were aged 16 years or older, sustained injuries raising suspicion of abuse, required IC admission or operative intervention. Characteristics: consenting and non-consenting parents (mean age: 34 years). Design: quantitative study; verbal questionnaires about participation in hypothetical clinical drug trial (RCT with Phenytoin).	Motivating factors: benefit to child (85%); benefit to other children (72%); further medical knowledge (60%). Discouraging factors: fear of adverse effects (54%); don't want child to be a research subject (39%); need to discuss with family first (27%); can't decide unless in actual situation (26%); fear of less than optimal treatment(10%); opposition to medical research (9%); do not understand study (9%); religious beliefs 3 (4%); do not have time to participate 2 (3%); financial concerns (3%); language barrier (3%); prior bad experience with research (1%); prior bad experience with medical profession (1%); other (21%). Other outcomes: ethnicity and household income associated with consent decision. Confounding: hypothetical protocols. Level of evidence: B Critical appraisal: large population size; good thing that questioning of reasons was not predefined. hypothetical study, and critical ill children were excluded, therefore maybe not applicable to real situation.
Berg, 2010	
Study population: 53 subjects who participate in a phase 1 anticancer drug study. Inclusion criteria: consent or dissent to PK sampling. Exclusion criteria: not mentioned. Characteristics: 8 adult subjects, 4 adolescents and 38 parents/legally authorized representatives; consenting and non-consenting. Design: quantitative study; written questionnaire administered within 4 weeks after consent to phase 1 drug study about (non)consenting to extra PK sampling within study.	Motivating factors: 97% defined altruistic reasons as very or extremely important; 83% ranked "no extra pain or harm to child" as very or extremely important. Discouraging factors: Large percentage defined time and need for an extra IV as important concern. Other outcomes: additional comments by subjects. Confounding: no attempt to control for demographic factors. Level of evidence: C Critical appraisal: bad quality; no distinction between children, parents and adult participants; content of questionnaire not clear.

Brody, 2005	
Study population: 36 adolescent-parent dyads (predominantly mothers) of which children had a prior diagnosis of asthma. Inclusion criteria: child with prior diagnosis of asthma. Exclusion criteria: not mentioned. Characteristics: 2 guardians, 34 parents (30-60 years) and 36 adolescents (11-17 years); consenters and non-consenters. Design: quantitative study; separate interviews about willingness to participate after presentation of 9 hypothetical asthma research protocols.	Motivating factors: parents: perception of research benefit (45%), Children: perception of research benefit (40%), financial compensation (10%). Discouraging factors: parents: concern over hassle (25%), risk (25%), discomfort (3%); children: concern over hassle (35%), risk (10%), discomfort (7%). Other outcomes: 60% of the time parents and adolescents held concordant views on participation decisions. Confounding: parents and children were interviewed separately, this differs from actual process; order of protocols was systematically varied but could have an influence on decision. Level of evidence: C Critical appraisal: positive and negative responses of willingness to participate are grouped together.
Brody, 2012	
Study population: 111 adolescents with asthma and their 111 parents. Inclusion criteria: prior diagnosis of asthma, English speaking, child between 11 and 17 years of age. Exclusion criteria: not mentioned. Characteristics: mean age adolescents 13.6 (range:10-17); parents mean age 41.9 years, 93% at least high school diploma; consenters and non-consenters. Design: quantitative study; development of conceptual model of research participation decisions is developed. adolescents and parents are interviewed about hypothetical asthma research protocol (informed by video).	Motivating factors: benefit and financial compensation are factors in model for adolescents and parents. Discouraging factors: perceived risks is factor in model for adolescents and parents. Other outcomes: 67% of parents and adolescents agreed on the participation decision. Confounding: demographic variables, level of comprehension. Level of evidence: C Critical appraisal: small sample size to build a model on with that many variables; single hypothetical protocol.
Broome, 2003	
Study population: 34 children and adolescents with DM or hematological malignancies requiring treatment who are/were previous enrolled in research. Inclusion criteria: consent from parent, > 7 years of age, diagnosed with a health condition requiring treatment, enrolled in a research study within the last 2 months, speaks English, at least one English-speaking parent who is also willing to be interviewed. Exclusion criteria: not mentioned. Characteristics: age range: 8-22 years; 23 with hematologic malignancy, 10 with DM; only consenters. Design: qualitative study; tape-recorded semi structured interviews at home or in hospital about various drug studies.	Motivating factors: the monetary incentive that was offered (DM patients). Discouraging factors: time involved and number of needle sticks (DM patients). Other outcomes: influence/relationship with parents. Confounding: not mentioned. Level of evidence: - Critical appraisal: bad quality, only results from DM patients presented, limited information from interviews, article does not answer their research question.

Buscariollo, 2012	
Study population: 166 parents of children with DM1. Inclusion criteria: not mentioned. Exclusion criteria: not mentioned. Characteristics: 81% female, 90% Caucasian; consenters and non-consenters; Design: quantitative study; 48-item written questionnaire including open-ended, yes/no and 5-point responses to assess parental attitudes towards DM1 clinical trials and willingness to participate (research in general and hypothetical trials).	Motivating factors: potential benefit for their own child (92%), potential benefit for other children in the future (87%), opportunity to contribute to science (43%), influences of family and friends (31%), financial compensation (32%), increased physician access at no additional cost (47%). Discouraging factors: risk of side effects associated with trial participation (57%), discomfort with consent by proxy or making decisions about trial participation for their children (27%), fear of having to pay for research treatment (30%), lack or cost of transportation (30%), child's fear of receiving injections (19%). Other outcomes: prediction factors for WTP; comfort scores with different types of trials. Confounding: possible non-response bias effects. Level of evidence: B Critical appraisal: extensive description of results, but very low response rate.
Cain, 2005	
Study population: 36 children who had participated in a trial comparing insulin detemir with NPH in a multi-injection therapy for type 1 diabetes. Inclusion criteria: from UK and Ireland; age between 6-17 years. Exclusion criteria: not mentioned. Characteristics: consenting children; 6-11 years: 17%; 12-14 years: 58%; 15-17 years: 25%. Design: quantitative study; non-validated, 23-item postal questionnaire, child friendly written with graded scales, numerical scales and free text responses to examine attitudes and experiences to drug trial participation.	Motivating factors: "I wanted to improve my blood sugar control": 30%; "I thought it would be interesting": 21%; "I wanted to help other people with diabetes": 19%; "My mum/dad thought it would be a good idea": 9%; "I wanted to know more about my diabetes": 6%; "My friend was doing it": 2%; "I wanted to use the pen": 4%; "I wanted to be helpful in any way I could": 2%; "I wanted more flexibility with my insulin/diabetes": 6%. Discouraging factors: not mentioned. Other outcomes: 81% would take part in a future trial; experiences during participation, information provided. Confounding: trial participants are a self-selecting group and sample used in this study is small; therefore, may not be representative of the general pediatric population Level of evidence: C Critical appraisal: child friendly questionnaire used, only consenters questioned, high response rate; non-validated questionnaire.
Caldwell, 2003	
Study population: 33 parents with sick children from children's hospital and with healthy children from local primary school. Inclusion criteria: not mentioned. Exclusion criteria: not mentioned. Characteristics: healthy children: 27%, acute illness: 18%, chronic illness: 15%, cancer: 18%, RCT participants: 21%; 73% with previous research experience. Design: qualitative study; 4 focus groups and 5 individual interviews to explore attitudes towards child's participation in RCTs; data coded using constant comparative methods and further examined to identify emergent overarching themes.	Motivating factors: perceived benefits, doctor factors, child factors. Discouraging factors: perceived risks, trial factors, parental factors. Other outcomes: proportionality. Confounding: not mentioned. Level of evidence: + Critical appraisal: comprehensive description of results; paid attention to different backgrounds and settings; no distinction between focus groups and individual interviews and no distinction based on previous research experience.

Cartwright, 2011	
Study population: 16 parents of 12 infants born with complications who had participated in an RCT (immunotherapy, ventilation, hypothermia). Inclusion criteria: parents read and speak English fluently; parents' infants had participated in a RCT in the previous 18 months while receiving intensive care in the NICU. Exclusion criteria: not mentioned. Characteristics: 10 mothers (27-36 years), 6 fathers (27-36 years); all white Europeans, all consenters. Design: qualitative study; semi-structured face-to-face interviews after trial participation; open-ended and closed questions.	Motivating factors: themes from interviews. Discouraging factors: not mentioned. Other outcomes: immediate reactions, interaction with clinician, implications of RCT, effect of RCT. Confounding: parental responses may have been affected by time lag between participation and interview. Level of evidence: + Critical appraisal: small sample size, elaborate results from interviews, no discouraging factors mentioned.
Cherill, 2010	
Study population: 98 healthy children at secondary school and 117 children with a chronic illness at outpatient clinic or hospital. Inclusion criteria: child and parent in agreement to participate. Exclusion criteria: not mentioned. Characteristics: healthy children: median age 13 (11-16) years. Chronic ill children: median age: 14 (11-16) years. Design: quantitative study; written questionnaire about viewpoints of research in general (including drug trial) including closed questions and 3 hypothetical scenarios.	Motivating factors: Helping others was the most common reason given for taking part in clinical trials. Altruistic nature of children in both groups was similar. Discouraging factors: not mentioned. Other outcomes: Alarming: 57-63% of children would participate in a cancer drug trials as a healthy volunteer. Confounding: not mentioned. Level of evidence: B Critical appraisal: bad quality, only small part of results published; abstract and discussion mention altruistic motives, but not results not presented.
Deatrick, 2002	
Study population: 21 parents of children participating in phase 1 oncology trial. Inclusion criteria: not mentioned. Exclusion criteria: not mentioned. Characteristics: 19 mothers, 2 fathers; children: 2-18 years. Only consenters. Design: qualitative study; descriptive cross-sectional study with secondary analysis techniques to analyze existing qualitative data from two studies of parents' decision-making at end of life for their children with cancer.	Motivating factors: prolong life for their child / delaying death; buying time for another therapy; providing treatment; working a miracle; desire to help other children with cancer in the future; practical concerns (including location and proximity of available treatment, ability to secure treatment in the near future and issues related to quality of life), child's physical condition (good shape). Discouraging factors: child's physical condition (weak). Other outcomes: all parents saw limited choices or no choices in the decisions about whether to enter their child in a phase 1 clinical trial. Confounding: not mentioned. Level of evidence: + Critical appraisal: article only mentions some aspects of parents' views; no systematic representation; but a lot of examples from interviews.

Harth, 1990	
Study population: 68 parents who had volunteered their child for a randomized, double, blind, placebo-controlled trial of ketotifen (new drug for asthma) and 42 parents who had refused this participation. Inclusion criteria: not mentioned. Exclusion criteria: not mentioned. Characteristics: majority Caucasian, majority between (20-29 years of age). Design: quantitative study; verbal questionnaire consisting of 48 structured and 2 open ended sections to assess perceptions, attitudes, and health seeking behavior of the parents.	Motivating factors: to benefit my own child: N=61; dissatisfaction with current treatment: N=56; to learn more about medical treatment: N=51; liked the people conducting the trial: N=49; to meet people: N=45; trust in the hospital: N=33; to gain better access to health care: N=26; advice of family doctor: N=10; advice of others: N=8; reimbursement of travel cost: N=8. Discouraging factors: fear of side effects of the new drug: N=40; inconvenience of frequent visits: N=35; dislike of becoming involved: N=33; lack of time: N=23; distrust of modern medicine: N=22; loss of privacy: N=14; Not interested: N=10; distrust of the hospital: N=8; extra cost entailed: N=5. Other outcomes: difference between consenters and non-consenters: socio-demographic characteristics, health seeking behavior, availability of social support. Confounding: no selection bias in recruitment. Level of evidence: B Critical appraisal: moment of questionnaire in relation to decision not clear. Large response rate, no response bias expected.
Hoberman, 2013	
Study population: 120 parents who were asked to provide consent for their child's participation in a randomized controlled trial of antimicrobial prophylaxis for vesicoureteral reflux. Inclusion criteria: not mentioned. Exclusion criteria: not mentioned. Characteristics: 48 consenters, median age: 31 years; 62 non-consenters, median age 33 years; majority Caucasian. Design: quantitative study; written questionnaire consisting of Likert scales and VAS. Examining difference between consenters and non-consenters in 7 constructs governing the decision to provide consent.	Motivating factors: significant differences between consenters and non-consenters: trust in research; perceiving researcher as friendly/professional; benefit to their child; benefit to others (altruism); importance of study. Discouraging factors: significant differences between consenters and non-consenters: interference of study with standard of care; feelings of anxiety and decisional uncertainty. Other outcomes: child-, parent- and study characteristics, parental perception of the study, parental understanding of study design, external influences, decision-making process. Confounding: overrepresentation of higher levels of education in non-consenters; less than 50% response rate (no difference between consenters/non-consenters. Level of evidence: B Critical appraisal: good quality. Questionnaire based on previous research. But very low response rate and no in and exclusion criteria mentioned.
Hoehn, 2005	
Study population: 34 parents of 24 neonates having cardiothoracic surgery invited to participate in a study evaluating the impact of prenatal diagnosis on parental permission for neonatal cardiac surgery. Inclusion criteria: not mentioned. Exclusion criteria: not mentioned. Characteristics: 14 fathers, 20 mothers; majority Caucasian. Design: qualitative study; Qualitative analysis of the unsolicited comments (spontaneously mentioned) of parents regarding reasons for agreeing or declining to participate in research studies.	Motivating factors: societal benefit (N=18/53%) (pro-reason); individual benefit to their infant (N=16/47%) (pro-reason); perception of no risk of harm (N=9/26%) (neutral reason). Discouraging factors: risk of study participation (N=10/29%) (con-reason); Anti-experimentation (feeling like a guinea pig) (N=4/12%) (con-reason). Other outcomes: comparison of reasons for consenters and non-consenters. Confounding: not mentioned. Level of evidence: + Critical appraisal: strong point: spontaneous comments, no predefined reasons. No linking of reasons to specific studies. Very little recall bias.

Koelch, 2009	
Study population: 19 child-parent dyads enrolled in an RCT with investigational drug or an open-label trial with licensed drug (psychopharmacology) Inclusion criteria: not mentioned. Exclusion criteria: not mentioned. Characteristics: children's mean age: 11 years, range: 7-15 years; all boys; 15 consenters, 3 non-consenters, 1 undecided. Design: qualitative study; interviews by use of MacArthur Competence Assessment Tool for Clinical Research; analyzed with qualitative content analysis.	Motivating factors: hopes for improvement of their own behavior based on experience (with benefit for themselves and/or for their families); Comfort (new medication easier to handle); explorative behavior/sensation seeking (the chance to test something new). Discouraging factors: changes in treatment settings; Time spent; Burden of study examinations (blood-drawings); feeling like a guinea pig. Other outcomes: proportionality, understanding, appreciation. Confounding: IQ and experience influences reasoning. Level of evidence: + Critical appraisal: comprehensive elaboration of interview results. Children and parents interviewed, but results of reasoning of parents not described, only reasons of children.
Lebensburger, 2013	
Study population: 14 parents or guardians of children (with SCD) with no prior experience with clinical trials or hydroxyurea therapy Inclusion criteria: not mentioned Exclusion criteria: not mentioned Characteristics: 3 males, 11 females; average age: 42 years (31-56); all African-American. Design: qualitative study; 3 focus groups addressing 7 main questions and a mock recruitment pamphlet for a hypothetical feasibility trial of hydroxyurea for prevention of secondary silent cerebral infarcts.	Motivating factors: improvement child's life, discuss trial with other participants, increased clinic visits Discouraging factors: General mistrust of research studies, emotional issues (burden for child), practical issues (time required, missing work etc.), randomization, long term unknown risks, Other outcomes: - Confounding: possibly response bias. Level of evidence: + Critical appraisal: Weak point: no in- and exclusion criteria and little info on patient characteristics. Strong point: accurate and visible coding of themes.
Liaschenko, 2001	
Study population: 12 fathers of children diagnosed with cancer and involved in a clinical cancer research study at a children's hospital. Inclusion criteria: fathers with a child who: was diagnosed with cancer, had participated in clinical research within last year, was at least 8 years of age, had at least one parent who was legally authorized to give informed consent. Exclusion criteria: not mentioned. Characteristics: majority Caucasian, children's mean age: 13.5 years. All consenters. Design: qualitative study; focused interviews in private setting to explore meanings of research and reasons for participation.	Motivating factors: altruism; no other option available; Possibility of and hope for direct improvement without significantly increasing the risk of more harm; Maximize the child's chance of survival. Discouraging factors: not mentioned. Other outcomes: description of life context, description of meanings of research Confounding: reasons for participation interact with meanings of participation and type of research. Level of evidence: + Critical appraisal: well defined methodology; Only brief description of results from interviews, very aggregated.

MacNeill, 2013	
Study population: 42 parents of children participating in a randomized double-blind placebo-controlled trial of Montelukast for preschool wheeze Inclusion criteria: not mentioned. Exclusion criteria: not mentioned. Characteristics: 10 males, 32 females; mean age: 36 years; 20 Bangladeshi, 10 white UK, 12 other. Design: qualitative study; semi-structured interviews to compare the motives and experiences of different ethnic groups.	Motivating factors: Benefit to child (21/42). Benefit to others (15/42); trust in the research team (3/42); Route to additional information, treatment and attention. Discouraging factors: No benefit, adverse effects, randomization to placebo. Other outcomes: experience of consent process; understanding research process, consulting others. Difference between ethnic groups. Confounding: No non-consenters and Bangladeshi parents underrepresented. Level of evidence: + Critical appraisal: Good quality; transparent: coding example in article. Elaborate description of results.
Masiye, 2008	
Study population: 81 female guardians of children participating in the Intermittent Prevention Therapy post-discharge (IPTpd) Malaria Research Inclusion criteria: not mentioned. Exclusion criteria: not mentioned. Characteristics: 39 from rural area, 42 urban area; mean age rural: 29 years, mean age urban: 28 years; education rural: 6 years, education urban: 9 years; All consenters. Design: qualitative study; 8 focus groups to assess the reasons why mothers enroll their children in malaria clinical research and how family members or relatives are involved in the decision-making process.	Motivating factors: majority wanted their children to receive better treatment, participants wanted to benefit from the material and monetary incentives that were given, sense of trust in the health workers, attention by health care workers Discouraging factors: Not mentioned Other outcomes: perspective on the informed consent process and role of partner in decision-making process. Confounding: not mentioned Level of evidence: + Critical appraisal: sufficient quality; Weak point: no in- and exclusion criteria mentioned. Strong point: inclusion of themes and quotations of participants.
Menon, 2012	
Study population: 54 non-consenting legal guardians who were approached for consent for any ongoing PICU research. Inclusion criteria: not mentioned. Exclusion criteria: surveys and chart audits. Characteristics: 54 non-consenters; Children's age: 0.6 years. Design: Quantitative study; prospective, observational study with recording of demographic data and unsolicited reasons stated by legal guardians for consent refusal.	Motivating factors: not mentioned. Discouraging factors: Guardian too stressed: N=24; Blood taking required for study: N=13; Medication administration required for study: N=3; Radiation required for study: N=2; Guardian does not agree with research: N=8; Already in another study: N=6 Discord between guardians: N=2; Child has been through enough: N=7 Other: N=28. Other outcomes: description of patient and study demographics. Confounding: not mentioned. Level of evidence: B Critical appraisal: Positive: unsolicited reasons, no suggestions. Only reasons for refusal stated by non-consenters.

Miller, 2013	
Study population: 20 adolescents with cancer who were offered participation in a phase 1 trial. Inclusion criteria: permission from parent and adolescent. Exclusion criteria: not mentioned. Characteristics: median age: 17.8 years; 7 participants: 14-17 years, 13 participants: 18-21 years; majority male and Caucasian; all consenters. Design: Quantitative study; verbal questionnaire with closed and open-ended questions to examine adolescents perspectives.	Motivating factors: Positive clinical effect: N=15 (75%); No other options: N=9 (45%); Positive impact on quality of life: N=8 (40%); Few or fewer side effects: N=8 (40%); Logistics related to participation (e.g., "It's easy to do."): N=6 (30%); Previous testing/ availability of trial drug: N=5 (25%); To help science and other children: N=4 (20%); Doctor's recommendation: N=3 (15%); Other: N=5 (25%). Discouraging factors: not mentioned. Other outcomes: Experience of process, expectations. Confounding: perceptions are likely not biased by trial participation or change in health status (due to little time between consent and interview). Level of evidence: C Critical appraisal: elaborate interpretation of results. Positive that reasons were not predefined, but an open question.
Norris, 2010	
Study population: 20 adolescents and their parents refused to participate in an RCT involving olanzapine for the adjunctive treatment of anorexia nervosa. Inclusion criteria: not mentioned. Exclusion criteria: not mentioned. Characteristics: all female, median age 15.4 years; all non-consenters. Design: Quantitative study; secondary descriptive analysis of reasons provided by patients and their parents for refusal of study participation. already available data.	Motivating factors: not applicable Discouraging factors: Adolescents: Not interested in taking any psychotropic medication / fears associated with effects of medication (i.e. weight gain): N=7; Refused randomization N=2; Fears associated with participation in research trial N=2. Parents: Not interested in or wanting child on any psychotropic medication / fears associated with side effects of medication (i.e. potential for diabetes) N=7; Refused randomization N=2. Other outcomes: 55% (n=11) of refusals were patient (adolescent) driven. Confounding: not mentioned. Level of evidence: C Critical appraisal: Bad quality; little information, too broad description of reasons, small sample size, very specific population, with specific reasons for refusal (probably related to effect of trial (weight gain), not generalizable.
Oppenheim, 2005	
Study population: mother who accepted her daughter to be included in a phase 1-2 oncology trial. Inclusion criteria: not applicable. Exclusion criteria: not applicable. Characteristics: mother of a child 7 years old treated since age of 2 for malignant germinal tumor, consented to trial. Design: Qualitative study; secondary analysis of an interview of a mother with a psycho-oncologist to discuss relational, psychological and ethical issues of phase 1-2 trials.	Motivating factors: motivating themes identified in interview. Discouraging factors: discouraging themes identified in interview. Other outcomes: other themes. Confounding: not mentioned. Level of evidence: + Critical appraisal: Only 1 subject, but elaborate analysis of interview.

Peden, 2000	
Study population: 23 caregivers of patients with SCD, 16 pediatric patients with SCD and (13 AYA's with SCD) Inclusion criteria: fluent in English Exclusion criteria: not mentioned Characteristics: 21 male/2 female caregivers, median age: 42.1 years; 8 female/8 male children, median age: 12.6 years; majority African American. Consenters and non-consenters. Design: Qualitative study; semi-structured interviews asking about previous research experience and reasons to enroll and assessment of 2 vignettes (placebo-controlled drug trial and psychosocial study).	Motivating factors: parents consenting to drug vignette: potential benefit (42.9%), altruism (43.5%), trust (13.3%), manageable study demands; children consenting to drug vignette: potential benefit (37.5%), altruism (37.5%), manageable study demands. Discouraging factors: parents dissenting to drug vignette: potential harm (71.9%), unmanageable study demands (28.1%); children dissenting to drug vignette: potential harm (55.6%), unmanageable study demands (44.4%). Other outcomes: reasons for previous participation, ranking of statements. Weighing of proportionality. Confounding: sampling bias. Results from hypothetical studies might not correlate with actual decision. Level of evidence: + Critical appraisal: Sufficient quality; no actual responses of participants visible, only coding groups. But elaborate results presented.
Pletch, 2001	
Study population: 33 mothers of children diagnosed with cancer or DM1 and involved in clinical research studies (including drug trials). Inclusion criteria: not mentioned. Exclusion criteria: not mentioned. Characteristics: 24 mothers of child with cancer (child's mean age: 12.5 years), 9 mothers of child with DM1 (child's mean age: 10.6 years); all consenters. Design: Qualitative study; Semi-structured interviews with mothers. Narrative analysis techniques used to identify patterns in experiences.	Motivating factors: Cancer group: to save the life of their child, benefit they were looking was life over death; DM1: consider personal benefits that might accrue for their child, as well as societal benefits, contribution to improved knowledge about diabetes care for other children. Discouraging factors: DM1: some mothers thought that diabetes was all the burden a child should be asked to bear, inconveniences. Other outcomes: other themes related to experiences, proportionality. Confounding: not mentioned. Level of evidence: + Critical appraisal: Positive: open questions about reasons, not predefined. Elaborate comparison between the two groups; No info about in- and exclusion criteria. Number of participants not consistent in article.
Pletch, 2001 (2)	
Study population: 9 mothers of children with DM1 and involved in clinical research (2 drug trials) at children's hospital. Inclusion criteria: child at least 9 years of age and prior experience with participating in a clinical trial. Exclusion criteria: not mentioned. Characteristics: Mean age mothers: 42 years, all European and high school graduates; mean age children: 10.6 years (range: 9-13 years). Design: Qualitative study; semi-structured interviews with mothers to identify patterns influencing consent to clinical research.	Motivating factors: Continued well-being of their child; must be some direct and immediate advantage for their child (personal benefit); opportunities. Discouraging factors: Risks. Other outcomes: 3 steps in decision-making; interaction parent/child. Confounding: sample cannot be taken as representative of the general population of mothers of chronically ill children nor all mothers of children with diabetes. Level of evidence: + Critical appraisal: Strength: 2 members independently performed analysis, very elaborate description and analysis of results; Weakness: very homogenous group.

Read, 2009	
Study population: 86 Adolescents and young adults diagnosed with cancer and 409 parents of children with cancer at 5 pediatric oncology centers. Inclusion criteria: recall of being offered participation in health research; >12 years of age Exclusion criteria: not mentioned. Characteristics: AYA's median age: 18 (12-22) years (50% consenters); parents median age: 40 (15-74) years (64% consenters). Design: Quantitative study; validated postal questionnaires to describe personal factors that may influence decision to participate. Descriptive statistics and associations between demographic characteristics and attitudes were described.	Motivating factors: I thought it would help others: AYA: 67%, P: 85%; I thought it would help me/my child: AYA: 26%, P: 60%; I thought it would not add too much discomfort: AYA: 19%, P: 20%; I felt pressure from my doctor to take part: AYA: 19%, P: 21%; I felt pressure from my family or friends to take part: AYA: 7%, P: 3%; I thought it would not add too much time: AYA: 6%, P: 13%; I did not have any choice taking part in the study: AYA: 2%, P: NA; Other: AYA: 1%, P: 8%. Discouraging factors: Study required too much of my time: AYA: 45%, P: 13%; I had too much else to think about at the time: AYA: 36%, P: 21%; I did not think it would help me: AYA: 18%, P: 13%; Study required me to undergo increased discomfort: AYA: 18%, P: 26%; I did not want to be a guinea pig: AYA: 9%, P: 11%; Study too hard to understand: AYA: 9%, P: 5%; I did not trust the person offering me the study: AYA: 0%, P: 3%; Too risky: AYA: 0%, P: 13%; Other: AYA: 1%, P: 37%. Other outcomes: factors influencing participation of parents themselves in research. Confounding: altruistic motives could have been influenced by social acceptability. Level of evidence: B Critical appraisal: Large sample size. Very little response on discouraging factors. AYA's include minors and adults.
Rothmier, 2003	
Study population: 44 parents or guardians of children less than 18 years of age who were currently involved in clinical asthma research. Inclusion criteria: not mentioned. Exclusion criteria: not mentioned. Characteristics: parents' mean age: 40 years, majority Caucasian females; children's age between 4 and 7 years. All consenters Design: Quantitative study; 2-page questionnaire administered in person containing 14 liker-type questions. Factors influencing parental consent were ranked on liker-scale.	Motivating factors: Most influential: Learn more about disease; Help medical knowledge; Newest drugs. Discouraging factors: not mentioned. Other outcomes: factors less convincing/ important influencing decision. Confounding: not mentioned. Level of evidence: C Critical appraisal: Small sample size for quantitative study. No distinction made between negatively influencing and not influencing factors.

Sammons, 2007	
Study population: 136 parents of children who were recruited for a multicenter randomized equivalence trial comparing oral and intravenous treatment for pneumonia. Inclusion criteria: children aged 6 months to 16 years with fever, respiratory symptoms or signs and radiologically confirmed pneumonia. Exclusion criteria: not mentioned. Characteristics: children's median age: 2.0 years (6 months-12 years). Consenters and non-consenters Design: Quantitative study. Short postal questionnaire administered after trial participation, with free text questions and agree/disagree questions to assess what motivates parents to consent to an RCT.	Motivating factors: benefit to all children in the future: 32%; contribution to science: 27%; benefit to their own child: 19%; asked by a doctor: 13%; no reason not to: 7%. Discouraging factors: wanting a specific treatment for their child / unwilling to undergo randomization (N=25); Do not want to participate in a trial (N=2); too distressed by their child's admission (N=2); PIF stated that the ethics committee would have access to their child's data (N=1). Other outcomes: factors influencing decision in future studies. Confounding: possible overestimation of positive attitudes, due to low response rate; recall bias (different recall windows). Level of evidence: C Critical appraisal: good quality of questions (mix of open-ended and closed questions). Little information about study population.
Tait, 2003	
Study population: 505 parents/guardians who had been approached to allow their child to participate in any one of 18-ongoing clinical anesthesia or surgery studies. Inclusion criteria: not mentioned. Exclusion criteria: not mentioned. Characteristics: parents' mean age: 37.1 years; child's mean age: 7.2 years; 411 consenters, 94 non-consenters. Design: Quantitative study; questionnaire filled in by parents during participation of their child in trial to identify factors influencing their decision.	Motivating factors: positive predictors for consent: perceived benefits to child; perceived importance of study. Discouraging factors: negative predictor for consent: perceived risk of study. Other outcomes: factors influencing decision for future studies; interaction parent/child. Confounding: not mentioned. Level of evidence: B Critical appraisal: Large sample size, large amount of data collected, elaborate description of results.
Tait, 1998	
Study population: 246 parents/guardians who had been approached for permission to allow their child to participate in any one of several anesthesia research studies currently underway at the C.S. Mott Children's Hospital. Inclusion criteria: not mentioned. Exclusion criteria: not mentioned. Characteristics: No demographic differences between consenters and non-consenters; 168 consenters, 78 non-consenters. Design: Quantitative study; written questionnaire detailing reasons for their decision. Reasons were analyzed by principal component analysis.	Motivating factors: Minimal risk to child: 86.1%; Other children might benefit: 83.7 %; Study was explained well: 77.9%; Understood the study: 77.5%; Study was important: 67.9%; Contribute to medical science: 69.1%; Risk was small in relation to the importance of the study: 68.8%; Child might benefit: 51.2%; The researcher put you at ease: 44.7%; Sufficient time to decide: 36.1%; Child would receive "better" care: 13.0%; Felt uncomfortable saying "no": 4.4 %; Felt obligated to consent: 3.1%. Discouraging factors: Fear for safety of child: 61,6%; Potential risk to child: 59,7%; Randomized to placebo or drug: 40,8%; Another "thing" to worry about: 35,6%; Fear of unknown: 35.2%; Study might interfere with care: 21,1%; Insufficient time to decide: 15,3%; Child would be a "guinea pig": 15,3%; Distrust of medical system: 5,6 %; Moral/religious reasons: 4,2 %; Did not understand study: 2,8%; No privacy to decide: 2,8%; No financial compensation: 1,4%; Researcher made you feel uncomfortable: 1,4%. Other outcomes: factors influencing decision for future studies. Confounding: not mentioned. Level of evidence: B Critical appraisal: large sample size and large response rate. Reliability of questionnaire tested.

Truong, 2011	
Study population: (205 adult patients) and 48 parents of pediatric cancer patients participating in phase I, II, or III clinical trials of cancer-directed therapy. Inclusion criteria: consent to a qualified cancer trial within the previous 14 days. Exclusion criteria: consent obtained by an investigator of the present study, consent obtained in another language than English, email-address outside USA, participant removed from trial within 14 days, participant died. Characteristics: parents' mean age: 38.8 years, majority Caucasian and female; 20% phase I, 18% phase 2, 961% phase 3. All consenters. Design: Quantitative study; postal questionnaire including 9 statements of motivations for participation (with a focus on altruism).	Motivating factors: To help future patients: 50%; To help advance medical science: 49%; To receive medical benefits: 48%; I trust the doctor: 46%; I trust this hospital: 54% To maintain hope: 54%. Discouraging factors: not mentioned. Other outcomes: Being motivated primarily by altruism was positively correlated with phase of trial. Confounding: limited socio-demographic diversity, therefore limiting generalizability. Level of evidence: C Critical appraisal: predefined reasons (socially acceptable answering?); Focus on altruism in results, therefore other reasons are underexposed.
Van Stuijvenberg, 1998	
Study population: 181 parents or guardians who had volunteered their child for a randomized, double blind, placebo-controlled trial of ibuprofen to prevent febrile seizure recurrences. Inclusion criteria: children between 1 and 4 years old; with a recognized risk of febrile seizure recurrence; parents were Dutch or English speaking; child had visited the emergency room of the Sophia Children's Hospital in Rotterdam or the Juliana Children's Hospital in Den Haag because of a febrile seizure. Exclusion criteria: not mentioned. Characteristics: 181 mothers (median age: 32.6 years) and 155 fathers (median age: 35.6 years) of 181 children; majority West-European; all consenters. Design: Quantitative study; postal questionnaire with structured and semi-structured questions to assess the quality of the informed consent process.	Motivating factors: Contribution to clinical science (n = 92; 51%); Benefit for their own child (n = 58; 32%); Give something in return for the care of their child (n = 12; 7%); Benefit for other children in future (n = 5; 3%); Benefit for the parent (n = 6; 3%); The doctor asked (n = 6; 3%); No major reason (n = 2; 1%). Discouraging factors: not mentioned. Other outcomes: comprehensibility of information, awareness of 6 major trial characteristics, perception of the informed consent procedure; factors influencing decision for future studies. Confounding: possible overestimation of positive experiences, possibility of socially desirable answers. Level of evidence: C Critical appraisal: Good quality; sufficient sample size, questionnaire partially validated.

Vanhelst, 2013	
Study population: 261 parents of children who participated in pediatric clinical research at Lille Clinical Investigation Centre of the Lille University Hospital. Inclusion criteria: Pediatric clinical research study conducted between 2004 and 2007; Child aged between 1 and 18 years. Exclusion criteria: Pediatric clinical research studies involving neonates hospitalized in the intensive care unit; Children enrolled in oncology pediatric clinical research studies, who were a highly specific group of patients with an immediate, potentially poor outcome; Babies enrolled in industrial milk formula studies; Other studies involving children aged less than one year. Characteristics: 126 parents of healthy children, 99 ambulant sick children, 36 non-ambulant sick children. All consenters. Design: Quantitative study; postal questionnaire with closed questions to identify motivating factors linked to child health status that affected consent to participation.	Motivating factors: Direct benefits to the parents' own child of participating in the study; Benefits to the general population; Low risk to the child of participating in the study; Understanding the study and its regulation (percentages per group). Discouraging factors: not mentioned. Other outcomes: factors that improve parents' acceptance for consent. Confounding: not mentioned. Level of evidence: B Critical appraisal: Large sample size, not clear what kind of research it consists of, only 4 predefined reasons questioned.
Wagner, 2006	
Study population: 90 youths and their parents who participated in the clinical treatment research program in child and adolescent psychopharmacology at an academic medical center. Inclusion criteria: not mentioned. Exclusion criteria: not mentioned. Characteristics: children's mean age: 12.37 years (range:6-17), 48% female, 72% Caucasian; parents' mean age: 40.91 years, 82% female, 79% Caucasian; all consenters. Design: Quantitative study; Written pre- and post-study questionnaire to assess attitudes and experiences prior to and upon completion of study.	Motivating factors: Parents: Get treatment for my child 60%, Find out about my child's problem 30%, My child's prior treatment was unsuccessful 5%, Financial reimbursement for visits 2%, Dissatisfied with my child's prior treatment 1%, Treatment is free 1%; Youths: To get help for my problem 43%, To find out what is bothering me: 20%, My parent told me to be in the study: 14%, I will get money when I come here: 11%, To help other people with problems: 4%, My doctor told me to be in the study: 4%, Other: 3%, Treatment is free: 1%. Discouraging factors: not mentioned. Other outcomes: post study questionnaire results. Confounding: not mentioned. Level of evidence: C Critical appraisal: very different drug trials included; people could only give one reason for participation; probably other reasons matter for them also; pre and post questionnaire is a surplus value.

Wendler, 2012	
Study population: 177 adolescents participating in research at the NIH Clinical Center or Seattle Children's Hospital and their parents. Inclusion criteria: Adolescents 13 to 17 years of age, enrolled in the previous 6 months in a research study for any disorder or as healthy controls at the NIH Clinical Center or Seattle Children's Hospital, spoke English or Spanish, had a parent or guardian who agreed to be interviewed; Parent or guardian of an eligible adolescent who agreed to be interviewed, spoke English or Spanish. Exclusion criteria: when both parents were present, fathers were invited to participate. Characteristics: adolescent's mean age: 15.1 years; 19.8% healthy, 5.1% minor illness, 75.1% significant illness; parents' mean age: 45.3 years; all consenters Design: Quantitative study; personal interviews (questionnaire) with parents and adolescents to conduct an explorative analysis to evaluate whether any of 13 potentially relevant, dichotomized variables were significant.	Motivating factors: "helping find better treatments for others who are ill" is pretty important or very important to their decision to enroll in research (for 84.7% of the adolescents and 87.1% of the parents). Discouraging factors: not mentioned. Other outcomes: willingness to undergo certain procedures. Confounding: not mentioned. Level of evidence: C Critical appraisal: Article focusses on only one reason for participation (helping others), Other reasons were not questioned and explored; researchers do not mention the social desirability of the answer to their main question (helping others); large sample size.
Woodgate, 2010	
Study population: 31 parents who had a child with a history of cancer at the outpatient pediatric cancer unit at the city's primary cancer treatment center. Inclusion criteria: Ability to speak and understand English; Parents of children with differing cancer diagnoses and at various stages of the treatment completion, from 6 months post diagnosis to 5 years after treatment completion. Exclusion criteria: parents of newly diagnosed cancer patients. Characteristics: parents' age range: 27-51 years; child's age range: 3-17 years; 29 consenters and 2 non-consenters. Design: Qualitative study; person-centered, individual, open-ended interviews. Analyzed with an interpretive descriptive qualitative method (identifying themes).	Motivating factors: doing "the best" for their child (all); the need to help other children with cancer and their families; not disappointing their child's physician. Discouraging factors: not mentioned. Other outcomes: 6 themes identified: living a surreal event (finding it almost an impossible decision to make), wanting the best for my child, helping future families of children with cancer, coming to terms with my decision, making one difficult decision among many, experiencing a sense of trust. Confounding: not mentioned. Level of evidence: + Critical appraisal: Good thing: open-ended question in interview, reasons were not predefined. But no special attention to 2 parents who refused participation in trial and their decision.

Wynn, 2010	
Study population: 796 parents of infants approached for BABY HUG trial (phase 3 RCT of hydroxyurea) Inclusion criteria: infant <18 months of age, diagnosis of HbSS or HbSb thalassemia. Exclusion criteria: not mentioned. Characteristics: 487 (61%) non-consenters and 309 (39%) consenters. Design: Quantitative study; evaluation of an anonymized registry of potential subjects. Reasons participants stated for decision were categorized in 5 categories.	Motivating factors: Desire to aid research in sickle cell anemia: 51%; Hope that the child would be randomized to receive hydroxyurea: 51%; Desire to closer follow-up through increased clinic visits: 51%; Perceived the child to be ill and therefore hoped for clinical benefit from participation: 16%. Discouraging factors: high frequency if required clinic visits, blood tests, and special studies: 25%; fear or distrust of research participation: 19%; limited access to transportation: 14%; perceived their child to be healthy and felt medicine was not needed at this time: 10%; wanted their child to receive hydroxyurea rather than possibly being randomized to receive placebo: 2%. Other outcomes: reasons for not approaching. Confounding: classification of responses may have resulted in some misinterpretation of reasons; 21% did not state a reason, could have caused bias. Level of evidence: C Critical appraisal: Good quality: large sample size, prospectively, answers were by free response; Minority group questioned, not generalizable.
Zupancic, 1997	
Study population: 140 parents who had recently given or declined consent to one of three controlled trials (including drug trial) in the neonatal intensive care unit. Inclusion criteria: not mentioned. Exclusion criteria: Limited English skills. Characteristics: child's median age: 2 days; 103 consenters, 37 non-consenters; no demographic differences. Design: Quantitative study; cross-sectional written questionnaire consisting of 15 socio-demographic items and 13 scaled responses to statements. Responses were subjected to factor analysis to identify underlying constructs. The sample was then randomly split, and multiple regression was performed on each half.	Motivating factors: Factor analysis and multiple regression showed factor: "risk, benefit, and attitudes" to be significantly correlated with consent; consenters had lower parental estimates of risk and higher estimates of benefit, were more likely to report altruistic motives, freedom to make the decision independently and positive attitudes toward research. Discouraging factors: not mentioned. Other outcomes: Factor analysis and multiple regression showed no difference between consenters and non-consenters on "illness severity" or socio-demographic factors. Confounding: not mentioned. Level of evidence: B Critical appraisal: Questionnaire was pretested, had good reliability and validity. Real consent decisions examined; Comparison of consenters and non-consenters; Good response rate.

LIST OF PUBLICATIONS

SCIENTIFIC PUBLICATIONS RELEVANT FOR THIS THESIS

PUBLISHED

Tromp K, van de Vathorst S. Patients' trust as fundament for research ethics boards. Am J Bioeth. 2018; 18(4):42-44

Tromp K, Zwaan CM, van de Vathorst S. Motivations of children and their parents to participate in drug research: a systematic review. Eur J Pediatr. 2016; 175(5): 599-612

Tromp K, van de Vathorst S. Gatekeeping by professionals in recruitment of pediatric research participants: Indeed an undesirable practice. Am J Bioeth. 2015; 15(11): 30-32

Kleiber N*, Tromp K*, Mooij MG, van de Vathorst S, Tibboel D, de Wildt SN. Ethics of drug research in the pediatric intensive care unit. Paediatr Drugs. 2015; 17(1): 43-53 *[*shared first co-authorship]*

Bos W*, Tromp K*, Tibboel D, Pinxten W. Ethical aspects of clinical research with minors. Eur J Pediatr. 2013; 172(7): 859-866 *[*shared first co-authorship]*

UNDER REVIEW

Tromp K, van de Vathorst S. Parents' perspectives on decisions to participate in pediatric clinical research: Results from a focus group study with laypeople *[submitted]*

Tromp K, van der Wiel E, van der Vaart I, van Dijk M, van de Vathorst S. Burden weighs more than risk: Why children and their parents decide to participate in clinical research? Results from a qualitative interview study *[submitted]*

OTHER PUBLICATIONS RELEVANT TO THIS THESIS

LETTER TO THE EDITOR

Kleiber N, Tromp K, Tibboel D, De Wildt SN. Trial recruitment in the pediatric intensive care: Ask consent before you start?! Crit Care Med. 2016; 44(5): e309-e310

DUTCH PEER REVIEWED JOURNAL

Tromp K, De Wildt SN. Ethische aspecten van geneesmiddelenonderzoek bij kritisch zieke kinderen. Ned Tijdschr Geneeskd. 2015; 159(36): A8824

BOOK CHAPTER

de Beaufort ID, de Beaufort AJ, Westra AE, Tromp K, van de Vathorst S, Verhagen AA. H28: Ethiek in: Leerboek Kindergeneeskunde (2e druk). Utrecht: De Tijdstroom; 2015: 781-784; ISBN: 9789058982711

POLICY ADVICE

Stukart MJ, Olsthoorn-Heim ETM, van de Vathorst S, van der Heide A, Tromp K, de Klerk C. Tweede evaluatie medisch wetenschappelijk onderzoek met mensen. Den Haag: ZonMw; 2012

OTHER SCIENTIFIC PUBLICATIONS

Smedinga M, Tromp K, Schermer M, Richard E. Ethical arguments concerning the use of Alzheimer's Disease biomarkers in individuals with no or mild cognitive impairment: a systematic review and framework for discussion. J Alzheimers Dis. 2018; 66(4): 1309-1322

Milne RJ, Bunnik EM, Tromp K, Bemelmans SASA, Badger S, Gove D, Maman M, Schermer MS, Truyen L, Brayne C, Richard E. Ethical issues in the development of readiness cohorts in Alzheimer's disease research. J Prev Alzheimers Dis. 2017; 4(2): 125-131

Bemelmans SASA, Tromp K, Bunnik EM, Milne RJ, Badger S, Brayne C, Schermer MH, Richard E. Psychological, behavioral and social effects of disclosing Alzheimer's disease biomarkers to research participants: a systematic review. Alzheimers Res Ther. 2016; 8(1): 1-17

Tromp K, Claessens JJ, Knijnenburg SL, van der Pal HJ, van Leeuwen FE, Caron HN, Beerendonk CC, Kremer LC. Reproductive status in adult male long-term survivors of childhood cancer. Hum Reprod. 2011; 26(7): 1775-1783

PHD PORTFOLIO

PERSONAL DETAILS	
Name	Krista Tromp
Affiliation	Erasmus MC - department of Medical Ethics and Philosophy of Medicine
Research school	Dutch Research School of Philosophy (OZSW)
PhD period	2012 - 2018
Promotors	Prof.dr. Suzanne van de Vathorst and Prof.dr. Inez de Beaufort

PHD TRAINING	Year	Workload (ECTS)
General courses		
Courses: Basic Teaching Qualification for Higher Education (BKO); certificate obtained June 2016 (Erasmus MC)	2015-2016	5.0
Course: Certificate for Proficiency in English (Masterclass English)	2014	3.0
Course: Research Integrity (Erasmus MC)	2013	2.0
Course: Systematic Literature search and Endnote (Medical Library Erasmus MC)	2012	2.0
Specific courses		
Matariki Summer School: Challenges in research ethics (University Tubingen)	2015	3.0
Course: Ethics of health and care (OZSW)	2014	5.0
Matariki Spring School: Challenges in research ethics (University Tubingen)	2014	3.0
Summer school: Ethical Challenges in a European Perspective (EUCOR Universities, Strasbourg)	2013	6.0
Course: Ethics and the empirical sciences (OZSW)	2013	6.0
Ethics course: Norms and values critically assessed (Institute for Philosophy)	2013	2.0
Winter school: Ethical theory and moral practice (OZSW)	2012	6.0
Seminars and workshops		
7th Hendrik Muller Summer Seminar: Academic freedom and scientific integrity (KNAW)	2015	5.0
Masterclass: Ethics in Pediatrics with John Lantos and Martha Montello (UMCG)	2015	1.0
Meetings: study group Ethics & Healthcare (OZSW)	2013	1.0
Masterclass: Ethical issues in clinical research: randomized controlled trials with Robert Truog (AMC)	2013	0.5
PhD seminars: on various ethical topics and research skills (OZSW)	2012 - 2015	2.0
International conferences		
13th World Congress of Bioethics (IAB); Edinburgh, United Kingdom (2 oral presentations)	2016	3.0
2nd World Congress on Controversies in Pediatrics; Budapest, Hungary (oral presentation + poster)	2015	3.0
12th World Congress of Bioethics (IAB); Mexico City, Mexico (oral presentation)	2014	2.0

Other presentations		
Various invited presentations (Erasmus MC/Sophia Children's Hospital; patient organization; ZonMw; Ministry of Health, Welfare and Sport)	2012-2018	3.0
TEACHING ACTIVITIES	**Year**	**Workload (ECTS)**
Classes concerning medical ethics and research ethics at bachelor, master and post academic level (including lectures, group/practical work, supervision students, examination and development material): - Bachelor Medicine - Master Medicine - Bachelor Clinical Technology - Minor Ethics of healthcare - Research Master Infection and Immunity - Research Master Molecular Medicine	2012-cont.	25.0
Day course: Healthcare R&D and Ethics (Philips Healthcare Eindhoven)	2013-2015	1.0
Lectures: Research ethics and integrity (BROK course; Erasmus MC)	2012-cont.	2.0
Assistance Integrity Ceremony (Bachelor Medicine and Clinical Technology)	2012-2014	1.0
Assistance White Coat Ceremony (Master Medicine)	2012-2014	1.0
ADDITIONAL ACTIVITIES	**Year**	**Workload (ECTS)**
Ethics member: Research Ethics Committee Erasmus MC, University Medical Center Rotterdam	2017-cont.	10.0
Member working group: Revision ethical considerations for clinical trials on medicinal products conducted with minors (Implementation Regulation (EU) No 536/2014) (Dutch Ministry of Health, Welfare and Sports)	2015-2017	2.0
Secretary: Dutch Association of Philosophy and Medicine	2013-2017	10.0
Member core working group: Guideline criteria research with children (Dutch Association of Pediatrics)	2012-2016	8.0

ABOUT THE AUTHOR

Krista Tromp was born in Dronrijp (Menaldumadeel), the Netherlands on the 2nd of May 1984. She studied Biomedical Sciences, with a master in Epidemiology and minors in Health Law and Legislation and Health Technology Assessment, at the Radboud University in Nijmegen.

After obtaining her master's degree in 2010, she started working at the department of Medical Ethics and Philosophy of Medicine of the Erasmus University Medical Center in Rotterdam. There she started as a junior researcher on a project regarding the second evaluation of the Dutch Medical Research (Human Subjects) Act (*WMO*). During that project she discovered her fascination with medical ethics and research ethics. She could further pursue this interest in a PhD project at the same department on ethical aspects related to pediatric clinical research. This project was supervised by prof.dr. Suzanne van de Vathorst and prof.dr. Inez de Beaufort. The project was funded by the ZonMw program Priority Medicine and was a collaboration between the department of Medical Ethics and Philosophy of Medicine of the Erasmus MC with the department of Pediatric Oncology/Hematology, the Pediatric Intensive Care and the department of Pediatric Pulmonology of the Erasmus MC-Sophia Children's Hospital.

In addition to her research work, she obtained a basic teaching qualification for higher education (*BKO*), and is involved in teaching medical ethics to e.g. medical students, clinical technology students, physicians in training and research professionals. During her PhD training, she was elected to participate in the 7th Hendrik Muller Summer Seminar of the Royal Netherlands Academy of Arts and Sciences (*KNAW*). Between 2013 and 2017 Krista was secretary of the Dutch Association of Philosophy and Medicine. Since January 2017 she is also member of the research ethics committee of the Erasmus MC.

Since June 2016 she combines her academic work with policy. She works half time as a policy advisor in ethics at the Royal Dutch Medical Association (*artsenfederatie KNMG*) in Utrecht. There her work mainly focusses on physician-patient confidentiality, end-of-life issues, and strengthening moral responsibility of medical professionals. She also continues working half time as a researcher at the department of Medical Ethics and Philosophy of Medicine of the Erasmus University Medical Center in Rotterdam. Her current research projects relate to the ethics of prevention trials and early diagnosis of Alzheimer's Disease and ethical aspects regarding the design of new screening strategies for female cancer.

This PhD thesis is a reflection of the research Krista Tromp has done at the department of Medical Ethics and Philosophy of Medicine of the Erasmus University Medical Center in Rotterdam in collaboration with the department of Pediatric Oncology/Hematology, the Pediatric Intensive Care and the department of Pediatric Pulmonology of the Erasmus MC-Sophia Children's Hospital.

The thesis aims to contribute to the optimal inclusion of children in pediatric clinical research in such a way that we can further clinical research to advance scientific knowledge and develop much-needed treatment options for children while protecting children against harm from research. It proposes a framework that tailors the process of recruitment and informed consent to the perspectives and needs of children and their parents.

Krista Tromp (1984) works as a researcher at the department of Medical Ethics and Philosophy of Medicine of the Erasmus University Medical Center in Rotterdam and as a policy advisor in ethics at the Royal Dutch Medical Association in Utrecht.