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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.

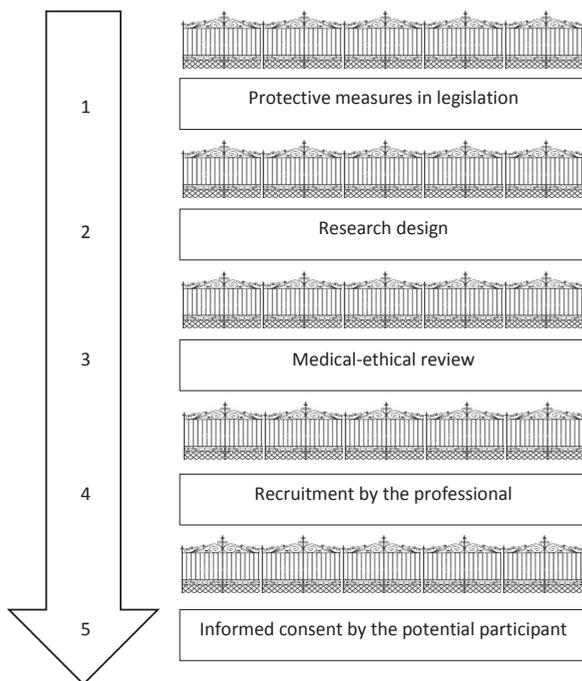


Figure 1: Overview of the gates in the research enterprise

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.

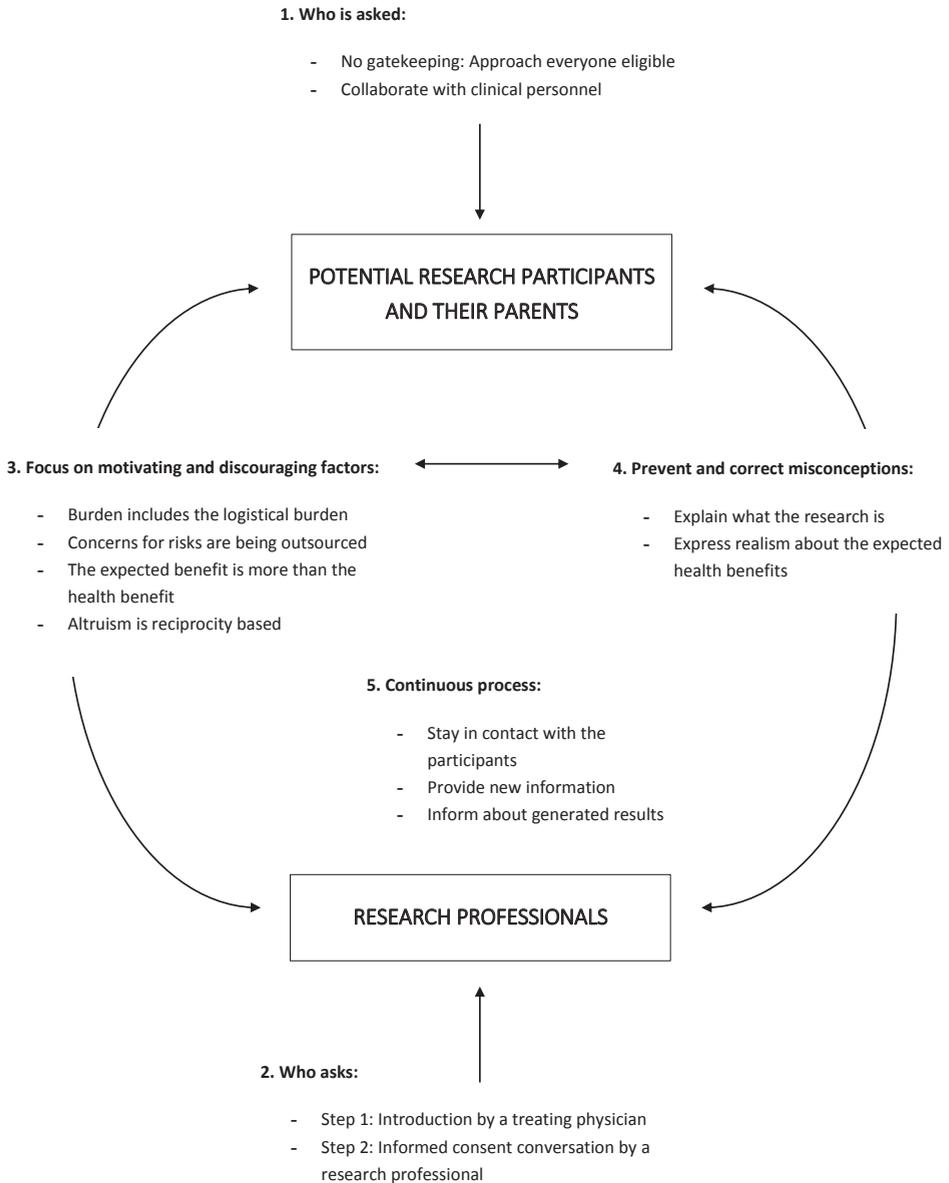


Figure 2: Overview of the framework for recruitment and informed consent

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).¹³³

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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