CHILDREN IN MEDICAL RESEARCH

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ETHICAL CHALLENGES

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Children in Medical Research – Ethical challenges
Bos, W.

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Ethical challenges

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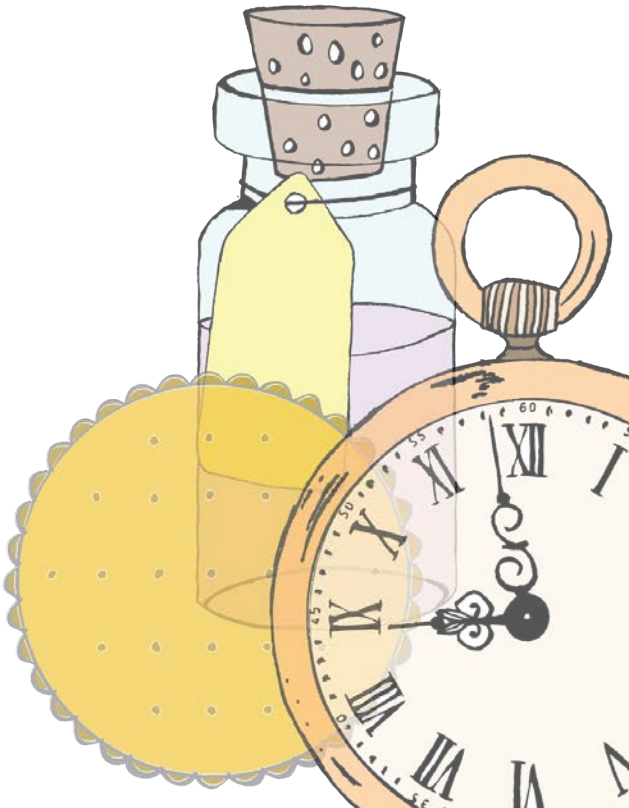


Hoi!

Leuk dat je deze brief leest. Ik wil je graag uitleggen waar mijn boek over gaat. Stel je voor: een meisje van 12 jaar is ziek en moet naar het ziekenhuis. De dokter vertelt welke ziekte ze heeft en hoe ze beter kan worden. Maar de dokter vertelt ook nog iets anders. Ze vraagt of het meisje mee wil doen aan een wetenschappelijk onderzoek. Daarmee wil de dokter een nieuw medicijn voor de ziekte testen. Er zullen 100 kinderen meedoen aan het onderzoek. De ene helft krijgt het nieuwe medicijn. De andere helft krijgt het oude medicijn. Je weet van tevoren niet welk medicijn je gaat krijgen. De dokter gaat dan kijken welk medicijn het beste werkt. Het meisje stelt er vragen over:

Meisje: wat moet ik dan allemaal doen?

Dokter: je moet een maand lang iedere dag het medicijn nemen. Eén keer per week moet je bloed laten prikken. Ook moet je één keer een hele dag naar het ziekenhuis komen. Dan krijg je een infuus in je arm. Daarmee wordt dan zes keer bloed afgenomen.

Meisje: doet dat pijn?

Dokter: dat kan soms een beetje pijn doen. Het ene kind vindt het vervelender dan het andere.

Meisje: wat is er mis met het oude medicijn?

Dokter: het oude medicijn werkt best goed maar we denken dat het nieuwe beter werkt. Het oude medicijn heeft ook bijwerkingen. Sommige kinderen krijgen er spierpijn van.

Meisje: waarom krijg ik dan niet gewoon het nieuwe medicijn als dat beter is?

Dokter: we weten nog niet zeker of het beter is. Dat gaan we juist onderzoeken. Misschien werkt het wel minder goed.

Meisje: kan ik er dan ook juist zieker van worden?

Dokter: dat is een goede vraag. We hebben vooronderzoek gedaan. Eerst hebben we kleine beetjes van het medicijn aan kinderen gegeven. En dan steeds iets meer. Als er bijwerkingen kwamen dan hielden we meteen op. De hoeveelheid die we nu geven is dus veilig. Maar er kan altijd iets onverwachts gebeuren.

Meisje: móét ik meedoen met het onderzoek?

Dokter: nee dat hoeft niet. Als je het niet wil dan hoeft het niet. Jij beslist samen met je ouders of je mee wil doen.

Meisje: wat gebeurt er als ik niet mee wil doen?

Dokter: dan krijg je gewoon het oude medicijn.

Meisje: en hoef ik dan niet het infuus?

Dokter: nee dat hoeft dan niet. Je moet dan wel een keer bloed laten prikken. Dat moet om te kijken of je echt weer beter bent.

Meisje: vindt u dat ik mee moet doen?

Dokter: ik vind daar niets van. Het is jouw keuze.

Meisje: moet ik nu beslissen?

Dokter: nee hoor. Je mag er thuis over nadenken, samen met je ouders. Je krijgt ook deze brief mee. Daarin staat alles nog een keer uitgelegd over dit onderzoek. Deze folder krijg je ook. Daarin staat wat wetenschappelijk onderzoek precies is en hoe het werkt.

Dit boek gaat over kinderen die net als dit meisje meedoen aan medisch-wetenschappelijk onderzoek. Daar komt veel bij kijken. Niet zomaar ieder onderzoek mag gedaan worden. Waarom mag dat eigenlijk niet? En waarom is onderzoek doen belangrijk?

Zieke kinderen willen we snel beter maken. Daar hebben we goede behandelingen voor nodig, bijvoorbeeld medicijnen. Een goede behandeling betekent een behandeling die veilig is en goed werkt. Maar dat moet wel eerst onderzocht worden, ook bij kinderen. Want een kinderlichaam werkt anders dan een vlwassen lichaam. Toch krijgen kinderen vaak medicijnen die nog niet goed zijn onderzocht. Er is dus meer onderzoek nodig.

Maar soms is onderzoek doen gevaarlijk. Je kunt bijvoorbeeld een onverwachte bijwerking krijgen of juist zieker worden van een nieuw medicijn. Dat kun je van tevoren niet weten omdat het nog niet is onderzocht. We noemen dat risico's. Ook is meedoen aan onderzoek vervelend of zwaar voor kinderen. Veel kinderen vinden het bijvoorbeeld eng om bloed te laten prikken. We noemen dat belasting. Kinderen kunnen vaak ook nog niet zelfstandig beslissen of ze mee willen doen aan onderzoek. Daarom zijn er regels waaraan onderzoekers zich moeten houden als ze een onderzoek willen doen met kinderen.

Onderzoek doen is dus nodig om zieke kinderen beter te kunnen maken. Dat is een goede reden om wel onderzoek met kinderen te doen. Maar meedoen aan onderzoek kan ook gevaarlijk en vervelend zijn. Dat is weer een reden om het niet te doen.

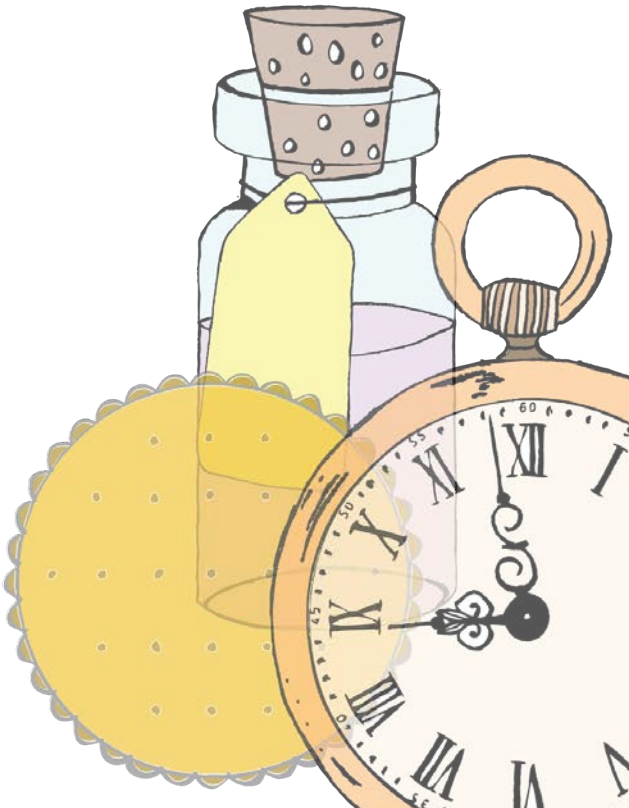
Dit heet een dilemma: een situatie waarin je niet weet wat je moet doen omdat er redenen voor én tegen zijn. Veel wetenschappers hebben al over dit dilemma nagedacht. Toch is het nog niet opgelost. Er zijn nog steeds vragen waarop nog geen goed genoeg antwoord is gekomen. Bijvoorbeeld: wat is de beste manier om erachter te komen of een onderzoek niet te gevaarlijk of te vervelend is voor kinderen? En hoe vervelend is meedoen aan onderzoek eigenlijk voor kinderen? Naar deze, en ook nog andere vragen heb ik onderzoek gedaan. Dit boek is een verslag van mijn onderzoek.

Met mijn onderzoek wil ik weer een stukje verder komen in het oplossen van het dilemma. We willen beter weten hoe we én zoveel mogelijk onderzoek kunnen doen, én kinderen goed kunnen beschermen. Het boek is geschreven voor andere wetenschappers. Daardoor is het best ingewikkeld en ook nog in het Engels. Maar dit boek gaat over kinderen, over jullie dus. Ik vind het belangrijk dat ook kinderen te weten kunnen komen waar mijn onderzoek over gaat. Aan het einde van het boek vind je een samenvatting voor kinderen. Daarin staat welke vragen ik heb gesteld en welke antwoorden ik heb gevonden. Dank je wel voor het lezen!

Wendy Bos

CHAPTER 1

GENERAL INTRODUCTION



'Begin at the beginning, go on till you come to the end, then stop.'(1) With these words, from his masterpiece Alice's Adventures in Wonderland, Lewis Carroll taught his readers an important lesson on storytelling. Silly as it may sound, it is in fact a rather important lesson that many still have to learn. The problem of a fuzzy and unclear story may well be that it did not begin at the beginning, or did not stop when it already came to the end. Yet, stories on ethics rarely come with endings, for the simple reason that ethics does not end. They are ever-evolving stories, because they are prone to changing perspectives, developing arguments and input from the real world. As such, there can never be a true ending. For good storytelling in the field of ethics, given the lack of true endings, we have to carefully choose where to stop and clarify why we chose that point. The same is true for the beginning.

This story is about the ethics of including children in clinical research and it began in 2011. By that time quite a long tradition of research into the moral justification and the moral limits of including children in clinical studies, had already arisen. This thesis builds on the rather large body of literature on this topic, as well as on the many legal and ethical regulations and guidelines that came into force ever since the horrific experiments with humans during World War II first proved on a large scale that such regulation is needed.(2) When I started my research project in 2011, another doctoral thesis on the moral limits of medical research with children had just been completed.(3) That thesis focused on regulating so-called non-therapeutic research, i.e. research from which the participants themselves are unlikely to benefit. Around that time, both paediatric researchers and the central committee on research involving human subjects (CCMO) had requested more opportunities for this kind of research.(4-6) In that thesis Westra researched how to facilitate more non-therapeutic research (specifically in the Netherlands) while still properly protecting participating children against undue research risks and burdens. At the end of that research project certain questions had remained unanswered. These questions are where my research project began.

BACKGROUND

THE CENTRAL DILEMMA

Paediatric research ethics evolves around a central dilemma, presenting two undesirable choices. To put it extremely simple; one choice is to accept that many childhood diseases cannot be (properly) treated and that many children receive treatments that have not been (properly) tested in children, and as such have not been (properly) proven safe and effective. The other choice is to include children, i.e. vulnerable persons who cannot (fully) consent, in medical research studies that can possibly harm them. As neither of the options are acceptable, the solution should be found somewhere in between those choices, and should be as balanced and as well-argued as possible. It is the main pursuit of paediatric research ethics to find the most reasonable balance.

First, let us look closer at those two choices. On one side there are those childhood diseases for which no cure has yet been found. Moreover, a large part of drug prescriptions for children occur off-label or unlicensed, i.e. are prescribed differently than how they are registered. Off-label drug use takes various forms, e.g. use for a different age group, a different indication or a different dosage.(7) Numbers of off-label and unlicensed drug use in paediatrics vary substantially between countries and hospitals. Percentages range from 11% to 80%. (8-13) The varying numbers partly relate to varying age- and patient groups, varying hospital settings, but also to the chosen methodologies and the lack of consensus on the definition of off-label and unlicensed drug use. Off-label prescription rates are highest in newborns, and mainly concern dosage adjustment.(7) The consequences of off-label use are not fully known. Clearly, children cannot be considered small adults, as their metabolism and capacity for drug absorption differs not only quantitatively from adults, but also qualitatively. Hence merely adjusting dosages to the body weight is potentially harmful. Metabolism, for example, differs a lot between the different age groups. Newborns still have an underdeveloped metabolism and need smaller doses than weight-adjusted doses, whereas toddlers and pre-schoolers have higher metabolising capacities and as such they might require higher doses than weight-adjusted doses.(14)

The lack of proper treatments for childhood diseases, plus the high off-label prescription rates show the need for more research in the field of paediatrics. Yet the development of new drugs and other interventions and testing them in humans (in this case children) is never without risk. The exact reason why medical

research is carried out is because the safety, the tolerability and/or the effect of the studied intervention are still unknown.

That brings us to the other side of the story. While the need for more paediatric research is compelling, research participation always comes with a certain degree of uncertainty and thereby with a certain degree of risk. To protect research participants against undue harm, all medical research with humans is strictly regulated. There are, among other requirements, two central ethical requirements for doing research with humans. Before any human participants can be included in a medical research study, the research protocol has to be approved by a research ethics committee (REC) and the participants have to provide informed consent.(15)

Children, however, are more vulnerable than adults. Moreover, the younger they are, the less capable they are of deciding about research participation.(16-18) Children therefore need and deserve extra protection, as compared to adults, and special protective measures for them have been put in place. Research with children may only be carried out if it is impossible to yield the same data with research in adults. Moreover, children cannot (fully) provide informed consent, but still research participation should not be involuntary.(19) As a solution, the parents have to provide proxy consent, and both the parents and research professionals should be vigilant to the child's (un)willingness to participate.(20) Children should be informed about the purpose, the procedures and the risk and burden of the study in a way that suits their level of understanding.(21) Also, they should be involved in the decision-making to an extent that suits them. Children who can provide assent; defined as affirmative agreement, should be asked for assent.(22-24) Should a child express dissent or objection, then that child should not be included in the study.(25)

Also with regard to the acceptability of risk and burden, stricter rules apply for research with children, especially for research without the prospect of direct benefit. For example, research that is designed to study the pharmacokinetics of a drug is usually not likely to benefit the participants themselves. Although the applicable (inter)national legal documents and ethical guidelines use different wordings, many require that the risks and burdens of a paediatric research study without the prospect of direct benefit are no more than minimal.(26-30) Yet, this seeming agreement on setting an upper limit for risks in paediatric research without potential direct benefit still leaves plenty of room for debate about the operationalisation of such a requirement. Both the content of the term *direct*

benefit and the definition of *minimal risk (and burden)* have been discussed extensively by paediatricians and ethicists. Examples are the question whether phase I studies should be regarded as offering direct benefit, and the question whether minimal risk should be an absolute or a relative standard.(31-38)

THE NETHERLANDS

The governance of paediatric research in the Netherlands has been criticised for being overly on the protective side. With studies that were not approved in the Netherlands, but nevertheless were allowed to be performed in other countries, the idea arose that the Dutch law was more restrictive than necessary.(39) This led to a debate about the question whether the law on medical research with human subjects should be changed in order to expand the possibilities for including children in research without direct benefit. The Dutch Medical research involving human subjects Act (WMO) in its former shape used a slightly stricter version of the minimal risk requirement, namely that research without direct benefit should involve no more than *negligible risk* and *minimal burden*.(30) Changing the law was a long process. Already in 2007, several paediatricians and the CCMO voiced their first requests for expanding the possibilities for including children in research without direct benefit.(4-6) The Committee Doek (named after the chairman) that got the task of investigating the need to expand the law, advised that the 'negligible risk and minimal burden' requirement should be removed altogether. The committee argued that research can be acceptable if it provides some direct benefit either for the participants themselves *or* to the patient group to which the participants belong. Arguments mentioned in the report were harmonisation with the European regulatory framework, and the recognition of children older than 12 as persons with rights who should have the opportunity to decide about higher-risk research participation themselves.(40) The arguments and the recommendations of the Committee Doek were criticised for focusing only on the Clinical Trials Directive (as almost all other relevant documents do set an upper limit for risk and burden, the Directive being an exception) and for arbitrarily setting a threshold at 12 years of age, while allowing higher risk and burden for all age groups.(41) Ultimately the advice of the Committee Doek was not adopted in the draft of the revised law. Instead, the American standard of 'a minor increase over minimal risk (and burden)' was used in the new proposal.(42) Meanwhile, the European Clinical Trials Regulation was drafted and approved in April 2014, which would, as soon as it would come into force, directly govern all drug trials in all EU member states. Any deviations from

the newly drafted Regulation that were less strict, could apply to non-drug studies only. In that light, the unavoidable outcome was that the national law got adjusted to the Regulation. Ultimately, the revised national law passed the House of Representatives (Tweede Kamer) in 2015, and the Senate (Eerste Kamer) in 2016. The new requirement is that research without the prospect of direct benefit imposes only 'minimal risk and minimal burden related to the standard treatment of the patient'.(29) The exact interpretation of this requirement still remains to be seen, but it has already been noted that relating the acceptable level of risk and burden to the standard treatment of the patient, is potentially harmful.(43)

RELEVANCE

Despite the fact that paediatric research ethics is a much-studied field, practice shows that there are still questions that have not yet been answered satisfactorily. Examples are questions about the acceptability of risk and burden and about how to react to signs of discomfort and dissent during research participation. REC members and research professionals recognise that these are still relevant and important questions. Improving ethical review practice as well as improving the monitoring of children during the performance of clinical research would expectedly contribute to the protection of children as research participants. In chapter 3 of this thesis a case is presented which illustrates clearly that there are still unsolved issues.

AIMS

With this thesis I aim to contribute to the strengthening of the existing ethical framework that protects minor research participants against undue harm. As said before, my work builds on quite a long research tradition in which moral positions and arguments have been discussed extensively.(3, 33, 44, 45) The bigger and broader issues have received much attention and nowadays the regulatory framework governing paediatric research is fairly well founded.(15) Central medical-ethical principles like non-maleficence, respect for persons and respect for (growing) autonomy have gained a firm position in all relevant guidelines.(46) Yet, nailing down important principles in legal documents is not the end of the story. What is written in laws and guidelines says little about the practical implications of those principles and requirements and even less about how they are complied with. For example, the principle of respect for a child's dissent is found in different wordings in all research ethics documents.(26, 28-30, 47) But the

content of the notion of dissent is inconsistent among these documents, as is guidance on operationalising this principle (this is discussed extensively in chapter 8).(48) The need for clarity, precision and transparency are recurring topics throughout this thesis.

An overarching aim of my work is to strengthen the position of children by providing them with the exact amount of protection they need and deserve, while at the same time recognising their capacities and respecting their views and experiences. Instead of regarding children as mere subjects of study, I would, among others, suggest to regard them as partners in the research project.(16) To respect children as persons and appreciate their involvement in research projects, would expectedly foster their sense of autonomy and the development of their self-esteem.(49) This idea is reflected in several parts of this thesis. In chapter 6, for example, I propose a more precise method for assessing risks and benefits during the ethical review process. This precision helps to identify more explicitly which studies can be reasonably proposed to children, while also making sure that acceptable studies are not rejected unnecessarily. Moreover, in chapter 8 recommendations are provided for monitoring children who participate in research, which focus explicitly on voluntariness and experienced burden.

METHODOLOGICAL APPROACH

Research ethics is an interdisciplinary field that investigates questions of different nature from various perspectives. Philosophical questions on the moral justification of, and on the moral conditions for including children in medical research are only part of the project of paediatric research ethics. As research with humans is so strictly regulated by law, research ethicists inevitably have to face legal questions as well. Moreover, research ethics is a discipline that aims to foster ethical research practice and for that reason it is of great importance to always look at what happens in practice. Empirical data are needed, for example to identify the actual problems and concerns, as well as to uncover experiences or views of the people involved.

This thesis is positioned on exactly that intersection of the philosophical, the legal and the empirical domain. The moral reasoning found in this thesis represents a process of theoretical testing, modification and experimentation.(50) It is a rather general and broad method of reflective thinking, taking into account possible moral positions and relating them to moral principles with the aim to reach a well-balanced conclusion.(51)

For this thesis, I used legal and empirical knowledge to inform and fuel my moral reflective thinking. A central research approach that can be found throughout all chapters is a strong focus on clarifying and defining concepts and problems as clearly and precise as possible. A clear and precise starting point is a prerequisite for a meaningful and progressive normative reflection. Chapter 6, 7, and 8 are the best examples of this research approach. The analysis of legal articles and articles from ethical guidelines and their relation to generally accepted ethical principles is interwoven in the normative reasoning. For our study on the procedure-level approach to ethical review (chapter 6) we have analysed research protocols and REC decisions from the archives of several RECs. To uncover the views of paediatricians on research burden for children, a questionnaire study was carried out (chapter 7). Throughout the entire course of our study we have discussed our research progress and results with professionals in the field of paediatric research (research nurses, paediatricians and REC members), through focus groups, workshops and group discussions. The normative conclusions presented in this thesis result from the combination of these methods.

OUTLINE AND RESEARCH QUESTIONS

The topics that are presented in the chapters 2 to 5 concern background questions. In **chapter 2** the European regulatory landscape is sketched in order to clarify against what legal background the ethical discussion takes place. After that, in **chapter 3** we discuss a case. This concerned a protocol on Duchenne Muscular Dystrophy that was approved in Belgium and Sweden but not in the Netherlands. We took the case of this protocol to start a discussion on the acceptability of risk and burden. This discussion revealed also other questions that are still unanswered. By means of a short epilogue these questions are pointed out. In **chapter 4** we focus on children as vulnerable research subjects, and compare them to another group of vulnerable research subjects; dementia patients. We investigated in what morally relevant aspects these two groups are different and on what aspects they are similar and how those differences and similarities are represented in laws and ethical guidelines. Then, during the course of our research project, the new European Clinical Trials Regulation was drafted and approved. In **chapter 5** we present a critical analysis of the new Regulation. In our view, the new Regulation fails to guarantee the quality of the review process. The main concerns described in this chapter are the quality of the risk-benefit assessment and the quality of ethics committees.

The chapters 6, 7 and 8 concern the three main subprojects of my research project. The subproject presented in **chapter 6** focuses on the risk-benefit assessment carried out by Research Ethics Committees. As the line between research that can, and research that cannot directly benefit the participating children can sometimes be rather thin and indistinct, several ethicists have proposed to shift the focus from protocols as a whole, to the individual procedures within that protocol.(52-55) Our study aimed at finding how large the grey area between research *with*-, and research *without* the prospect of direct benefit actually is and thereby to identify the need for assessing risks and benefits on the procedure-level. Secondly, we aimed at exploring possible practical drawbacks of the implementation of a procedure-level approach in the practise of ethical review. To this end the following research questions were formulated:

- *To what extent are there elements without direct benefit in paediatric intervention studies with direct benefit and vice versa?*
- *What are the practical drawbacks for using a procedure-level approach to ethical review?*

In **chapter 7** the second subproject is presented. For Research Ethics Committees it is often difficult to estimate how burdensome research participation will be for children. Existing data on this topic are rather limited and it would be helpful if more empirical data on the burden of medical research procedures for children were available.(56-59) This study aimed to generate more knowledge on the burden associated with several widely used research procedures. The following research question was asked:

- *What is the burden of several research procedures for children, according to paediatricians?*

The third subproject is presented in **chapter 8**. When participating in clinical research, children sometimes show signs of discomfort, discontent, distress and/or dissent. Such signs can be rather vague and hard to interpret, especially in young children. If such behaviour continues, the question may rise whether it is still justified to keep a child in a trial. Guidance on this issue is scarce, incomplete and inconsistent.(25, 60) With our study we aimed to provide clear guidance and practical recommendations for deciding whether to stop research participation of a certain child. In order to provide such guidance the following research question had to be answered:

- *When, and on what ground should signs of discontent and dissent lead to withdrawing a child from a trial?*

Ultimately, all parties involved need practical proposals for the improvement of ethical research conduct. In **chapter 9**, the general discussion, I will not only present the main conclusions of our research project, but will also identify missed opportunities concerning the recent regulatory changes, and I will present my ideas on the possible ways forward for the future of paediatric research ethics.

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CHAPTER 2

PAEDIATRIC RESEARCH: CENTRAL ETHICAL ISSUES AND THE REGULATORY LANDSCAPE

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Ethical aspects of clinical research with minors.
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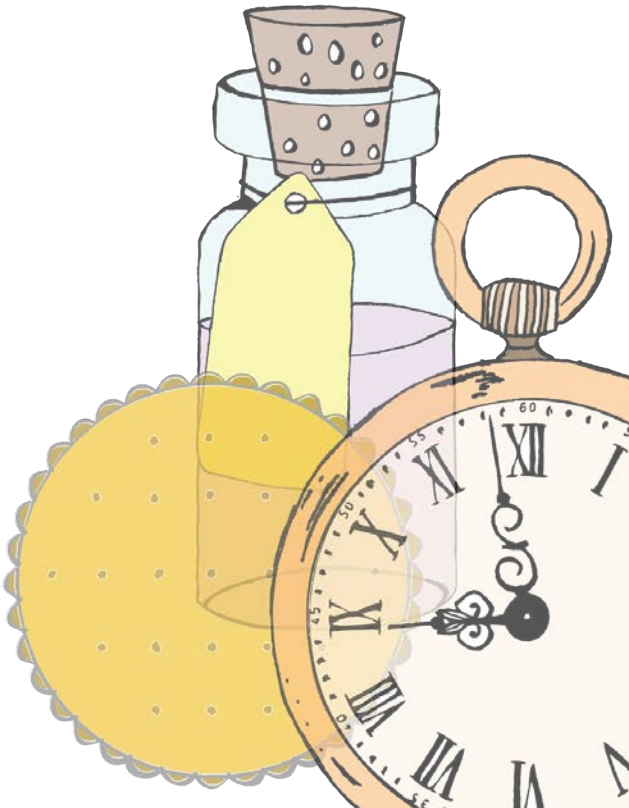

ABSTRACT

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, however, has created an ambivalent attitude towards paediatric 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. 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 paper, we will explore the legal regulation and ethical guidance that currently governs paediatric clinical research in the European Union and discuss the future challenges in this field. In addition, we will discuss major ethical concerns in paediatric 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 paediatric clinical research and implementing ethical and legal requirements in the actual paediatric research conduct.

INTRODUCTION

Over the past decades, clinical research has increasingly been subjected to ethical requirements and legal regulation. Since World War II, landmark codes of ethical research conduct have been drafted and legal regulation has been issued in the United States, 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 paediatric clinical research. On the one hand, minors are regarded as a vulnerable population that deserves additional protection against the risks and burdens of clinical research. Such protection could not be maximised 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 unlicensed in paediatric practice however, clearly indicates that research in competent adults does not automatically generates timely advancements in the diagnosis, care, and treatments for minors.(1) Minors are not just small adults, and omitting to conduct clinical trials in the population of minors turns minors into so-called therapeutic orphans.(2, 3) By consequence, the conduct of paediatric clinical trials is indispensible to catch up with the lack of licensed drugs that are labelled for paediatric use.

However, from an ethical and legal point of view, the conduct of paediatric clinical trials is a precarious enterprise. 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 paediatric clinical research), and restrictive regulation (e.g. risk thresholds for research without the prospect of direct benefit) may be hard to surpass.

In this paper, we will explore the legal regulation and ethical guidance that currently governs paediatric clinical research and discuss the future challenges in

this field. It must be emphasised that the applicable ethical and legal frameworks are often formulated in general terms, while paediatric 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. Box 1 lists a number of such issues.

Box 1: Recognised problems from a clinical point of view in critically ill minors

1. The compassionate use at an individual base of a last resort drug (Imatinib) for pulmonary hypertension originally 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 birth weight 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 foetal 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 PAEDIATRIC CLINICAL RESEARCH IN THE EUROPEAN UNION

In the European Union, diverse legislative bodies have promulgated various supranational and national regulations over the past 15 years. They aimed to harmonise existing standards of good clinical practice and to facilitate and encourage paediatric clinical research.(6) At the supranational level, three different regulations govern paediatric 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 paediatric research in Article 17 (Box 2).

Box 2: Oviedo Convention—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 authorisation 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 authorised 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.

Second, Directive 2001/20/EC (further, the Clinical Trials Directive) mainly aims at a harmonisation of the provisions regarding good clinical practice and the facilitation of multicentre 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 implemented the Clinical Trials Directive. Obviously, differences in domestic requirements between EU member states have to 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 (Box 3).

Third, Regulation (EC) No. 1901/2006 (further, the Paediatric 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 paediatric investigation plan after phase I 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 Paediatric Regulation offers considerable rewards in the form of a prolongation of market exclusivity. The Paediatric Regulation also arranged the establishment of a paediatric committee within the European Medicines Agency that is (among other tasks) primarily responsible for the scientific assessment and agreement of paediatric investigation plans and for the system of waivers and deferrals thereof. In contrast to the European Convention and the European Directive, the Paediatric Regulation is exclusively dedicated to clinical research in minors.

Box 3: Clinical Trials Directive—Article 4

Clinical trials on minors

(a) In addition to any other relevant restriction, a clinical trial on minors may be undertaken only if:
(b) 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;
(c) 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;
(d) 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;
(e) no incentives or financial inducements are given except compensation;
(f) 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;
(g) the corresponding scientific guidelines of the Agency have been followed;
(h) clinical trials have been designed to minimise 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;
(i) the Ethics Committee, with paediatric expertise or after taking advice in clinical, ethical and psychosocial problems in the field of paediatrics, has endorsed the protocol; and
(j) the interests of the patient always prevail over those of science and society.

DIVERSITY AND INCONSISTENCY OF THE CURRENT REGULATION

Unfortunately, the legal frameworks that govern paediatric 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. However, Article 4e of the Clinical Trials Directive simply requires 'some direct benefit' for the group of patients. 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 wish 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. This 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 rather 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 I trials or the use of healthy controls in paediatric 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 PAEDIATRIC 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 paper, we will discuss two major ethical concerns in paediatric 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 set up to review the acceptability of risks and burdens in paediatric 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 or beneficial research (research that is likely to generate a direct benefit for the subject involved) is often distinguished from non-therapeutic or non-beneficial 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 benefits, risks and burdens 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, the law makes no explicit distinction between therapeutic and non-therapeutic research, and proportionality between risks and benefits is not linked to specific risk thresholds.

INFORMED CONSENT FOR PAEDIATRIC 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 meant 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 paediatric 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 majority.(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 enrol 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 proxy decision maker is thus most often required to enrol 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, and (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 realise in practice. For example, research shows that parents sometimes do not remember having consented to enrol their child in a clinical trial.(14-16) Also the understanding of information and recalling what one has consented to are difficult tasks. 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) In a study by Ballard and colleagues, only 5% of the parents who understood the study also 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 paediatrics, however, research does not necessarily start where

therapy ends. This is particularly true for the setting of paediatric oncology, where nearly all patients are receiving their treatments in the context of research. 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 misconceptions' 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 research 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 and rational decision. 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 that are made in life. 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 research and emotional distress.(16-18, 20, 30, 31) Moreover, 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) Also, 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 paediatric 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 ten 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 paediatric 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 emphasised 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 realisation of ethical research conduct. The evolution of newer ways of data acquisition such as opportunistic sampling, dry blood spot technology, and the development of bio banks 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 paediatric 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 maximising 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 under-

standing 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 paediatric 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 paediatric clinical research.

APPENDIX

The paper on which this chapter was based, was written in 2012 and published in 2013. At that time the new European Clinical Trials Regulation was being drafted but not yet approved. On April 2nd 2014 the European Parliament approved the new Regulation, which will repeal the Clinical Trials Directive as soon as it comes into force, expectedly in 2017.(33)

With regard to research with children, the Regulation differs from the Directive on several points. Some differences concern small details, while others are more substantial. The relevant article from the Directive (article 4) was shown in box 3 of this chapter. Article 32 of the Regulation is presented underneath. Important differences as compared to article 4 of the Directive are underscored. In chapter 4, chapter 5 and in the general discussion of this thesis, the changes in the Regulation and their implications are further discussed.

Box 4: Clinical trials on minors (article 32 of the Clinical Trials Regulation) – differences as compared to article 4 of the Clinical Trials Directive are underscored

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.

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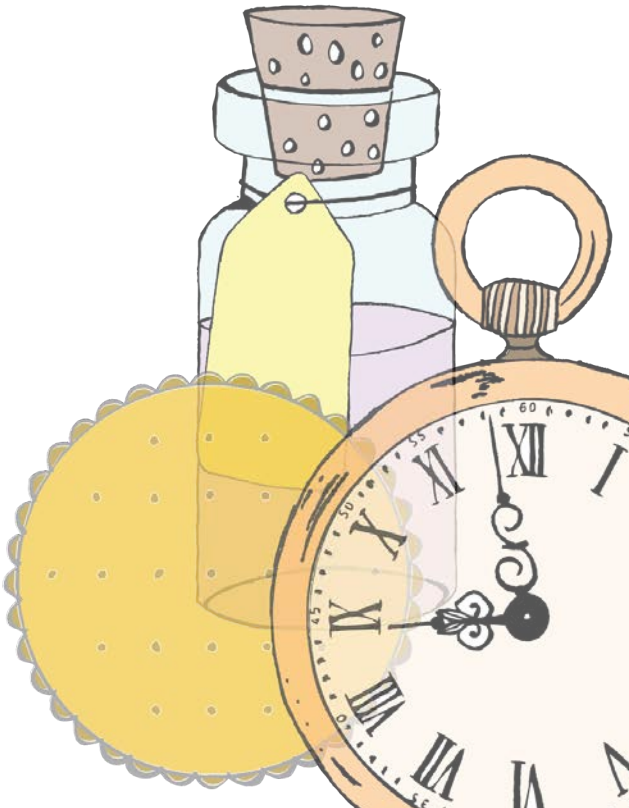
CHAPTER 3

A CASE: RESEARCH IN CHILDREN WITH DUCHENNE MUSCULAR DYSTROPHY

Wendy Bos, Anna E. Westra, Wim Pinxten, Matthew P. Mayer, John D. Lantos.
Risks in a Trial of an Innovative Treatment of Duchenne Muscular Dystrophy.
Pediatrics. 2015;136(6):1173-7.



ABSTRACT

Studies of innovative therapies for muscular dystrophy raise unique ethical issues. The disease is currently untreatable and relentlessly progressive. A number of potentially efficacious treatments are being developed. Those treatments, like all treatments, may have unforeseen adverse effects. But patients and families, facing a bleak future, may be willing to take the gamble and try those treatments. Many doctors are eager to study them. But should research ethics committees (RECs) approve them? This chapter discusses these issues and recounts the ways that one such study elicited different responses from different RECs.

INTRODUCTION

To protect minors from undue harm in clinical trials, a variety of protective measures exist in national and international legislation and ethical guidelines. Some measures are used worldwide, such as the requirements of proxy consent and ethical review. Other measures differ between countries. For example, some countries use the minimal risk threshold for non-therapeutic research while others do not.

The European Union (EU) offers a fascinating setting to consider the strengths and weaknesses of various protective measures, since regulations vary within the EU. In 2001, the European Parliament and the Council of the European Union issued The Clinical Trials Directive to govern research involving human subjects.(1) This directive did not adopt a specific risk threshold for non-therapeutic research in children. In fact, the directive does not distinguish between therapeutic and non-therapeutic research at all. Recently, a new regulation that will replace the current directive has been voted in the European Parliament. In this regulation, which is directly applicable in all EU member states, the assessment of risks for paediatric clinical trials will be harmonised.(2, 3) The Council of Europe's Convention on Human Rights and Biomedicine (1997), which is only binding upon those European countries that have signed and ratified it, requires that non-therapeutic research in children entails no more than minimal risk and minimal burden.(4) By consequence, applicable regulation and corresponding review practices may vary among member states, and by consequence the risks in a single protocol may be assessed differently in different member states. Note that, not unimportantly, if a trial results in a market authorisation for a new drug, it will cover the entire EU, including the member states in which the trial was rejected.

It is beyond dispute that minors should be protected against risks of harm when participating in research. A minimal risk threshold for non-therapeutic research can help protect minors in two ways. First, the threshold itself is a way of prohibiting studies that are deemed too risky. Second, the focus on non-therapeutic research can remind ethics committees of the fact that exposing children to risks and burdens solely for research reasons requires adequate justification. The concept of minimal risk is, however, notoriously difficult to define. Different definitions can lead to decisions about research protocols that might prevent breakthroughs for patients with urgent and unmet medical needs.

This chapter discusses a trial carried out in 2008, with minor patients with Duchenne Muscular Dystrophy (DMD). It was approved in Belgium and Sweden, but

rejected in the Netherlands, where the law and review practices are more restrictive.

THE CASE

In 2008, a Dutch research team submitted a protocol of a clinical trial investigating the safety, pharmacokinetics, and effects of subcutaneous injections of an antisense oligonucleotide (AON) in children with DMD for review in three EU member states simultaneously: The Netherlands, Belgium and Sweden.

The trial concerned a follow-up of a proof-of-concept study in the Netherlands, in which a single dose of PRO-051 (GSK-2402968, Drisapersen) was administered intramuscularly to 4 patients.(5) DMD patients would be eligible for the study if they were between 5 and 16 years of age, and had no evidence of dystrophin on previous diagnostic muscle biopsies. They also had to have mutations that could be corrected by means of inducing exon 51 skipping. This might lead to dystrophin production in the muscles. The eligibility criteria also included an estimated life expectancy of 6 months or more, no serious pre-existing medical conditions, and no respiratory insufficiency that made them assisted ventilation dependent. Concurrent treatment with glucocorticoids was allowed.

Children enrolled in the study would receive weekly abdominal subcutaneous injections of an AON (0.5 to 6 mg per kilogram of body weight, with 3 patients receiving each dose) for 5 weeks. During that time, they would have blood and urine samples collected for pharmacokinetic and safety measurements. Adverse events would be recorded. Efficacy would be assessed by measurements of muscle strength, pulmonary function tests and (two or three) muscle biopsies. No control group was included in the study. Instead, the pre-study state of each child would be the control. After an interval of 6 to 15 months after the last dose, all patients would enter a 12-week open-label extension phase, during which they all would receive the AON at a dose of 6.0 mg per kilogram body weight per week.

The submitted protocol was approved in Belgium and Sweden. In the Netherlands, however, the reviewing ethics committee regarded the protocol as unacceptable and proposed major changes to the design of the trial. As a consequence, the researchers decided to conduct their study only in Belgium and Sweden. The different responses turned on different ideas about the riskiness of the trial.

To support the discussion of the strengths and weaknesses of the different regulatory regimens that apply within the EU (and the appropriateness of the

strategy chosen in the new European Clinical Trials Regulation, that was recently voted in the European Parliament), we invited the principal investigator, a representative from both the Dutch and Belgian reviewing committees and a patient advocate to comment on this case. Lastly, two independent professionals, who have not been involved in this case, comment on this case.

JAN VERSCHUUREN - *PRINCIPLE INVESTIGATOR*

The trial should have been approved for several reasons. First, the objectives were important: DMD is most frequently caused by a genetic defect which prevents the RNA from translating into protein and results in no (or only a trace amount of) dystrophin in the muscles. The study was designed to show whether the administration of AON could restore the production of dystrophin protein. Second, although clinical trials should preferentially be conducted in adults who are capable of giving informed consent, the mode of action of the AON and the clinical features of DMD make it impossible to conduct a trial in adult patients with the disease. More specifically, the severe muscle loss that DMD patients develop over time makes it impossible to find a sufficiently large group of eligible adult patients. In addition, healthy volunteers would provide no alternative to adult patients, since the AON would actually cause DMD in healthy persons.

Objections to the study focused on the unknown risks of AON. Because the risks could not be precisely quantified, they were deemed to be too high for a trial that involved children. This assessment ignores important features of DMD. The severity of DMD, its profound impact on the lives of the children and parents, its relentlessly progressive nature, and the fact that there is no treatment to modify the course of the disease make DMD a unique clinical problem. These features of the disease should be considered in weighing the risks of an experimental treatment against the risks of untreated disease. DMD patients may be willing to accept more risks and burdens than others would allow them to. That is not irrational. It must therefore be recognised that an objective risk standard may not do justice to this subjective experience of risks and burdens. Finally, the distinction between therapeutic and non-therapeutic (in the Dutch law described as research with or without a direct benefit to the research subject) may be arbitrary and unnecessarily block research. By definition, a clinical trial is not a therapy. The whole track from phase I tot phase III clinical studies together, however, may potentially result in therapy for the patient and the group. In this track, it is hard to define exactly where the therapeutic dimension starts in.

MONIQUE AL AND GERARD KOËTER - *DUTCH ETHICS COMMITTEE*

The Dutch Central Committee on Research with Humans (CCMO), a national ethics committee, reviewed both this study and the initial safety study to which this study was a follow-up.

With respect to the trial design, the follow-up study changed the mode of administration, the dosage and the frequency of administration in comparison to the initial safety study. The CCMO judged that such a profound change could hinder the correct interpretation of the data and considered the step from a singular intramuscular administration to a multiple subcutaneous administration unjustified. The committee recognised the importance of the trial, but preferred a more step-by-step approach where PRO-051 would be administered to healthy adults first, to see whether it would reach the muscle after subcutaneous administration.

The CCMO also focused on the burdens of the research protocol. We judged them to be more than minimal. The protocol called for twelve hospital visits, including five 24-hour hospitalisations, a skin biopsy, two muscular biopsies, twelve blood samples, two insertions of a venous cannula, an MRI of the lower legs, many walking tests, muscle tests (including spirometry) and five subcutaneous injections. The CCMO suggested that the protocol would be more acceptable if fewer muscle biopsies were required.

Therefore, the committee proposed changes in the design leading to a lower burden in the investigated boys. If the researchers had adopted these changes, the protocol could have been reconsidered by the CCMO.

ELIZABETH VROOM - *PATIENT REPRESENTATIVE*

The Duchenne Parent Project has been involved in the development of the antisense technique and the use of AON for DMD in the Netherlands since 1998. Our organisation was very disappointed in the decision by the Dutch CCMO that led researchers to move their study of this novel technology to other European countries. Not having the protocol approved in the Netherlands made the Dutch Duchenne community miss out on the opportunity to build up experience with this new technology in the Netherlands. In addition, Dutch patients, who could potentially benefit from this compound, were prevented access to the trial compound, not only during the 4 weeks of the trial but also during the open label extension trial that followed. In neighbouring countries, research did enable therapeutic breakthroughs for which we are very grateful. We were disappointed, of course, that follow-up studies showed less success than we hoped for. We

continue to work with regulatory agencies in Europe and the United States to see whether this approach to treatment can be approved.

We regret to have encountered several hurdles to having this trial taking place in the Netherlands. First, in spite of plans to change it, the Dutch law is stricter than in some other European countries, which made it more difficult to get approval for this trial. Second, we feel that some of the suggestions of the Dutch ethics committee were ethically questionable. For example the suggestion to give the drug to healthy volunteers did not acknowledge prior work showing that, in healthy patients, the drug could cause harm by disrupting dystrophin production. In such situations, ethics committees need to ask for the advice of external experts.

Most importantly, the ethics committee should have considered the opinions of patients and parents regarding risks and burdens of the treatment protocol.(6) After all, they are the ones who take the burdens and the risks when participating. Many parents and patients would have been willing to participate. By not considering the viewpoints of patients and parents, the committee made it impossible for Dutch centres to participate in studies that were approved in other European countries.

WALTER VAN DEN BOGAERT - *BELGIAN ETHICS COMMITTEE*

The Belgian law governing clinical trials and the protection of research subjects has specific requirements for trials in minors. In January 2008 this trial was accepted by the Ethical Committee of the UZ Leuven. The committee judged that the protocol was fully compliant with the Belgian law. More specifically, the committee judged that the legal requirement of a 'potential medical benefit' was met. It also assessed that appropriate measures had been taken to provide minor patients and their parents (or other legal representative) with correct and complete information. By consequence, no additional comments or enquiries were sent to the principal investigator.

INDEPENDENT COMMENTATORS

MATTHEW P. MEYER

For DMD, emerging therapeutics such as exon skipping PRO-051, in addition to protein regulators, cellular therapies and gene replacement therapies offer the ability to treat the root causes of disease rather than merely the symptoms. In

what would be an historic achievement, we may learn to slow, stop or even reverse the course for this terrible, progressive genetic disease. To do so, however, it may be necessary to challenge accepted norms in paediatric research ethics. We may need to develop new ways to think about the how discoveries travel from bench to bedside.

The central question in new drug research is one focused on whether it is acceptable to expose children to unknown and potentially great risks while testing drugs that may not have any immediate benefits. In this case, the Dutch ethics committee is criticised for following established guidelines stipulating that research protocols must not be burdensome to paediatric participants and that the potential for harm must be firmly established from previous safety trials in adult subjects. By maintaining those standards, the research review board's decision clashes with the values of the parents and patients, and ultimately obstructs potentially valuable clinical research for a vulnerable population of children. Parents, doctors, and ethicists all want to do what is best for children. But parents and doctors think that the best thing would be to accept research risks in the hope for a cure, while the ethicists maintain that risky research will be more harmful than beneficial for the child and should thus be restricted.

In scenarios such as this, there is a delicate balance between parental values, patient assent, and objective measures of risk and benefit. All of these must be considered and held in perspective by research ethics committees. As evidenced by the Dutch chapter of the international organisation, Parent Project Muscular Dystrophy, families and patients are better informed and better connected with one another than ever before in history. As the ultimate stakeholders, members of this and other similar organisations for rare, serious and life-limiting diseases may have more influence on the design and conduct of clinical trials than they have had in the past. In situations such as muscular dystrophy, it will be harder and harder to maintain an inflexible framework of research ethics without taking into account the hopes of the patients and the burden of the disease on patients and families. It is my opinion that patients and families should be given a greater voice in the approval process for ethical research oversight. This needed change of the current standards will bring balance to the value of informed participation when risk cannot be completely avoided.

Without changes in current standards, we will not be able to do research on rare and fatal paediatrics diseases. We will never be able to test potentially curative treatments. Research ethics committees must allow higher risk studies when a

child faces a progressive disease for which treatment must be provided during childhood. The usual idea that research be done first in competent adults does not apply in these situations. The research must be done in children or it will not be done at all.

Children need to be protected from research risks. But the standard for judging those risks must be the risks associated with the child's underlying disease. Regulations should recognise that it may be quite rational for parents and patients to consent to clinical research on drugs that have never been tried in humans and thus that may have unforeseen and unforeseeable risks. Such research is best done in settings where patients can be closely monitored, where risks and benefits are carefully quantified, and where data safety monitoring boards do not allow studies to continue when there is evidence that they are not working. But the only way to know what will work and what will not is to allow responsible clinical research trials on important emerging therapeutics.

JOHN D. LANTOS

In most countries, laws and regulations governing biomedical research were developed without much input from the patients who would be the research subjects. In many cases, those patients (or their parents) are not very happy with the current regulatory systems. The most famous instance in which patients opposed the regulations (and ultimately changed them) was the early days of research on treatments for Acquired Immunodeficiency Syndrome. Today, many other patient groups are trying to change the rules that govern research. Research regulations should reflect the values and preferences of the people who participate in research. This shouldn't be a terribly radical suggestion. But current systems, both in the United States and in Europe, often fail by these criteria. Research participants have little input into the choice of study questions, the study design, data analysis, or publication of results. More importantly, they have little input into the regulations that will allow or prohibit them from participating in studies. Perhaps it is time to change those regulations in order to better reflect the preferences of the research participants.

FURTHER DEVELOPMENTS

The study generated promising results that were published in the *New England Journal of Medicine*.(5) Follow-up research was initiated, and the AON was given breakthrough therapy designation by the US Food and Drug Administration.

Notwithstanding this impressive track record, it was recently announced that a Phase III placebo controlled trial of Drisapersen did not show a clinically meaningful treatment difference between the active compound and the placebo for its primary endpoint showing clinical relevant improvement including a 12-minute walking test. Researchers and the company that manufactures the drug, plan further research with the compound.

EPILOGUE

This case, which resulted in opposing ethical review outcomes, evoked emotional reactions. This is not surprising. Duchenne Muscular Dystrophy is a relentless disease that has a huge impact on families. It is reasonable and understandable that DMD patients and their parents urgently wish for medical-scientific progress. The discussion in this chapter evolved for the greater part around taking the patient- and parent perspective into account during the ethical review process. While this is undoubtedly important, it has left some other important topics undiscussed. Those topics will be discussed in other chapters of this thesis.

The actual main ethical question that we intended to discuss in this case was whether the risks and burdens of this protocol were acceptable and why. Should the research risks and burdens, as several of the commentators suggested, have been compared to those usually encountered by this patient group, or should they be compared to an absolute standard of minimal risk and burden? Moreover, it seems that according to the Dutch REC (CCMO), not only the actual degree of burden was problematic, but also that the burden was not minimised. Another question relevant to the ethical review process was whether this protocol could have offered possible direct benefit to the participants. Precise assessment of the risks, burdens and benefits is needed to properly answer these questions. This topic will be discussed in chapter 6 of this thesis. Remarks on a relative or an absolute standard of minimal risk and burden are given in the general discussion of this thesis.

Secondly, after the risk-benefit assessment it may turn out that while the risks and/or burdens are higher than what the applicable law permits, the research project is so valuable and promising that it makes higher risks/burdens acceptable and should anyway be approved. It is important to create space for allowing such exceptions, but that should be done accurately and transparently. Also this topic is further discussed in the general discussion of this thesis.

In one of the commentaries the need for close monitoring of research participants was mentioned. Not only should monitoring focus on the safety of the participating children, but the voluntariness and the experienced burden should also be monitored. Obviously, this is important for all paediatric research. Yet it gains more importance once higher risks or burdens are accepted in exceptional cases. The need for proper guidance on monitoring children during research participation, as well as practical recommendations, is explicated in chapter 8. In the general discussion I reflect on making exceptions to the legal requirements for extra valuable and promising research.

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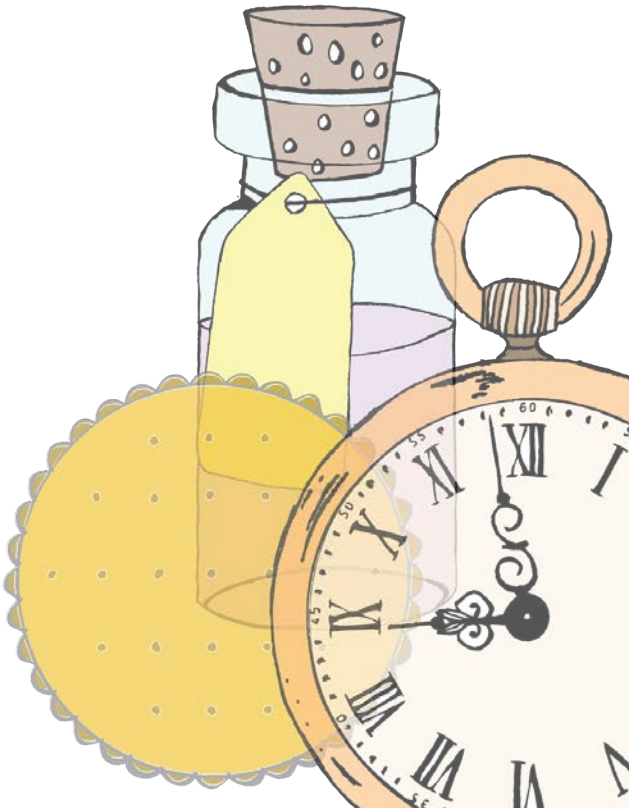
CHAPTER 4

CHILDREN AS VULNERABLE RESEARCH SUBJECTS

Karin Jongsma, Wendy Bos*, Suzanne van de Vathorst.
Morally Relevant Similarities and Differences between Children and Dementia Patients as Research Subjects: Representation in Legal Documents and Ethical Guidelines. Bioethics. 2015;29(9):662-70. *shared first authorship



ABSTRACT

Children and patients with dementia are both vulnerable populations. Both groups are also relatively seldom included in biomedical research. Still, including them in clinical trials is necessary, since both groups are in need for scientific innovation and new therapies. Their dependence and limited decision-making skills increase their vulnerability, necessitating extra precautions when including them in clinical trials. Beside these similarities there are also differences between the groups. The most obvious one is that children have an entire life ahead of them and will become persons with certain ideals and preferences, while adults with dementia have lived a life in which they have expressed their ideals and preferences. While some of the available research guidelines recognise these differences and set specific requirements for groups of incapacitated adults and others for children, other documents do not differentiate and only set requirements for subjects unable to consent as a single category of subjects. In this chapter we analyse to what extent the similarities and differences between the two groups are represented in legal documents and ethical guidelines. The chapter presents an overview and an analysis of the requirements for doing research with children and dementia patients. We conclude with suggestions about how to better incorporate the morally relevant aspects of these two groups in legislation and ethical guidelines.

INTRODUCTION

Children start their lives being dependent and without the capacities to make decisions. Adults who suffer from dementia, live their lives similarly being dependent and having limited decision-making capacities. In informal language the analogy between young children and people with dementia is frequently referred to. People with dementia are said to behave childlike, or to 'go back to childhood'.(1, 2) There are, however, profound differences between the two groups. The most obvious one being the fact that children have an entire life ahead of them and are expected to become persons with certain ideals and preferences, while people with dementia have lived an entire life and have expressed their ideals and preferences earlier on. Children are presumed to be (partly) incompetent by default, while for adults it has to be demonstrated that they are incompetent. Moreover, dependence on others is normal for children, as well as a temporary state. For the elderly dependence on others is a loss after having lived their lives independently.

One thing children and adults with dementia have in common is that medical research is highly needed for them.(3, 4) For many childhood diseases, as well as for dementia, no effective treatment exists and interactions with other medications are often unknown. Performing clinical trials on these groups is therefore absolutely necessary. At the same time the vulnerability of children and of dementia patients demands extra precautions when including them in research. The available legal documents and ethical guidelines regulating biomedical research therefore contain specific articles regulating research with incompetent populations. While some of the available laws and guidelines differentiate and set specific requirements for groups of incapacitated adults and other specific requirements for children, others do not differentiate and set generic requirements for all populations unable to consent.

In this chapter we will provide an overview of the relevant articles in international legal documents and ethical guidelines concerning biomedical research with children and incapacitated adults. By pointing out the few differences and many similarities between protective measures for these two groups, we will show that only some of the morally relevant differences between the groups are acknowledged in legislation and ethical guidelines. Furthermore, we will provide suggestions about how to better incorporate the morally relevant aspects in legislation and ethical guidelines, in order to better respect the dignity and well-being of these two groups of vulnerable research subjects.

METHODS: ANALYSIS OF LEGISLATION AND ETHICAL GUIDELINES

We selected eight influential legal and ethical documents that set rules or guidelines for conducting biomedical research with human subjects, and have focused on the articles that refer to subjects who are not able to provide informed consent. None of the guidelines state specific rules for dementia patients. They are included in the group of incapacitated adults, which also includes for example mentally disabled persons and persons in a coma. Table 1 shows an overview of the documents that we analysed, as well as their scope and legal status.

In each document we looked for articles addressing three topics related to the incompetence of children and dementia patients, namely 1) requirements for the consent procedure and dissent to participation, 2) the acceptability of risk and burden, and 3) protection during the trial including dissent to continue participation. All documents require that research with incompetent research subjects is group-related, meaning that research is only possible with this population and cannot be conducted with competent subjects. We will not elaborate any further on this requirement since it is fairly straightforward and the same in all selected documents.

Table 1: Overview of analysed documents

Document	Scope	Legal Status
Declaration of Helsinki	Medical research involving human subjects	No legal force, ethical guideline of global influence
Directive 2001/20/EC or Clinical Trials Directive	Clinical drug trials	Legally binding in all EU member states after implementation in national law
Clinical Trials Regulation	Clinical drug trials	Directly binding upon all EU member states without prior implementation. Expected to come into force in 2016

European Convention on Human Rights and Biomedicine or Oviedo Convention	Full range of research activities in the health field involving interventions on human beings	Applicable to those member states of the Council of Europe that have signed and ratified the convention
Guideline for Good Clinical Practice or ICH GCP guideline	Clinical drug trials	International ethical and scientific quality standard. No legal force directly, but incorporated in (inter)national laws
International Ethical Guidelines for Biomedical Research Involving Human Subjects or CIOMS guidelines	Biomedical research involving human subjects	Ethical guideline, no legal force
Medical Research involving Human Subjects Act or WMO (Dutch abbreviation)	All biomedical research involving human subjects, with specific requirements for drug trials (implementation of the Clinical Trials Directive)	National law in the Netherlands
US Code of Federal Regulations	Biomedical research involving human subjects	National law of the USA, no legal force in Europe but influential to European policymakers

OVERVIEW OF REQUIREMENTS IN LEGISLATION AND ETHICAL GUIDELINES

REQUIREMENTS FOR THE CONSENT PROCEDURE

The golden standard for acquiring a person's permission to be included in research is informed consent.(5) Clearly, incompetent persons cannot provide valid informed consent for research participation. All analysed documents require consent by a legal representative if the research subject himself cannot provide informed consent. The Dutch WMO and the European Clinical Trials Directive specifically mention that the consent of the legal representative should reflect the presumed will of the research subject.

In addition to the consent of the legal representative, assent of the research subject is sometimes required. Assent can be understood as the incompetent participants' agreement to participate in the trial and does not require full understanding of the study and the consequences of participation; therefore it does not have the same status as informed consent. What exactly assent is, is not always clear, as it is formulated diffusely in the analysed documents. An explicit or implicit refusal to participate in a trial is called dissent. Table 2 shows the relevant articles for the requirements for proxy consent, assent and dissent, and their exact wording.

The Declaration of Helsinki requires seeking assent for all groups of incompetent research subjects.(6) The ICH GCP states that for all groups who cannot provide informed consent 'the subject should, if capable, also sign and personally date the written informed consent'.(7) There is no further explanation of the meaning of this requirement; therefore it remains unclear whether this should be considered as assent. The other documents differentiate between incapacitated adults and children. Only some of the documents ask for the child's assent when possible.(8-12) The CIOMS guidelines, the Oviedo Convention and the US Code of Federal Regulations recognise the growing capacities and maturity of children throughout their childhood. Moreover the US Code of Federal Regulations states that the assent should actively be given and not merely result from failure to object. The Clinical Trials Directive and the Clinical Trials Regulation both set specific requirements for the adaption of information about the trial to the age and level of maturity of children, by investigators trained or experienced in working with children.(13, 14) The Clinical Trials Regulation and the CIOMS guidelines require that in case the minor reaches the age of legal competence to give informed

consent during the research trial, informed consent then has to be obtained from them.

Regarding incompetent elderly, the documents that do differentiate between children and incapacitated adults, have the prerequisite that the incapacitated adult takes part in the authorisation process as far as possible (Oviedo Convention) or according to his capabilities (CIOMS guidelines). Both the Clinical Trials Directive and the Clinical Trials Regulation state that research with incapacitated subjects is 'only allowed if they have given, or have not refused to give, informed consent before the onset of their incapacity'. This can be interpreted as having to respect the wish of the research participant who was formerly competent to consent or to dissent to research participation. That would imply that this requirement is only set for adults who previously have been able to make competent decisions and not for adults who have never been competent in the first place. In addition, the Clinical Trials Regulation states that 'incapacitated adults will receive information about the trial in view of their capacity to understand it' and that 'the subject shall as far as possible take part in the informed consent procedure'. Interestingly, both the Dutch WMO and the US Code of Federal Regulations differentiate between children and incapacitated adults, and require the assent of children, but not of incapacitated adults.

With respect to dissent to research participation, the Declaration of Helsinki states that dissent should be respected. This requirement applies to all groups of incompetent research subjects. The Clinical Trials Directive states that the explicit wish of both a minor and of an incapacitated adult 'who is capable of forming an opinion and assessing this information to refuse participation (…) from the clinical trial (…) is considered by the investigator or where appropriate the principal investigator'. In the Clinical Trials Regulation the wording was changed from 'considered' to 'respected'. The CIOMS guidelines state that a child's refusal to participate should always be respected, while it states for incapacitated adults that in exceptional cases the refusal to participate may be overruled.

Table 2: Requirements for the consent procedure

	Consent by a legal representative	Assent/dissent of minor	Assent/dissent of incapacitated adults
Declaration of Helsinki	Informed consent from the legally authorised representative (art. 27)	When able to, assent [..] dissent should be respected (art. 29)	When able to, assent [..] dissent should be respected (art. 29)
ICH GCP	Consent by the subject's legally acceptable Representative (art. 4.8.8)	The subject should, if capable also sign and personally date the written informed consent (art. 4.8.12)	The subject should, if capable also sign and personally date the written informed consent (art. 4.8.12)
Clinical Trials Directive	The informed consent of the legal representative has been obtained; consent must represent the subject's presumed will (art. 4a & 5a)	The explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation [..] is considered by the investigator or where appropriate the principal investigator (art. 4c)	Inclusion in clinical trials of incapacitated adults who have not given or not refused informed consent before the onset of their incapacity (art. 5) The informed consent of the legal representative has been obtained; consent must represent the subject's presumed will [..] (art. 5a) The explicit wish of a subject who is capable of forming an opinion and assessing this information to refuse participation [..] is considered by the investigator or where appropriate the principal investigator (art. 5c)

Clinical Trials Regulation	Consent by a legal representative (art. 31.1a & art 32.1a)	The minors have received the information about the trial 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 (art. 32.1b) The minor shall take part in the informed consent procedure in a way adapted to his or her age and mental maturity (art. 32.2) In case the minor reaches the age of legal competence to give informed consent, during the research trial his or her express informed consent has to be obtained (art. 33.2)	Research with incapacitated subjects is only allowed if they have not given, or have not refused to give, informed consent before the onset of their incapacity (art. 31) The incapacitated subjects have received the information about the trial in a way adapted in view of their capacity to understand it (art. 31.1b) The subject shall as far as possible take part in the informed consent procedure (art. 31.3)
Oviedo Convention	Authorisation by a legal representative (art. 6.2 & 6.3)	The opinion of the minor shall be taken into consideration as an increasingly determining factor in proportion to his or her age and degree of maturity (art. 6.2)	The individual concerned shall as far as possible take part in the authorisation procedure (art. 6.3)

CIOMS guidelines	Consent by a parent or legal representative is given (Guidelines 14 & 15)	If such research subjects, including children, become capable of giving independent informed consent during the research, their consent to continued participation should be obtained (Guideline 9) Agreement of each child has been obtained to the extent of the child's capabilities (Guideline 14)	The consent of each subject has been obtained to the extent of that person's capabilities. (Guideline 15)
WMO	Written consent of the subject's parents or legal guardian (art. 6.1.c) The substitute consent [..] must represent the presumed will of the subject (art. 6.3)	Assent is required only if child is older than 12 years of age (art. 6.1b)	
US Code of Federal Regulations	The investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative (45 CFR 46.116) Adequate provisions are made for soliciting the permission of each child's parents or guardian (45 CFR §46.408)	Children capable of assenting must also express their willingness to participate (45 CFR §46.408) Failure to object should not, absent affirmative agreement, be construed as assent (45 CFR 46.402(b))	

ACCEPTABILITY OF RISK AND BURDEN

To protect incompetent populations against disproportionate harm, specific protective rules regarding the acceptability of risk and burden in research trials have been formulated. The concept of risk is understood to refer to the combination of the probability and magnitude of some future harm.(15) A distinction can be made between research offering direct benefit to the participant (therapeutic research), and research that is unlikely to provide any direct benefit to the participant (non-therapeutic research). If the research is non-therapeutic, the general idea is that the research should contain no more than minimal risks and burden. If the research is therapeutic, all documents state that the benefits must outweigh the risks, as they also do for therapeutic research with competent adults. The requirement that research can be justified on the basis of a favourable risk/benefit assessment bears a close relation to the principle of beneficence.(5)

Table 3 shows how exactly the requirements for accepting risks and burden in non-therapeutic trials are formulated. Most, though not all, documents allow for non-therapeutic research with incompetent subjects when the risks and burden are no more than minimal. The Clinical Trials Directive, however, does not make any distinction between therapeutic and non-therapeutic research and thereby does not set any upper limit for risk and burden for non-therapeutic research with children. All it requires is minimisation of risk and burden. For incapacitated adults however, research should either have a prospect of direct benefit to the group of patients, or, in case no such benefit is expected, produce no risk at all. It remains unclear why the distinction between therapeutic and non-therapeutic research only applies to incapacitated adults and not to children, as well as why, compared to research with incapacitated adults, higher levels of risk and burden would be acceptable for research with children.

Some documents (the Declaration of Helsinki, the Clinical Trials Regulation and the Oviedo Convention) allow for non-therapeutic research with incompetent subjects when the risk and burden are no more than minimal. Similar requirements, such as negligible risk, minimised and low risk and a minor increase over minimal risk are found in other documents (WMO, ICH-GCP, US Code of Federal Regulations). The exact wordings can be found in table 3. The US Code of Federal Regulations does not provide any protective upper risk limits for research with incapacitated adults (while it does for minors). On the contrary, the Clinical Trials Directive sets stricter rules with respect to risks and burden for non-therapeutic research with incapacitated adults than for research with children. Research with

incapacitated adults is only allowed when there is a prospect of benefit outweighing the risks or when it produces no risk at all.

Children and dementia patients are both vulnerable populations with limited decision-making capacities. It remains unclear what the basis would be for accepting different levels of risks and burden for the two groups of research subjects, as the Clinical Trials Directive and the US Code of Federal Regulations do. In our view, there are no relevant differences between these groups that could justify these differences in accepting risks and burden.

Table 3: Requirements for non-therapeutic research

	Children	Incapacitated adults
Declaration of Helsinki	Minimal risk and minimal burden (art. 28)	Minimal risk and minimal burden (art. 28)
ICH GCP	The foreseeable risks to the subjects are low (art. 4.8.14.b) Negative impact on persons well-being is minimised and low (art. 4.8.14.c)	The foreseeable risks to the subjects are low (art. 4.8.14.b) Negative impact on persons well-being is minimised and low (art 4.8.14.c)
Clinical Trials Directive	Some direct benefit for the group of patients is obtained from the clinical trial [..] (art. 4e)	There are grounds for expecting that administering the medicinal product to be tested will produce [..] or produce no risk at all (art. 5i)
Clinical Trials Regulation	Minimal risk and minimal burden (art. 32.g.ii)	Minimal risk and minimal burden (art. 31.g.ii)
Oviedo Convention	Minimal risk and minimal burden (art. 17.ii)	Minimal risk and minimal burden (art. 17.ii)
CIOMS guidelines	Risks are no more likely and not greater than the risk attached to routine medical or psychological examination of such persons. Slight or minor increases above such risk may be permitted when there is an overriding scientific or medical rationale for such increases and when an ethical review committee has approved them (Guideline 9)	Risks are no more likely and not greater than the risk attached to routine medical or psychological examination of such persons. Slight or minor increases above such risk may be permitted when there is an overriding scientific or medical rationale for such increases and when an ethical review committee has approved them (Guideline 9)
WMO	Negligible risks and minimal burden (art. 4)	Negligible risks and minimal burden (art. 4)
US Code of Federal Regulations	Minimal risks (§46.404) or the exception of a slight or minimal increase over minimal risk (§46.406)	

PROTECTION DURING THE TRIAL - MONITORING AND WITHDRAWAL

Competent research subjects always have the possibility to withdraw their consent at any time, for whatever reason. Incompetent research subjects do not have this option, as they could not consent in the first place. They therefore depend on others for protecting their well-being during the trial. In this paragraph we discuss protective measures that aim to safeguard the well-being of incompetent subjects during the performance of the trial. They can roughly be categorised into monitoring the risk and burden and the obligation to withdraw a subject from a trial when necessary. If the subject is capable of expressing his wish to discontinue participation, in other words objects to further participation, this wish should be respected; in the guidelines this is also called dissent. Dissent in this context means 'the wish to discontinue participation' and is not the opposite of consent or assent prior to inclusion. The measures being discussed in this paragraph appeal to the principles of respect for autonomy (even if this autonomy is underdeveloped or partly diminished) and of non-maleficence.(5) Table 4 shows the articles relating to these two categories.

The need for monitoring the risks and burdens for research subjects seems to be obvious and important (ICH GCP, Clinical Trials Directive, Clinical Trials Regulation, WMO), however, not all analysed documents have explicit rules for this. In order to provide sufficient protection for vulnerable research subjects, one needs to be sure that the level of risk and burden does not exceed the level that was found acceptable during the reviewing procedure. Only the ICH GCP guidelines state explicitly what the consequence of monitoring should be. Namely, subjects should be withdrawn if they appear unduly distressed. Monitoring should aim to protect the research subject against unexpected disproportionate harm. Withdrawing subjects who are unduly harmed or distressed, thus seems to be a logical consequence.

Most documents set requirements for subjects who want to discontinue their participation in research. The Declaration of Helsinki stipulates that dissent should be respected. The Oviedo Convention phrases this slightly differently, mentioning that research may only be performed when 'the subject does not object'. Further elaboration on how to interpret 'objection' is lacking. The Dutch WMO states for both incapacitated adults and children that, should they 'object (…) the person in question will be excluded from participation'. How to respond to signs of objection is written in accompanying codes of conduct. There are separate codes for research with children, with incapacitated elderly persons and with mentally

disabled persons.(16-18) The US Code of Federal Regulations itself has no requirements of this kind, but the accompanying guidebook for IRBs states that the child's dissent should normally be respected. Only in cases of 'research that offers the child the possibility of a direct benefit that is important to the health or well-being of the child and is available only in the context of the research, (...) a child's dissent, which should normally be respected, may be overruled by the child's parents, at the IRB's discretion.(15)

The Clinical Trials Directive states that the explicit wish of a minor and incapacitated subject 'who is capable of forming an opinion and assessing 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'. In the Clinical Trials Regulation the wording is changed from 'considered' to 'respected', which makes the requirement slightly stricter. Only the CIOMS guidelines differentiate between requirements for children and incapacitated adults. Whereas the CIOMS guidelines state that a child's refusal to continue participation should always be respected, the CIOMS guidelines do allow overruling refusal of incapacitated adults in exceptional cases. It remains unclear on what ground this differentiation is based.

Table 4: Protection during the trial

	Monitoring	Withdrawal
Declaration of Helsinki		The potential subjects dissent should be respected (art. 29)
ICH GCP	Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed (art. 4.8.14)	Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed (art. 4.8.14)
Clinical Trials Directive	The risk threshold and degree of distress are closely monitored (art. 3g)	The explicit wish of a minor/incapacitated subject who is capable of forming an opinion and assessing 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 (art. 4c & 5c)
Clinical Trials Regulation	The risk threshold and the degree of distress are specifically defined in the protocol and constantly monitored (art. 28.1.e)	The explicit wish of an incapacitated subject/ minor who is capable of forming an opinion and assessing 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' or where appropriate the principal investigator (art. 31.1c & 32.1c)
Oviedo Convention		The person concerned does not object (art. 17.1.v)

CIOMS guidelines		For children: Refusal to participate or continue participation should always be respected (Guideline 14) For incapacitated adults: a prospective subject's refusal to participate in research is always respected, unless, in exceptional circumstances, there is no reasonable medical alternative and local law permits overriding the objection (Guideline 15)
WMO	The risk threshold and the degree of distress have to specially defined and constantly monitored' (art. 13.e.c), only for clinical trials	Should an incompetent research subject object to the treatment administered or behavioural strategy imposed, the person in question will be excluded from participation (art. 4.2)
US Code of Federal Regulations		In cases of research that offers the child the possibility of a direct benefit that is important to the health or well-being of the child and is available only in the context of the research, [..] a child's dissent, which should normally be respected, may be overruled by the child's parents, at the IRB's discretion' (IRB guidebook chapter 6)

DISCUSSION

The wide variety of requirements found in legal and ethical guidelines concerning medical research with vulnerable groups of research subjects, shows that the morally relevant particularities of the different groups are not always acknowledged. Children and dementia patients are morally similar in some respects, but rather different in others. Table 5 shows which documents differentiate between children and incapacitated adults and which documents do not. Besides some noteworthy differences between the groups of incapacitated adults and children, we have seen that there are a great number of legal documents and ethical guidelines with a variety of rules for conducting research with groups of incompetent participants. The variation in these documents may hinder the guiding function these documents aim to provide. Both ethical guidance of research trials and the adequate protection of research subjects are not served by a multitude of requirements.

SIMILARITIES

Children and dementia patients both form vulnerable populations. They have reduced capacities to protect themselves from harm, and deserve additional protection against disproportionate harm in research. Beside their vulnerability they share the characteristic of having limited decision-making capacity. Their (partial) incapacity to make decisions is, however, not a permanent condition. The gradual process of either gaining or loosing autonomy is an important similarity between the two groups. For both children and dementia patients, there is a phase in which they are not yet, or not anymore, fully capable of deciding about research participation. People in a state of partial incapacity to decide need guidance or assistance in decision-making. Requiring proxy consent combined with the assent of the person concerned for participation in research would respect this state of partial decision-making incapacity. In our overview we showed that respect for the gradual process of gaining or loosing autonomy is expressed in some, but not all discussed documents. We argue that a phase of shared decision making is equally important and feasible for subjects who loose their decision-making capacity, as it is for subjects who are gaining competence, and that it should be a requirement for the research participation of both children and incapacitated adults.

Table 5: Legal documents and ethical guidelines with different/similar requirements for children and incapacitated adults.

	Documents that set different requirements for children and incapacitated adults	Documents that set the same requirements for children and incapacitated adults, or make no distinction between the two groups
Assent	Clinical Trials Directive Clinical Trials Regulation Oviedo Convention WMO US Code of Federal Regulations	Declaration of Helsinki ICH GCP CIOMS guidelines
Acceptability of risks and burden in non-therapeutic trials	Clinical Trials Directive US Code of Federal Regulations	Declaration of Helsinki ICH GCP Clinical Trials Regulation Oviedo Convention CIOMS guidelines WMO
Monitoring burden		ICH GCP Clinical Trials Directive Clinical Trials Regulation WMO
Withdrawal/dissent	CIOMS guidelines US Code of Federal Regulations	Declaration of Helsinki ICH GCP Clinical Trials Directive Clinical Trials Regulation Oviedo Convention WMO

With respect to the acceptability of risk and burden, there is no good reason for not providing elderly patients with the same level of protection as children. As for respect for dissent, one could even argue that signs of resistance and expressions of dissent should be taken more seriously in dementia patients than in children. Children are dependent beings by default, and are used to have decisions being taken for them, whereas elderly people might experience embarrassment and humiliation when things do not go according to their choice and their wish is not taken seriously enough. Such differences between children and dementia patients are morally relevant when it comes to how to treat them as research subjects, but are not represented in any of the analysed documents.

DIFFERENCES

Despite the similarities between the two groups, there are also profound differences that are morally relevant. In our view, the most important difference is the fact that children have not yet (fully) formed preferences and wishes, whereas dementia patients have formerly lived independent lives and have had the chance to express their wishes earlier on. Interestingly, only two of the documents we analysed have a special requirement that appeals to the prior wishes of incapacitated adults. Only the European Clinical Trials Regulation and the European Clinical Trials Directive require that the incapacitated adult has given or not refused to give informed consent before the onset of their incapacity. Possibly this is because there are no specific articles concerning dementia patients, as they fall under the broader category of incapacitated adults. We recommend taking into account formerly expressed wishes of dementia patients when possible, for example by means of advance directives specified for research participation. Dementia patients differ from some other groups of incompetent adults, for example mentally disabled persons, who have never been competent. It might be unfeasible to set requirements that do justice to the particularities of all groups of incapacitated adults. In order to respect the past autonomy of dementia patients, it is however necessary to treat them as a separate group, not as a part of the larger group of incapacitated adults or of incompetent persons in general (including children).

Children are in the process of becoming autonomous beings, and should be treated as such. Even though their growing capacities are recognised by requiring assent when possible, only two of the documents require the consent of the child as soon as it reaches the legal age of competence. However, in long-term research studies, children may become competent during the study. From the discussed documents, only the Clinical Trials Regulation and the CIOMS guidelines require explicitly that a child should be asked for his/her consent when he/she becomes competent during the trial. This may be a relatively rare situation, but it is nonetheless important to assure correct consent practices in these cases as well. We recommend that legislation and guidelines require the consent process to be repeated once a participating child reaches legal age during the performance of the research study.

We have shown that children and dementia patients are morally similar in some respects, and different in others. These particularities should be reflected in legal documents and ethical guidelines concerning biomedical research. In our view, the

extra protective measures we suggest, contribute to better respecting the morally relevant particularities of both groups of research subjects.

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CHAPTER 5

THE NEW EU CLINICAL TRIALS REGULATION

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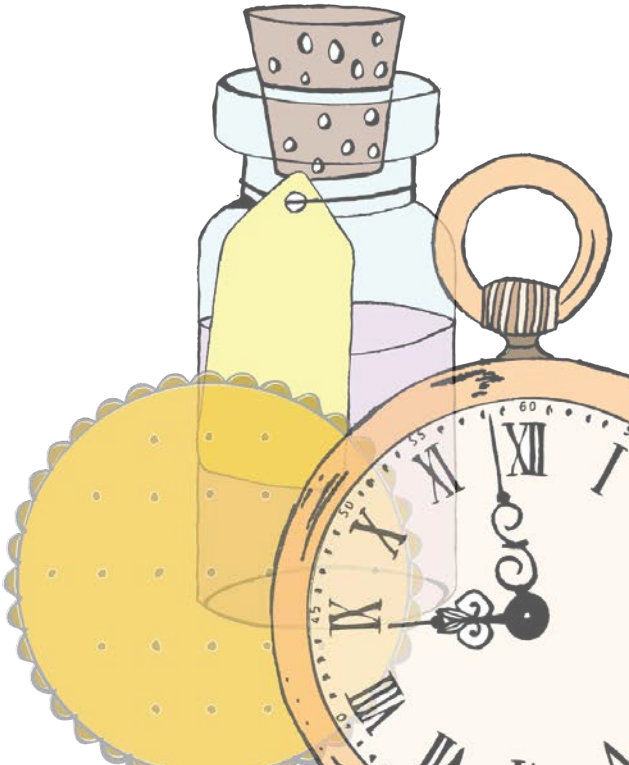
New EU clinical trials regulation.
BMJ (Clinical research ed). 2014;348:g3710.



On 2 April 2014, the European Parliament approved the new European Union Clinical Trials Regulation.(1) This regulation will replace the Clinical Trials Directive, which has failed to achieve its goal of simplifying the scientific and ethical review of clinical trials in the EU.(2, 3) Unlike the directive, the regulation has binding legal force in all EU member states. Important innovations include a central database and a partly coordinated review system. Both of these steps could help simplify the review system and improve the quality of assessments.

However, when it drafted the regulation, quality improvement did not seem to be the European Commission's main concern. Despite serious criticisms and several adjustments, the approved document may still impair, rather than improve, the quality of the ethical review of trial protocols.(4-9) This puts the protection of European research subjects at risk.

Before discussing our two main concerns, we need to explain the new review system. Currently, all member states assess the request for authorisation of a multinational clinical trial independently of one another. To simplify and speed up authorisation, the European Commission has decided that the risk-benefit assessment (and the preceding scientific assessment) should be performed in a coordinated manner.(5, 9) With this in mind, sponsors propose one member state to be the reporting one, and this member state makes the final decision on the risk-benefit assessment. The other member states are asked for their input, but within a very tight time frame. Their main task is to assess the ethical and local aspects, such as the informed consent material, the investigators' qualifications, and the suitability of the trial site, for their own territory. Thus, two types of assessment run in parallel: the coordinated risk-benefit assessment (by the reporting member state, binding on all member states), and the assessment of the ethical and local aspects mentioned above (by all member states acting individually).

We approve the idea of coordinating the assessment of multinational clinical trials. However, in the case of such centralised judgments, the quality of these judgments should be guaranteed. This is not the case.

We are mostly worried about the risk-benefit assessment being taken out of the ethical domain. The European Commission fails to acknowledge that this assessment is widely regarded as a crucial part of ethical review.(10) As a result, the regulation does not require input from an ethics committee.(9) This is worrying because the purpose of ethics committees is to focus on the protection of potential research subjects. This perspective is indispensable when the risks of

harm and potential benefits of a clinical trial are being assessed. It is worth noting that studies may be ethically unacceptable, despite having a scientifically favourable harm-benefit balance, if the research question could be answered with fewer risks or burdens for the research subjects.

Furthermore, some studies have a favourable harm-benefit balance because of the expected benefits for society but are not expected to benefit the research subjects themselves. Such studies should be evaluated very carefully, particularly when they involve children or others who are considered unable to provide informed consent.(10) The regulation provides guidelines for research in these groups, but applying these guidelines appropriately requires specific ethical expertise.(9) Ideally, a multidisciplinary committee with wide ethical expertise should critically assess the risks and potential benefits and demand changes in the design when needed.

A complicating factor is that sponsors are free to choose the reporting member state. This might tempt sponsors to choose member states that are known for their less onerous assessments. Thus, when aiming for high quality review, the question of which body should perform the risk-benefit assessment cannot be left to the member states' own discretion.

Our second concern relates to the quality of the ethics committees. During the first public consultation round many respondents asked for quality standards and an accreditation system for these committees,(4) but the European Commission has ducked this request—a truly missed opportunity. This is because even though ethical matters are regarded as a national affair, the new regulation would provide a great opportunity for improving the widely varying quality of the EU's ethics committees by setting clear quality standards.(11) Leaving these committees just as diverse as before means that European citizens of different member states cannot rely on the same level of protection. Moreover, if ethics committees are also involved in the coordinated risk-benefit assessment, which we have just argued for, every opportunity to improve their quality should be taken. The judgment of the ethics committee of the reporting member state will then cover the protection of the research subjects in all member states.

We recognise that it will be difficult to make substantial changes to the new regulation now that it has been approved. However, it is wrong to rush through a system that is clearly inadequate. European research subjects deserve a clinical trials regulation that has a sound ethical basis. Therefore, we recommend that this new legislation is adjusted before coming into force.

In practical terms, we recommend that the ethics committee of the reporting member state should be assigned as the key figure in an integrated risk-benefit assessment system. In addition, this committee should be allowed enough time to take scientific advice from experts and to cooperate effectively with the ethics committees of the other member states. Lastly, a quality and accreditation system should be established for all ethics committees so that all trials are reviewed by competent committees.

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CHAPTER 6

A PROCEDURE-LEVEL APPROACH TO THE RISK-BENEFIT ASSESSMENT

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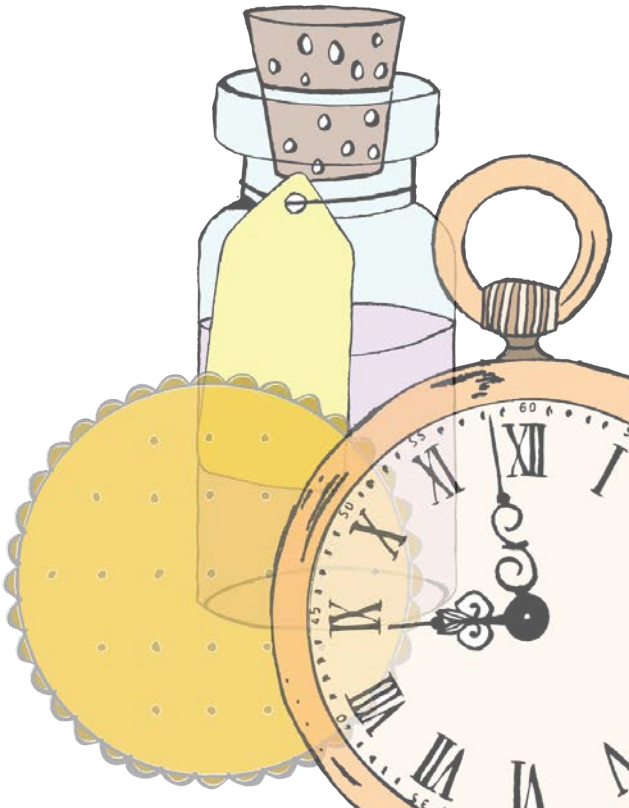
Submitted



ABSTRACT

Background: Paediatric research protocols often consist of a combination of procedures *with*-, and procedures *without* the prospect of direct benefit (i.e. only for research purposes). However, the risks and anticipated benefits of a study are usually reviewed for the protocol as a whole. Our primary objective was to assess how frequently paediatric research protocols consist of a combination of procedures *with*-, and procedures *without* the prospect of direct benefit. A secondary objective was to identify possible practical drawbacks of a procedure-level approach for RECs, which could impede the implementation of this method.

Methods: 36 protocols labelled and reviewed as *with*-, and 36 protocols labelled and reviewed as *without* the prospect of direct benefit were analysed. For the secondary research question group discussions were held with research ethics committees.

Results: Of the 36 protocols labelled *without* the prospect of direct benefit, in 15 cases the study intervention was found to potentially benefit the participants (besides containing several procedures conducted for research purposes only). Of the 36 protocols labelled *with* the prospect of direct benefit, 34 were found to contain procedures that were done solely for research purposes (in addition to the potentially beneficial study intervention). Remarks during the group discussions included the extra time and special expertise the methods would require during the review process, as well as the need for a clear format and definitions.

Conclusions: Most paediatric research protocols include both procedures *with*, and procedures *without* direct benefit. A procedure-level approach may improve ethical review by doing more justice to the complexity of protocols. We propose a new definition of direct benefit, needed to distinguish between procedures *with*- and *without* the prospect of direct benefit.

INTRODUCTION

Including children in medical research requires sensitive and careful ethical review of the risks and burdens involved. The reason is that children are vulnerable and not (fully) able to freely and deliberately choose to participate in research.(1) It is crucial to assess whether research protocols entail any potential direct benefits for the participants that can compensate for the risks and burdens.(1, 2) In the absence of direct benefit stricter requirements apply with regard to the permitted levels of risk and burden.(3-5)

Usually the risks and benefits of a study are assessed for protocols as a whole. But in practice research protocols often consist of a combination of procedures conducted purely for research reasons, and procedures that might also directly benefit the participants.(6) For example, participation in interventional drug research may offer potential direct benefit to the subjects by administering a new drug, but frequently also involves undergoing extra procedures for the purpose of data collection. These two types of procedures require a different moral evaluation. Procedures that are done solely for generating data should involve no more than minimal risk and burden, whereas for procedures that offer potential direct benefit, the risks and burdens should be proportional in relation to the anticipated benefit. If such complex research protocols are classified *in totality* as offering direct benefit, research ethics committees (REC) may not assess them sufficiently critically. As a result, children may be exposed to undue risks and burdens. And vice versa, when reviewing protocols *in totality* as not offering potential direct benefit, RECs may reject protocols unnecessarily.

To tackle this problem, several ethicists have proposed to shift the primary focus in the risk-benefit assessment from the protocol as a whole, to the separate procedures within the protocol.(6-9) These procedure-level approaches, as we call them, focus on assessing the risks/burdens and potential benefits of the separate procedures before making an overall risk-benefit assessment for the study in total. Figure 1 provides a graphic representation of a procedure-level approach.

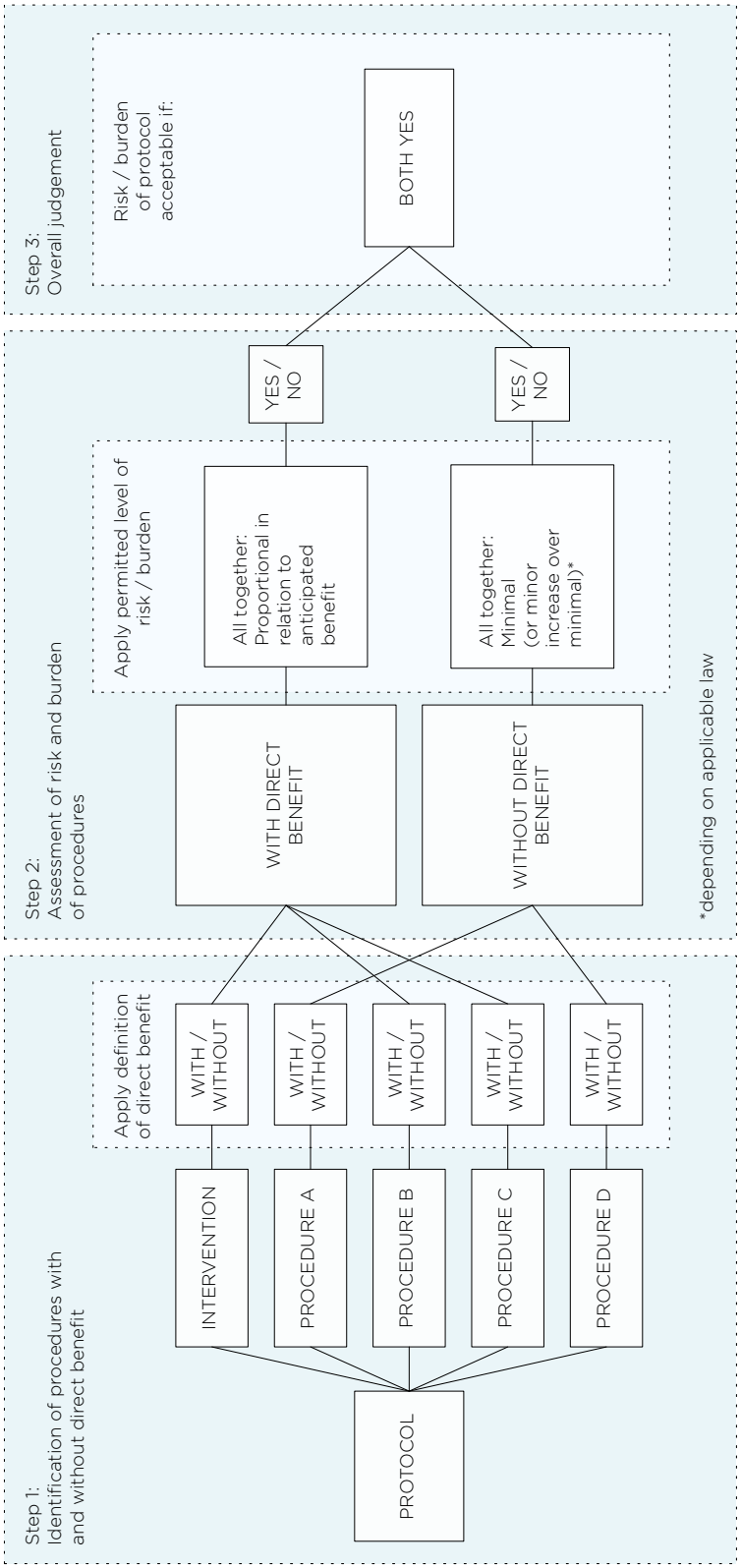


Figure 1: Schematic overview of the three steps in the procedure-level approach

So far, only the new and yet to be approved CIOMS-guidelines clearly state that RECs must focus on separate procedures first. In paragraph 4 it is stated that "The risks and potential benefits of each individual research intervention or procedure in the study must first be evaluated. Then, in a second step, the aggregate risks and potential benefits of the entire study must be assessed and must be considered appropriate".(10) However, neither the recently revised Declaration of Helsinki, nor the new European Clinical Trials Regulation makes any reference to a procedure-level focus.(3, 11) The US Code of Federal Regulations is ambiguous, as it speaks in some paragraphs of intervention or procedure and in others of study.(4)

AIM

With this paper we aim to give insight into the need for and feasibility of a procedure-level approach. Our primary objective was to assess how frequently paediatric research protocols consist of a combination of procedures *with*-, and procedures *without* the prospect of direct benefit. A secondary objective was to identify possible practical drawbacks for RECs, which could impede the implementation of this method.

METHOD

CONCEPTS AND DEFINITIONS

The data analysis in this study relies on the chosen definitions of the used concepts. We used the following definitions.

- *Procedure* is used as an umbrella concept for all separate parts of a clinical study, including the studied interventions.
- By *procedure-level approach* we mean a risk-benefit assessment that focuses first on each separate procedure, instead of a primary focus on the protocol as a whole.
- By *procedures without the prospect of direct benefit* we mean procedures performed for data collection purposes; i.e. procedures that are not also in the medical interests of the participants. By *procedures with the prospect of direct benefit*, we mean procedures that may also directly benefit the participants. These definitions are most common in the guidelines and literature; terms like (non-)therapeutic or (non-)beneficial are more

controversial and therefore avoided. We use the same terminology for the full protocols; but this classification depends on the RECs that labelled and reviewed these protocols.

- In our analysis we used the most common and rather general definition of *direct benefit*, namely; medical benefit that can reasonably be expected and is caused directly by a procedure in the study. It is broadly accepted that other types of benefit, such as collateral benefit, indirect benefit, aspirational benefit and inclusion benefit, should not count as direct.(12-15)

PILOT

A pilot study was done in which we analysed four research protocols labelled *without* the prospect of direct benefit. We designed a case-record form to collect data from the protocols and adjusted it after the pilot study.

DATA COLLECTION

In the Netherlands RECs are supervised by a central committee (named CCMO) that reviews protocols that require special expertise, among them paediatric intervention studies *without* the prospect of direct benefit. We selected all 106 files of the paediatric intervention studies in the database of the CCMO from the years 2006-2012. We excluded 1) protocols that had not been reviewed by the CCMO (for example because the researchers retracted them, or because they were passed on to another REC), 2) protocols that did not concern drug trials, vaccination trials, nutrition trials, diagnostic trials or surgical trials, 3) protocols that were rejected for reasons like poor quality or incompleteness, 4) protocols of which the researchers objected against us having access to their files and 5) protocols labelled and reviewed *with* the prospect of direct benefit (that were reviewed by the CCMO either because they required special expertise, or because they were labelled protocols *with* direct benefit later on in the review process). This resulted in a selection of 36 files. We selected an equal amount of paediatric protocols *with* the prospect of direct benefit (36 files) reviewed during the same period of time, from 3 of the 23 local Dutch RECs (these are qualified for reviewing paediatric protocols *with* the prospect of direct benefit), namely the committee of the Leiden University Medical Centre in Leiden, the MEC-U in Nieuwegein and the committee of the Erasmus University Medical Centre in Rotterdam. We signed a confidentiality agreement before starting data collection.

ANALYSIS

The first research question was how frequently protocols consist of a combination of procedures *with*- and procedures *without* the prospect of direct benefit. Initially, WB analysed the protocols labelled *with* the prospect of direct benefit and AW analysed the protocols labelled *without* the prospect of direct benefit. Both analysed complex cases in either category.

In the protocols labelled *without* the prospect of direct benefit, we identified the procedures that could potentially provide direct benefit for the participants. We limited ourselves to identifying the *possibility* of a direct benefit and did not judge whether the possible benefit could compensate for the risk and burden involved, as this is the next step in the risk-benefit assessment.

For the protocols that were labelled *with* the prospect of direct benefit, we first looked for procedures that the researchers reported in the application form as not offering the prospect of direct benefit. We also checked every intervention that was the object of study, to see whether these study interventions could indeed provide any direct benefit, as the researchers claimed.

GROUP DISCUSSIONS

Our second research question was whether REC members would see practical drawbacks that could impede implementation of the procedure-level approach. To explore this question, we met with two Dutch RECs as well as with the assembly of chairmen of all accredited RECs in the Netherlands. After presenting our results, we asked REC members what they would need to implement a procedure-level approach in their review process. The practical applicability and feasibility of a procedure-level approach were discussed. The group discussions, which had an explorative character, were recorded and the mentioned concerns and ideas were collected.

Table 1: Characteristics of protocols

	Protocols with prospect of direct benefit (36) N (%)	Protocols without prospect of direct benefit (36) N (%)	Total (72) N (%)
Type of intervention			
Drug	30 (83)	15 (42)	45 (63)
Vaccination	1 (3)	3 (8)	4 (6)
Nutrition	2 (6)	10 (28)	12 (17)
Diagnostic	1 (3)	8 (22)	9 (13)
Surgical	2 (6)	0 (0)	2 (3)
Phase			
I	0 (0)	7 (19)	7 (10)
I / II	3 (8)	3 (8)	6 (8)
II	3 (8)	1 (3)	4 (6)
II / III	1 (3)	0 (0)	1 (1)
III	15 (42)	0 (0)	15 (21)
IV	5 (14)	1 (3)	6 (8)
Not applicable	6 (17)	23 (64)	29 (40)
Other research that involves drugs	3 (8)	1 (3)	4 (6)
Age of participants			
Premature / preterm neonates	3 (8)	2 (6)	5 (7)
Term neonates	6 (17)	5 (14)	11 (15)
1 - 23 months	9 (25)	13 (36)	22 (31)
2 - 5 years	12 (33)	14 (39)	26 (36)
6 - 8 years	18 (50)	18 (50)	36 (50)
9 - 11 years	20 (56)	21 (58)	41 (57)
12 - 15 years	20 (56)	22 (61)	42 (58)
16 - 18 years	18 (50)	17 (47)	35 (49)
unspecified	4 (11)	1 (3)	5 (7)
Health status			
Having / at risk for the disease studied	36 (100)	28 (78)	64 (89)
Not having / at risk for the disease studied	0 (0)	6 (17)	6 (8)
Unknown	0 (0)	2 (6)	2 (3)
Number of participants			
1 - 10	0 (0)	4 (11)	4 (6)
11 - 20	0 (0)	11 (31)	11 (15)
21 - 40	6 (17)	7 (19)	13 (18)
41 - 75	7 (19)	1 (3)	8 (11)
76 - 100	6 (17)	5 (14)	11 (15)
101 - 250	9 (25)	4 (11)	13 (18)
250 +	8 (22)	4 (11)	12 (17)
Ethics approval			
Positive	32 (89)	25 (69)	57 (79)
Negative	2 (6)	10 (28)	12 (17)
Not yet approved at time of data collection	2 (6)	1 (3)	3 (4)

Many protocols included children from various age groups; therefore the sum of the percentages is more than 100%.

RESULTS

PROTOCOLS: GENERAL CHARACTERISTICS

The characteristics of the analysed protocols are presented in table 1. Of the 72 protocols 45 were drug trials, 12 were nutrition trials, 9 were diagnostic trials, 4 were vaccination trials and 2 were surgical trials. The majority of the studies (89%) were carried out with children who either had the disease studied or were at risk for the disease. Children between the ages of 9 and 15 were represented most in the studies. 57 protocols were approved and 12 were rejected. The remaining 3 protocols were still under review at the time of data collection.

PROTOCOLS *WITHOUT* THE PROSPECT OF DIRECT BENEFIT

Of the 36 protocols that were labelled *without* the prospect of direct benefit, 15 were found to contain a procedure that could offer a direct benefit (in addition to one or more procedures that could not). In all of these cases it was the study intervention that offered the prospect of direct benefit. In 13 of the 15 cases, the researchers mentioned the possible benefit when applying for ethical review, but the REC nevertheless classified the protocol as *without* the prospect of direct benefit. Interestingly, in 8 of the other 21 protocols, i.e. the protocols in which we could not identify the possibility of direct benefit, the researchers also mentioned possible benefit.

The 15 protocols in which the study intervention could be regarded as offering possible direct benefit, can be grouped into the following five categories:

1. Five protocols concerned **early phase drug trials** studying a disease for which no or insufficient treatment exists. In these cases the drug would be administered in such a way (duration and dose) that a therapeutic benefit could reasonably be expected.
2. In three cases, the protocol concerned research on the pathophysiology of a disease or on a new diagnostic test, but **also included an intervention that could directly benefit the subjects**. An example of a protocol in this category is a study aimed at a better diagnosis of early-stage asthma in children. As part of this study, recurrently wheezing children were treated with inhalation corticosteroids for two months, which could directly benefit their health.
3. Two protocols concerned **pilot studies**. These studies were labelled without a prospect of direct benefit because a possible therapeutic benefit

could not be statistically demonstrated; however, this effect nevertheless could be expected for the few individual participants.

4. In three cases, the research intervention was not likely to directly benefit the subjects, but was likely to **generate knowledge about the individual subjects that could contribute to better care for these subjects** immediately after, which could be regarded as offering a diagnostic benefit. An example of a protocol in this category is a study on the more detailed imaging of a certain brain tumour including its susceptibility for a particular type of therapy. By participating in this study, the subjects could gain information that could afterwards help their doctors finding an adequate therapy, albeit in the form of experimental therapy or a follow up trial.
5. The last two **protocols included interventions of which part of the subjects, despite the aim of the study, could gain a preventive benefit**. An example of a protocol in this category is a study on the responses of children with impaired immune systems to hepatitis A and B immunisation. Children at risk for these diseases could benefit from participating in this study if they appeared to respond well to the immunisation, by being protected against hepatitis A and/or B.

PROTOCOLS *WITH* THE PROSPECT OF DIRECT BENEFIT

Of the 36 protocols that were labelled *with* the prospect of direct benefit, 34 contained procedures that could not offer any direct benefit. The shortest list of procedures *without* the prospect of direct benefit in a study labelled *with* the prospect of direct benefit was only one extra blood draw from an arterial line that was inserted in the context of standard care. At the other end of the range were a study that included 144 extra hospital visits during 11 years, and a study that included physical examinations, keeping a diary, a skin test, a chest radiograph, an ECG, a food intolerance test and 33 venipunctures. In between those two ends we found protocols with various lists of procedures. For example a randomised trial on monitoring strategies for asthma included completing 10 questionnaires, keeping a diary and undergoing a (not clinically indicated) bronchial provocation test.

Such procedures *without* the prospect of direct benefit mostly concerned measures for monitoring (side) effects of the (beneficial) intervention, but in some cases also concerned measures related to a separate research question, such as pharmacokinetics/dynamics. Occasionally, a protocol even contained an additional intervention solely for research purposes. An example is a study consisting of two parts. For the first part 30 children would receive a new drug for 14 days in

order to test its safety and tolerability. Only in the second part of the study the drug would be compared to placebo. The committee did not approve the first part because it could not be considered as offering direct benefit. The first part was then only carried out in the United States.

The two protocols that did not contain any procedures *without* a prospect of direct benefit were both trials in which all the data needed for the trial were obtained through procedures that were already done in the context of standard care of these patients.

In 3 of the 36 protocols the potential direct benefit of the study intervention was questionable. For example one of the studies patients with obesity had to follow a certain diet for four weeks. It is doubtful whether a lasting effect can be expected from a four-week diet. One protocol raised doubt about whether it was an intervention study at all, as the participants were already using the drug that was studied. The REC eventually labelled it as an intervention study, even though it had the same doubts.

REMARKS AND IDEAS FROM GROUP DISCUSSIONS

The three group discussions with RECs led to remarks on the feasibility and workability of a procedure-level approach as well as to ideas on how to improve the method. Several REC members were concerned about the extra time the approach would cost, as reviewing protocols is already a time-consuming task. They were worried that differentiating between the two types of procedures would be difficult and would require a lot of experience with the method. Moreover, the need for a clear format was put forward, not only regarding the first step (categorising all research procedures), but also regarding the second (assessing these procedures) and third (making an overall judgment) steps. Several members mentioned that a procedure-level approach should not complicate the risk-benefit assessments more than necessary.

Moreover, some participants made suggestions related to the quality of the method. They wondered whether the distinction between two types of procedures is precise enough. During all three group-discussions it was suggested that it might be worthwhile to also differentiate between primary and secondary research questions within a research protocol. This would describe the value of each part of a protocol more precisely and it would make it easier for RECs to have protocols adjusted or to reject a part of the study. It was suggested that procedures that measure the safety and effect of the intervention should be

considered as procedures *with* the prospect of direct benefit, whereas those procedures that answer secondary research questions should be considered as offering no prospect of direct benefit. Lastly, the idea was raised that the risks and burdens of procedures *without* the prospect of direct benefit in research *with* the prospect of direct benefit, are usually outweighed by the net-benefit of the intervention. We will explore these issues further in the next section of this paper.

DISCUSSION

The assessment of risks in paediatric research protocols is usually done for the protocol as a whole, thereby labelling and evaluating the entire protocol as either *with*- or *without* the prospect of direct benefit. However, protocols often consist of a combination of procedures that can directly benefit the participants, and procedures that cannot. For this reason, several ethicists have proposed to focus on procedures instead of protocols when assessing the research risks and burden.(6, 7, 16) We analysed 72 paediatric intervention studies to assess how frequently protocols consist of a combination of the two types of procedures. The majority of the protocols we analysed contained a combination of procedures *with*- and procedures *without* the prospect of direct benefit (68%). This number suggests that a protocol-level approach does not do enough justice to the complexity of paediatric research protocols and contributes to the idea that a procedure-level approach is a better way forward.

42% of the protocols labelled *without* the prospect of direct benefit included a study intervention that could be regarded as offering a prospect of direct benefit for the participants. This is surprising, as one would suppose that with this possibility of direct benefit, the protocol would have been labelled *with* the prospect of direct benefit. We expect that a more detailed definition of direct benefit will lead to a more accurate and uniform risk-benefit assessment, be it with the standard approach or with a procedure-level approach.

When defining direct benefit, it is important to realise that when performing a risk-benefit assessment, labelling a procedure as holding the prospect of direct benefit (step 1), does not mean that this benefit automatically compensates for the risks and burdens (step 2). We suggest the following definition of an intervention or other procedure *with* the prospect of direct benefit: *an intervention or other procedure that forms a valid therapeutic, diagnostic or preventive option for the participants in the study at stake.* By a valid option we mean that it can expectedly compete with other available (therapeutic/diagnostic/preventive)

options for the patient concerned, so that the patients will not receive inferior care.(6) Our proposed definition does justice to the fact that both the magnitude and the probability of the benefit may vary among the valid options. Moreover it excludes non-medical benefits (which cannot reasonably compensate for medical risks) as well as medical, but insignificant benefits.

Using this definition would mean the following for the examples that we presented in the result section, where we grouped the procedures *with* direct benefit in protocols labelled *without* direct benefit into five categories. The benefit in the example from category 2, the asthma diagnosis study, would qualify as direct benefit when only patients with an indication for inhalation steroids would be included in the study. The example from category 5, the hepatitis vaccine study, is similar. It would have fit our definition if only participants with a medical indication for hepatitis A and B prevention would have been included. In both examples this was not the case. Categories 1, 3 and 4 (the early phase drug trials with sufficient dosage and duration, the pilot studies and the studies likely to generate valuable knowledge about the individual patient) do fit our definition.

Almost all of the protocols that were labelled *with* the prospect of direct benefit also contained procedures conducted purely for research purposes (94%). Of concern are the long lists of such extra research procedures. One can wonder whether RECs are always sufficiently critical to the risks and burdens of extra research procedures once there is a benefit expected for the subjects. This practice has been referred to as package deals, in which the possibility of direct benefit is used to justify disproportionally many extra research procedures.(13) Two of the examples in the result section (a study with 144 extra hospital visits during 11 years, and a study that included physical examinations, keeping a diary, a skin test, a chest radiograph, an ECG, a food intolerance test and 33 venipunctures) may have been such package deals as they included so many extra research procedures, that they certainly raise doubt about whether the risks and burden of all those procedures could reasonably be compensated for by the benefit of the intervention. Both protocols were approved by the reviewing committee. In these cases a procedure-level approach would probably have provided a more accurate and fair risk-benefit assessment.(16)

To explore the feasibility of a procedure-level approach, we discussed the method with REC members. Several members were concerned that the method would be too time consuming. We understand this concern, yet we expect the first step to be fairly easy once there is a more clear definition of direct benefit available, like

the one we suggested. In addition, a clear format would be helpful. Distinguishing between primary and secondary research questions, as was suggested, could provide more insight into the value of separate procedures. By making both distinctions, committees may get a clear view on the purpose and the importance of separate parts of a protocol. It should however be clear that these are two different distinctions. Not all procedures related to the primary research question automatically provide direct benefit. Procedures that are performed to monitor the safety of the (beneficial) intervention are indeed not performed for data collection only. However, in a research setting such monitoring is often performed more frequently than strictly required for monitoring the safety of the participants. Moreover, when not participating in the study, the participants would not have needed the monitoring procedures at all.

Thus, claiming that they offer direct benefit is not the right way to justify their risks and burdens. Net benefits of the intervention can compensate for higher than minimal risks and burdens of procedures that relate to the intervention, but the procedures themselves should not be considered as offering direct benefit. RECs should assess the risks and burdens of those procedures critically and transparently and should be convinced that these are not higher than what the net benefits can justify. In our analysis we found some studies that contained many extra research procedures. It would require a lot of expected benefit to outweigh that many, sometimes rather burdensome, procedures. As the intervention itself already entails certain risks and burdens, it is doubtful whether that intervention can offer that much benefit at all.

It would probably help if researchers were asked to make the proposed distinctions already in their protocols and indicate which procedures offer possible direct benefit and which do not, as well as which procedures relate to the primary research question and which to the secondary ones. This could result in adjustments to the design in an earlier stage, more precise protocols and hence to quicker and easier ethical review.

Concluding, we argue that both RECs and research professionals should adopt a procedure-level focus. Not only does this expectedly lead to better ethical review, it may also potentially improve informed consent and research practices. A procedure-level approach requires a clear definition of what direct benefit is, like the one we suggested. Providing clear formats for dividing between procedures *with*- and *without* the prospect of direct benefit to researchers and RECs can also be helpful for implementing the method in practice.

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CHAPTER 7

PAEDIATRICIAN'S VIEWS ON RESEARCH BURDEN FOR CHILDREN

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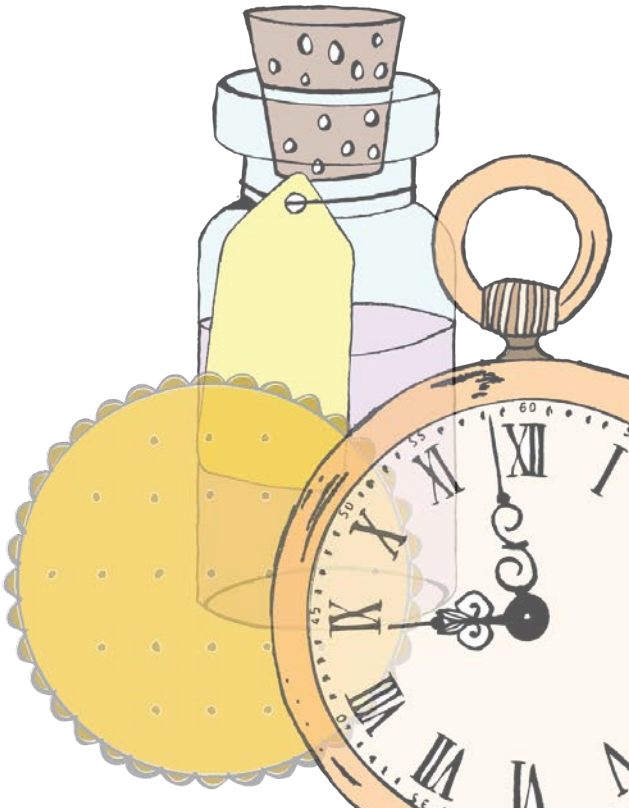
Submitted



ABSTRACT

Background and objective: More empirical data on the burden of research procedures for children is needed for RECs to accurately assess paediatric research protocols. Our objective was to assess how paediatricians estimate the burden of research procedures for children, related to the categories of *minimal burden* and (more than) *a minor increase over minimal burden* and which factors they think may influence the experienced burden.

Methods: Data were collected using a two-page questionnaire. Respondents classified thirteen research procedures into three categories. Second, they ranked the procedures and third, they wrote down factors that influence the experienced burden.

Results: The majority categorised buccal swab, echocardiography and spirometry as *minimal burden*. Allergy skin test, hospitalisation and insertion of a venous cannula were categorised as *a minor increase over minimal burden*. *More than a minor increase over minimal burden* was chosen for repeated venipunctures, bone marrow aspiration, lumbar puncture and muscle biopsy. There was no majority opinion on a single venipuncture, bronchial challenge test and MRI. Buccal swab was ranked as least burdensome and bone marrow aspiration as most burdensome. Age and former experience with hospitals were mentioned as influencing factors most.

Conclusions: There is disagreement on how burdensome certain procedures are for children. We hypothesise that this is partly due to differing experiences of the same procedure by various children. It implies that categories like *minimal burden* should be used with caution. Empirical data can help RECs, but during trials the experiences of all individual children should have the primary focus.

INTRODUCTION

How burdensome research procedures are for children is very relevant in the context of paediatric research ethics. Research ethics committees (RECs) are responsible for assessing the burden (and the risks) of paediatric research protocols.(1) They have to assess whether the burden is minimised, and whether the burden is acceptable in relation to the anticipated benefit (if any) for the participants. In the absence of direct benefit, paediatric research is usually considered justifiable if, among other requirements, the research burden is no more than minimal.(2, 3) This demand appears as a common requirement in laws and ethical guidelines.(4-6)

Burden is both a difficult and a diverse concept. It has not yet exactly been fully explicated what does, and what does not fall within in the scope of burden. Moreover, different ideas exist about how the concept of burden relates to the concept of risk. Regarding the scope of burden, it can reasonably be concluded that both discomforts (like pain, itchiness, nausea and anxiety) and inconveniences (like missing a school day and going to the hospital) are types of burden.(7, 8) However, not all legal and ethical documents clearly recognise that.

With regard to the relation to risk, there seem to be two approaches. One approach regards burden as incorporated in the concept of risk. The rationale is that regardless of whether the possible negative outcomes concern harm or discomfort, both include a certain probability and are therefore to be considered risks.(9) This interpretation appears in the US Code of Federal Regulations as *risk of discomfort*. The definition of *minimal risk* given in the US Code is: 'the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life and of routine examinations'.(5) This definition was also chosen in the recommendations for implementing the European Clinical Trials Directive.(10) A disadvantage of this approach is that it makes no reference to inconveniences and it is difficult to see what place inconveniences could have, as inconveniences do not necessarily include a probability component. Westra and colleagues proposed a new definition for *minimal risk of discomfort* that incorporates empirical evidence and expert experience, namely that the risk of discomfort is minimal when: 'empirical data, expert opinions and/or the procedural characteristics (e.g. invasiveness; disturbance of normal routines) suggest that at most a quarter of the persons concerned will experience considerable discomfort'.(9)

A second approach is to regard burden as a separate concept. Examples of this

approach are the new European Clinical Trials Regulation (that will replace the Clinical Trials Directive), the European Convention on Human Rights and Biomedicine (Oviedo Convention) and the Declaration of Helsinki.(4, 6, 11) These documents separate burden from risk, but are still not very explicit about what constitutes a burden. The Additional Protocol to the Oviedo Convention defines *minimal burden* as: 'it is deemed that it bears a *minimal burden* if it is to be expected that the discomfort will be, at the most, temporary and very slight for the person concerned'.(12) During the drafting of the Dutch national law on medical research with humans, a definition of *minimal burden* was provided that includes both discomforts and inconveniences, namely that the research is 'altogether not disruptive; the disturbance of daily life that research participation involves is limited and the burden in the sense of pain may not be more severe than for example a blood draw'.(13, 14)

Regardless of the relation to risk, the fact remains that RECs have to assess whether the expected burden of a proposed study is acceptable for the participants. To do so, placing research procedures in the categories of *minimal burden*, *a minor increase over minimal burden* and *more than a minor increase over minimal burden* may be helpful but also challenging. Obviously, assessing the accumulated burden of the totality of research procedures within a protocol is even more complicated. Burden has both an objective and a subjective component. The objective component is what is imposed on children, which can be described factually; e.g. the child will undergo an allergy skin test that takes 30 minutes, will probably cause itchiness and possibly some mild pain. The subjective component is how the child concerned *actually* experiences the procedure. The same level of pain might not at all bother the first child, but may cause panic in the second.(15) While a venipuncture is generally known to cause more distress in toddlers than adolescents, there is still a considerable amount of adolescents that experience high levels of distress.(16)

Some data are available on the self-reported levels of pain children perceive while undergoing medical procedures, but little research is done on the overall level of burden (pain, fear, nausea, etcetera) of medical procedures.(8, 15, 17, 18) Evidence on burden related to the categories of *minimal burden* and so on, is especially scarce. To properly estimate the expected burden of a protocol, RECs need more empirical data on how burdensome procedures are for children.(19) There are tables that categorise medical procedures by degrees of risk (including risk of discomfort) for paediatric subjects, but it is unclear what evidence supports these

categorisations.(20, 21)

The objective of our study was to assess how paediatricians estimate the burden of research procedures for children, related to categories like *minimal burden*. The procedures that are used in research are also frequently carried out in the setting of medical care. Paediatricians often have plenty of experience with these procedures and therefore are a valuable source of information.

METHODS

RESPONDENTS

Respondents were recruited at meetings in paediatrics departments in four Dutch hospitals. We recruited respondents at regional training days in academic hospitals for paediatricians from non-academic hospitals (at Leiden University Medical Centre and VU University Medical Centre, Amsterdam), at routine meetings at paediatrics departments (Leiden University Medical Centre and Juliana Children's Hospital, the Hague) and at a monthly meeting of the paediatric department (Isala Hospital, Zwolle). This selection included academic and non-academic hospitals from different regions. All attendees of the meetings were asked to fill out the questionnaire.

QUESTIONNAIRE

The visits to the paediatric departments took place between September and December 2015. Our two-page questionnaire included a short introduction about the rationale, the purpose of our research project and the definition of *minimal burden* as used in the drafting of the Dutch national law.(14) In question 1 and 2 the respondents were asked to specify their exact profession and their years of experience working in paediatrics.

In question 3 the respondents were asked to classify 13 procedures (bronchial challenge test, a single venipuncture, repeated venipunctures (8x in 6 months), spirometry/pulmonary function test, muscle biopsy, insertion of a venous cannula, allergy skin test, lumbar puncture, buccal swab, bone marrow aspiration (with sedation), 1 hour MRI scan (without sedation), echocardiography and hospitalisation for two days), into the categories of *minimal burden*, *a minor increase over minimal burden* and *more than a minor increase over minimal burden*, or *I can't judge about this*. In question 4, the respondents were asked to rank the procedures from *least burdensome* (1) to *most burdensome* (13). In question 5 we asked

which factors, according to them, influence the burden of research procedures for children. Finally, in question 6 there was space for any further remarks. The selected procedures were chosen because (1) some of the procedures are very common in paediatric research and (2) some are procedures with which research ethics committees experience difficulty when deciding whether the procedure is (more than) minimally burdensome. The Dutch Central Committee on Research in Human Subjects provided us with a list of procedures they perceived as complicated.

ANALYSIS

We included all questionnaires that were completed by physicians. Medical students and specialised nurses were excluded. The classification and ranking of the procedures were analysed using descriptive statistics. For the classifications the percentages of each category were calculated for the individual procedures. For the ranking the median was calculated for each individual procedure. The answers to question 5 were collected and the answers that related to the same subject were grouped into categories.

RESULTS

RESPONDENTS

A total of 122 respondents returned the questionnaire, of which 86 respondents were physicians. The remaining 36 respondents, which were excluded from the analysis, were mostly medical students in residency, some specialised nurses and a physician assistant. Of the included 86 physicians, 36 were general paediatricians, 27 were subspecialists, 12 were specialist registrars, 4 were senior house officers and 7 reported another profession (for example general practitioner). Experience in paediatrics varied from 0 to 40 years (see table 1). The subspecialisms included neonatology (7), pulmonology (4), endocrinology (3), gastroenterology (3), cardiology (2), social paediatrics (2), allergology (1), congenital diseases (1), hemato-oncology (1), nephrology (1), neurology (1) and rheumatology (1). Those who reported 0 years of experience in paediatrics were visiting physicians from other departments, such as neurology.

Table 1: Characteristics of respondents

Characteristics of respondents	Number (%) of physicians (N=86)
Profession	
General Paediatrician	36 (42)
Subspecialist	27 (31)
Paediatric resident in training	12 (14)
Intern	4 (5)
Other	7 (8)
Years of experience in paediatrics	
0-2 years	9 (10)
3-5 years	11 (13)
6-10 years	11 (13)
11-20 years	33 (38)
21-30 years	16 (19)
31+ years	6 (7)

Table 2: Classification of procedures (including I can't judge about this)

Procedure	N (N=86), (%)	I can't judge about this (%)	Minimal burden (%)	A minor increase over minimal burden (%)	More than a minor increase over minimal burden (%)
Buccal swab	83 (97)	3 (4)	77 (93)	2 (2)	1 (1)
Echocardiography	82 (95)	1 (1)	62 (76)	16 (20)	3 (4)
Spirometry/pulmonary function test	83 (97)	3 (4)	56 (67)	24 (29)	0 (0)
Single venipuncture	83 (97)	0 (0)	32 (39)	40 (48)	11 (13)
Allergy skin test	83 (97)	10 (12)	18 (22)	46 (55)	9 (11)
Hospitalisation (2x 1 day)	81 (94)	2 (2)	15 (19)	46 (57)	18 (22)
Bronchial challenge test	81 (94)	19 (23)	12 (15)	33 (41)	17 (21)
MRI scan (unsedated, 1 hour)	83 (97)	1 (1)	9 (11)	36 (43)	37 (45)
Insertion of a venous cannula	82 (95)	0 (0)	7 (9)	50 (61)	25 (30)
Bone marrow aspiration	83 (97)	4 (5)	4 (5)	15 (18)	60 (72)
Repeated venipunctures (8x in 6 months)	82 (95)	0 (0)	2 (2)	26 (32)	54 (66)
Muscle biopsy	82 (95)	7 (9)	1 (1)	6 (7)	68 (83)
Lumbar puncture	83 (97)	0 (0)	0 (0)	19 (23)	64 (77)

Figure 1: Classification of procedures (excluding I can't judge about this)

CLASSIFICATION

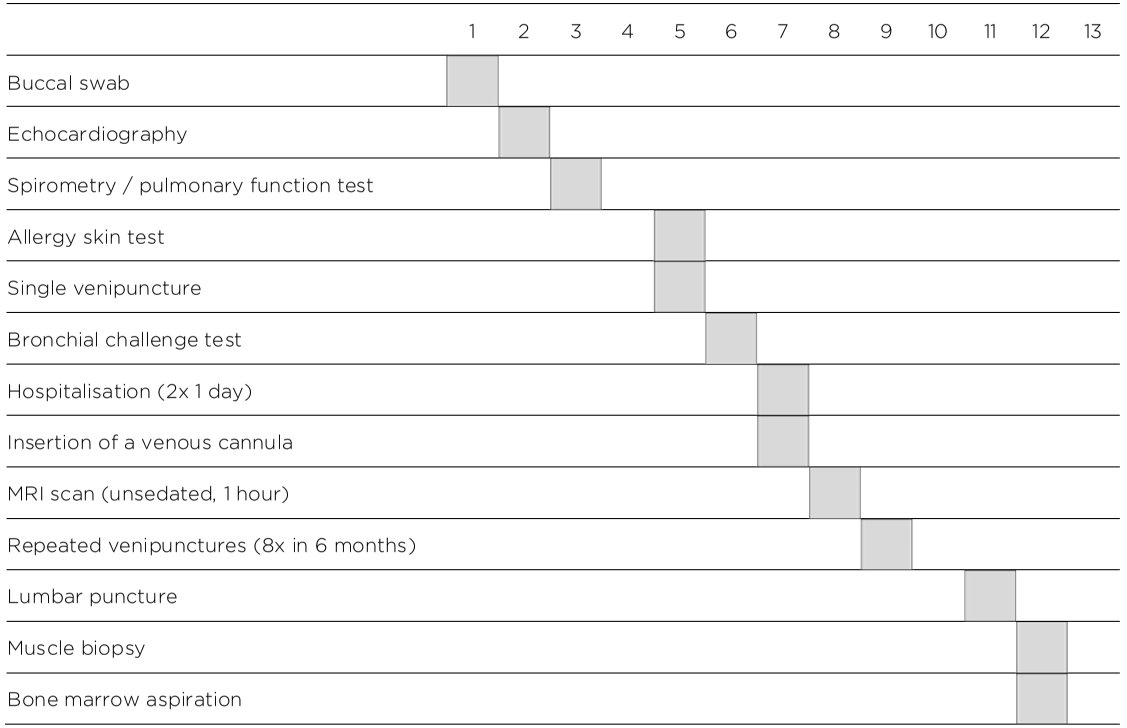
Table 2 shows the number and percentage of each category per procedure, including *I can't judge about this*. In figure 1 this category is left out, as it would give a distorted image of the distribution over the three categories. Therefore, figure 1 is a graphical representation of only those respondents who gave an actual estimation of the burden of the procedure.

The majority of the respondents categorised buccal swab, echocardiography and spirometry as *minimal burden* (respectively 93%, 76% and 67%). Allergy skin test, hospitalisation of two days and insertion of a venous cannula were categorised as *a minor increase over minimal burden* by the majority (55%, 57% and 61%). The category *more than a minor increase over minimal burden* was chosen by a majority of the respondents for repeated venipunctures (8x in 6 months), bone marrow aspiration, lumbar puncture and muscle biopsy (66%, 72%, 77% and 82%). There was no majority opinion for the remaining three procedures. A single venipuncture was categorised as *minimal burden* by 39%, as *a minor increase over minimal burden* by 48% and as *more than a minor increase over minimal burden* by 13%. For a bronchial challenge test the distribution was respectively 15%, 41% and 21%. For a 1 hour MRI scan without sedation the distribution was respectively 11%, 43% and 45%.

RANKING

The ranking (question 4) was completed by 61 respondents, though not all of them included all procedures in the ranking. For example, respondents who felt they could not judge about a certain procedure did not include that procedure in their ranking. By calculating the median of the rank allocated per procedure, we came to the following ranking from *least* to *most burdensome* (the median is between brackets). Buccal swab (1), echocardiography (2), spirometry (3), allergy skin test (5), a single venipuncture (5), bronchial challenge test (6), hospitalisation for two days (7), insertion of a venous cannula (7), 1 hour MRI without sedation (8), repeated venipunctures (8x in 6 months) (9), lumbar puncture (11), muscle biopsy (12), bone marrow aspiration (sedated) (12). Note that these numbers only describe an order and that the steps between the numbers might not be equally large (see figure 2).

Figure 2: Ranking of procedures



FACTORS THAT INFLUENCE BURDEN

The answers to question 5 (which factors influence the burden of medical procedures for children) were grouped into 11 categories. We ordered the categories of answers from *most* to *least mentioned*. Age of the children was mentioned the most (57 times). Whether children had previous experience with research, with undergoing the procedure or with hospitals in general, was mentioned 40 times. Factors related to the parents (attitude, behaviour, stress, fear of the parents) were mentioned 39 times and factors related to the child (character, developmental stage, fear, attitude of the child) 30 times. Both preparing the child and parents (including informing and explaining) and guidance and support during and after study participation were mentioned 25 times. Characteristics of the procedure (e.g. whether it causes pain and whether it is possible to provide relief) were mentioned 24 times. 14 answers referred to the length of the procedure, the time investment and the point of time. The experience and skilfulness of the person who performs the procedure was mentioned 10 times. Lastly, sedation (5 times) and distraction (3 times) were mentioned. Eighteen remaining answers could not be categorised. Not enough respondents used the space for further remarks to yield significant information.

DISCUSSION

It is often rather difficult for REC members to classify the burden of a paediatric research protocol into the categories of *minimal burden*, *a minor increase over minimal burden* and *more than a minor increase over minimal burden*. It could help REC members to have access to more empirical data on the burden of research procedures for children. To this end we investigated how paediatricians estimate the burden of research procedures for children.

Our results show that there is more agreement among physicians on the burden of some procedures than on others. A buccal swab is clearly considered to pose only *minimal burden* by a vast majority of the respondents, whereas a muscle biopsy is clearly seen as posing *more than a minor increase over minimal burden* to children. What strikes as remarkable is that for most procedures the answers are distributed over all three categories, which shows explicit disagreement among doctors.

Some research ethics documents provide tables that classify procedures in categories like *minimal risk* etcetera, to provide guidance to ethics committees.

On some procedures these tables differ from the results of our study. Although these tables do not explicitly focus on burden, it can reasonably be assumed that burden is incorporated in these tables, as both documents that provide such a table, regard burden as risk of discomfort. The table on risk for paediatric research subjects of the NHRPAC classifies a single venipuncture as *minimal risk*, and both a lumbar puncture and a bone marrow aspiration (with topical pain relief) as *a minor increase over minimal risk*.(21) All three procedures were classified as more burdensome by a majority of the respondents in our study. In the table from the ethical considerations accompanying the European Clinical Trials Directive, a venipuncture is labelled as *minimal risk*, a MRI scan and a bone marrow aspiration as *a minor increase over minimal risk* and a biopsy (not specified) as *more than a minor increase over minimal risk*.(20) The respondents of our study classified venipunctures and bone marrow aspirations as more burdensome than the table does and classified MRI and biopsies (in our study specified as muscle biopsy) the same as in the table.

What could explain the diversity in classifications that we found, as well as the differences with the existing tables? It could be the case that physicians have actual varying experiences because their patient groups differ, for example with regard to age.(16) Moreover, the severity of the disease of the patient groups they work with and whether it concerns chronic or acute diseases may also (partly) explain the diverse answers. The respondents in our study also indicated that age and prior experience with doctors and hospitals are important influencing factors. More data on burden related to various age groups and to various patient groups would therefore be helpful for reviewing paediatric protocols. In addition to that, children differ from each other in many respects. There are fearless children who find hospitals and doctors exciting, but there are also children who are scared already by the idea of seeing a doctor. The physicians in our study acknowledged that individual differences between children are an influencing factor.

Another possible explanation is that the content of the three classifications is not clear enough. Although we have provided a definition of *minimal burden* alongside the questionnaire, it is still likely that people interpret it differently. If, for instance, two physicians both share the experience that about 50% of all children cries when undergoing a venipuncture, the first may classify that as *minimal burden*, whereas the second may regard it as more than that. A more operational definition of *minimal burden*, like the one suggested by Westra et al may help to solve the problem of interpretation, although terms like *considerable discomfort*

are still multi-interpretable. However, a certain degree of indistinctness in definition of *minimal burden* seems inevitable.

As the concept of burden itself is already difficult to define, it is even more difficult to know what level of burden can be considered minimal. And if there is, as our study shows, much disagreement on the level of burden that specific procedures pose to children, how can categories like *minimal burden* be used in a meaningful way? Empirical data on the burden of protocols, whether reported by children themselves, or derived from the experience of physicians, can at best provide an overall idea on how burdensome procedures are for most children. However, they cannot take into account those children who diverge from the majority. The variation in answers that the physicians in our study gave, as well as the varying experiences of children, are reasons to apply categories like *minimal burden* with caution. In ethical review these data should be used as guidance in decision-making. Yet RECs and researchers should be aware that even if a study is reviewed as posing *minimal burden*, that does not necessarily mean that this will be the case for all children. During the performance of trials, the experiences of all individual children should be closely monitored. If a child in a study experiences a higher burden than what was deemed acceptable, the researcher should intervene.(22) We recommend paying special attention to those procedures about which the physicians in our study disagreed with regard to how burdensome they are.

CONCLUSION

Our study showed that paediatricians estimate the burden of research procedures for children rather differently. Some procedures were clearly classified as posing *minimal burden* (buccal swab, echocardiography, spirometry), or as *more than a minor increase over minimal burden* (lumbar puncture, muscle biopsy, repeated venipunctures). For the other procedures, our study shows substantial disagreement on the burden for children. Our results imply that the categories of *minimal burden* and *(more than) a minor increase over minimal burden* should be used with caution.

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CHAPTER 8

PROTECTING CHILDREN DURING THE PERFORMANCE OF RESEARCH

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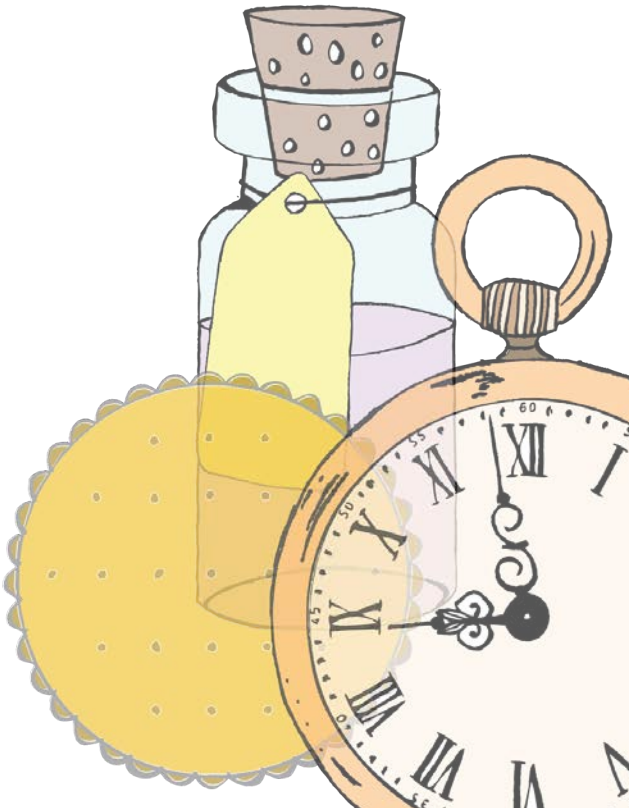


ABSTRACT

Children participating in clinical research may show signs of discomfort, discontent, dissent and so on, which cannot be solved by comforting the child. When, and on what ground, should such signs lead to the decision to withdraw the child from the trial? In order to adequately protect children participating in clinical research, it is important to know how to determine during the course of a trial whether participation is still justified. Yet to date, legislation, ethical guidelines and medical ethical literature do not provide sufficient guidance. Therefore, in this chapter we aim to provide the required clarity. We identify two types of reasons for taking signs of discomfort, discontent, dissent and so on, very seriously: 1) the principle of respect for the growing autonomy of the child, in those cases where a child expresses a clear, explicit and persistent wish to be withdrawn from the study; and 2) the principle of non-maleficence, in those cases where for an individual child, the research burden appears to be higher than acceptable. We recommend to closely monitor each child during the course of the study, thereby being vigilant to whether the child still wants to continue and to whether the actual burden the child experiences is still acceptable in relation to the permitted levels of burden.

INTRODUCTION

Think of a healthy 11-year-old girl participating in a clinical trial. A research ethics committee (REC) approved the trial and a good informed consent procedure ensured both the child and the parents were well informed about the research. One of the procedures in the study is an MRI scan. When the girl is in the tube, the scan scares her more than she expected, she feels uncomfortable and she resents the noise. She tells the nurse she wants to get out. She also clearly says that she no longer wants to participate in the study.

Now, imagine a 5-year-old boy participating in another trial. While undergoing physical examination he screams and wrestles. Both his mother and a nurse try to comfort him, but when the researcher starts to examine him again, the same thing happens. He is clearly uncomfortable and not willing to be examined. Obviously, it is unclear whether he is protesting against the trial or just had a bad night and protests against anything? Moreover, he could have shown rather different signs. What if he would literally say: 'don't touch me' or what if he would not scream and wrestle, but would silently tremble?

Why these examples? These are children participating in clinical trials and their behaviour raises the question whether their participation is (still) morally acceptable. There is a general consensus that children need and deserve to be protected extra carefully when participating in clinical trials. The main reason is that they are a vulnerable population, dependent on others and not yet (fully) capable of making a rational and voluntary decision to participate. A certain risk of exploitation exists, especially in cases of research without any prospect of direct benefit for the participants (also called non-therapeutic or non-beneficial research), as there is no benefit to outweigh the research related risk and burden they have to undergo. Children in research with the prospect of direct benefit (or therapeutic or beneficial research) however also deserve extra protection, as their vulnerability and incompetence is the same.(1)

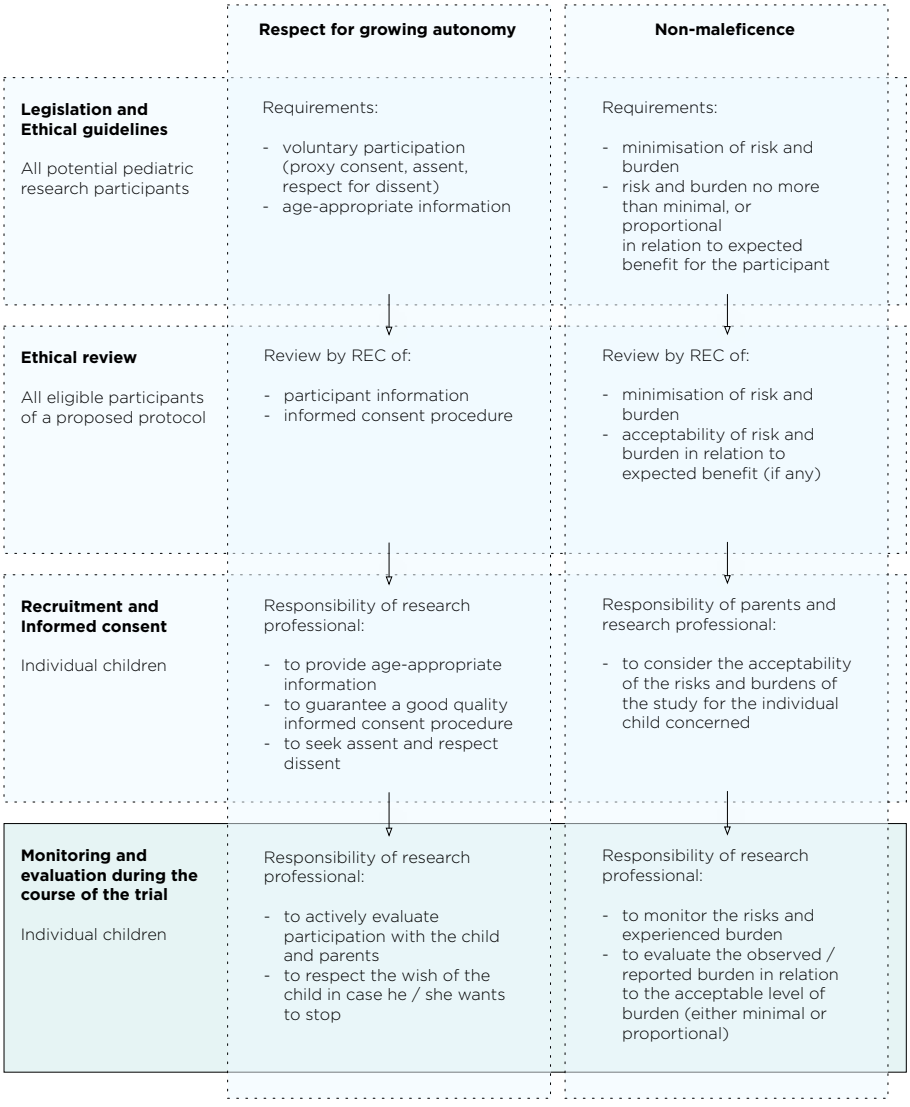
Several measures have the purpose of guaranteeing this extra protection. First, laws and ethical guidelines set stricter requirements for research with children than for research with competent adults. These include requirements regarding the proxy consent of parents/caregivers and the assent of older children, as well as strict upper limits on the acceptable levels of risk and burden in research without the prospect of direct benefit. Second, RECs review whether research protocols comply with these requirements. Third, during the informed consent process, researchers, parents/caregivers and (if possible) the individual child

concerned carefully estimate whether participation is acceptable for that child.(2) Children must be informed about the study and involved in the decision making process in a way that suits their level of understanding.

Protection should continue after inclusion, but the rules and safeguards that need to be in place during the course of the study are not yet clear enough. Most research ethics guidelines and regulations do mention the need for the monitoring of risks and some also mention possible consequences this may have for trial participation, but the requirements remain vague and are not related to the acceptable levels of risk and burden.(3, 4) In addition, they all state that adults are free to withdraw their consent for whatever reasons, during the entire course of the trial. However, despite the fact that laws and guidelines require respect for dissent, they fail to clearly define what dissent is, what expressions count as dissent and how they should be acted upon. Children usually do not provide any formal consent, so there is no consent to withdraw. Once included, they can only be formally withdrawn from the study when the researcher and/or the parents think that is necessary. The researcher and parents may base their decisions on the behaviour of the child. Yet, how exactly should they do this? How should it be guaranteed that children are withdrawn from a study when their behaviour suggests that participation may no longer be justified?

In this chapter we will formulate recommendations on how to react to signs of discomfort, discontent, dissent and so on that cannot be solved by comforting the child. The central question is when, and on what ground, such signs should lead to withdrawing a child from a study. We present our normative analysis and also discuss how this problem is currently dealt with in legislation and ethical guidelines. We argue that there are two types of reasons related to signs of discomfort, discontent and dissent for deciding that a child should be withdrawn from research, related to two basic ethical principles. In cases where a child shows actual dissent, the need to withdraw follows from the principle of respect for the developing autonomy of the child, as failing to act upon the child's wish would violate this principle. In cases where a child is unduly burdened by the study, the need to withdraw follows from the principle of non-maleficence because the higher burden may affect the child to an unacceptable extent. The two principles also play an important part in other protective measures, such as legislation, ethical review and informed consent (see figure 1). Our recommendations are directed towards law- and policymakers, as well as to research professionals directly.

Figure 1: Operationalisation of the principles of respect for growing autonomy and non-maleficence (on top) within the various protective measures (on the left) concerning paediatric research. The texts in the boxes present the content of the principles in each form of protection.



RESPECT FOR THE GROWING AUTONOMY OF THE CHILD

The first type of reasons for having to withdraw a child from a trial relates to the principle of respect for the growing autonomy of the child. As children grow they gradually become autonomous persons and become increasingly capable of expressing their wishes. Having their wishes respected helps children develop their autonomy further. Most research ethics guidelines recognise this developing autonomy by demanding that all children are involved in the informed consent procedure in a way that fits their developmental stage and level of understanding. Those children who are capable of co-deciding should provide assent. The child's dissent should be respected. The Declaration of Helsinki (article 29) is an example of the use of this terminology.(3) Instead of using the term 'dissent', some documents speak of 'objection' or 'deliberate objection'.(5, 6)

Aside from dissenting during the informed consent procedure prior to inclusion, children can express a wish to stop during the study. The first example in the introduction illustrates that. The 11-year old girl is not yet considered fully capable of providing informed consent, but is capable of expressing an explicit wish to stop participation. Being 11-years old will qualify her as not fully autonomous, but her autonomy may well be established enough to not be ignored. Figure 1 displays the existing protective measures related to the principle of respect for growing autonomy, and also how protection with respect to this principle can be continued during the course of a study.

As the concept of dissent is put forward in almost all documents, it seems that for those children who are capable of expressing an explicit wish, the option for them to withdraw themselves from a study is safeguarded. However, some unanswered questions remain; we name three. First of all, many documents only discuss the concepts of assent and dissent in relation to the informed consent process prior to inclusion. They do not explicitly state that these concepts may also play a role in a later phase, when the study is already being carried out. Some guidelines are explicit about this though, and it seems reasonable to assume that the others hold the same intention. The European Clinical Trials Directive (CTD), for example, states in article 4c: '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'.(4) Moreover, the accompanying ethics document on trials in minors emphasises that assent is a continuous process, which means that it can be withdrawn at any time during the trial. It also states

that the child should not be forced to provide reasons for withdrawal.(7) We agree with this view and recommend other regulations and guidelines adopt this as well.

The second question asks at what point children should be considered old enough to express meaningful dissent. Unfortunately it is impossible to point at an exact age at which children are capable of providing assent. This relates to the fact that there is no consensus on the exact aim and content of assent.(9) Furthermore, age in years is not the only relevant factor.(8) The age-limits for assent mentioned in guidelines and literature vary from 7 till 14 years of age.(9) To set an age limit for dissent is even more difficult. While there is a growing body of literature about the concept of assent(10-12), the notion of dissent is not thoroughly discussed and not (yet) clearly defined. There is some agreement that dissent does not necessarily require the same level of understanding of the study and the same decision-making capacities as assent does.(13) As a consequence, the term objection has even been used for expressions of objection in preverbal children.(6, 14) We suggest reserving terms like dissent and objection for those children who can express a clear, explicit and persistent wish to stop participating. The age at which this is the case may differ between children and even between situations. This does however not mean that children who can not express a clear, explicit and persistent wish do not deserve any respect for their developing autonomy. It means that if a child cannot meaningfully answer the question whether they want to stop or not, dissent should not be put forward as the reason to stop. In these cases the decision can better be based on the burden the child experiences, which will be explained more thoroughly in the next section of this chapter.

The third question is whether this explicit wish should always and automatically be respected. It is remarkable that in the European Clinical Trials Regulation, which will replace the Clinical Trials Directive next year, the wording of the aforementioned article 4c is changed from *'considered'* to *'respected'* (article 31.1.c).(15) This seems to imply that the child's wish should be respected without exceptions. A similar statement can be found in the Declaration of Helsinki.(3) For research without the prospect of direct benefit, we think this is the right approach. Participation in this kind of research is not a moral duty and refusal to participate or the wish to stop participation does not need to be informed and rational, like the decision to stop of an adult also does not need to be informed and rational.(16) But the situation is somewhat more complex for children in research *with* the prospect of direct benefit. In certain select cases a child is likely to benefit from, or

even dependent on a particular treatment that is not available outside the context of research. Only in such select cases, where participation is critical to the health of the child because there are no valid alternatives, can it be reasonable to overrule the wish of the child. So far, only the CIOMS guidelines and the IRB guidebook that accompanies the US Code of Federal Regulations point out these important nuances.(6, 8)

NON-MALEFICENCE

The second type of reasons relates to the principle of non-maleficence. When the research related burden for an individual child turns out to be higher than what was found acceptable during the ethical review of the study concerned, trial participation might become unjustified. A child who cries, screams, wrestles, trembles etcetera, might be burdened by research participation to a more than acceptable extent. The example of the 5-year old boy illustrates this. His screaming and wrestling could mean that he is scared or stressed by the physical examination; especially as comforting him does not help. This boy may experience burden that is higher than justified and that probability should be taken seriously.

Most research ethics guidelines and regulations do not explicitly touch upon this issue. Some address the younger age groups by suggesting that their concepts of 'dissent' or 'objection' can be used for all ages, but as we argued before, non-explicit signs of discomfort should not qualify as meaningful dissent. For example, the code of conduct accompanying the Dutch law on research with human subjects explicitly includes infants and toddlers (see box 1). Other documents argue for the need to monitor the levels of distress, discomfort and so on that children may experience during research. The CTD for example states in article 4g that 'both the risk threshold and the degree of distress have to be specially defined and constantly monitored'.(4) This requirement is valuable because it is generally recognised that the way children experience procedures can vary a lot between children and even for the same child between situations.(17) That means that there is always a fair chance that a child experiences a higher level of distress than expected. However, how such monitoring should take place and what the consequences should be is not specified.

Box 1: Dutch code of conduct relating to objection by minors participating in medical research

The Dutch national law on medical research with human subjects requires that children who object against trial participation are being withdrawn: 'If a subject involved in trials (...) should object to the treatment administered or behavioural strategy imposed, the person in question will be excluded from participation' (Art 4.2).(18) In order to explicate how the concept of 'objection' should be used, a code of conduct was written in 2001. The code acknowledges that every child behaves differently and that identifying cases of actual objection is especially difficult with neonates. However, the code states that 'as a general rule it is reasonable to suggest that a child may be thought to object if its behaviour clearly differs in nature or degree from that normally displayed by the child when confronted with situations not encountered in everyday life'.(14) This means that if a child reacts differently or more severely to a research procedure than he or she would normally do to an unusual situation, the child should be withdrawn from the trial.

The Dutch approach reveals the weaknesses of applying concepts such as dissent or objection to younger children. It is very difficult to translate the signals of a child unable to clearly express itself, into a term like dissent or objection. The problem seems to be that such terms suggest that a child knowingly and actively states that he or she wants to stop participating. But this is not the case for young children who can express discomfort or distress but cannot express an explicit wish to be withdrawn. Therefore, using terms like dissent and objection does not help to interpret signs of distress in a meaningful way. The primary question should be: what level of distress is unacceptable?

We suggest relating the observed signs to the level of burden that was found acceptable for that study. Again, strict limits are set for the risks and burdens children may be exposed to during research. In research *without* the prospect of direct benefit these are no more than 'minimal' (or a 'minor increase over minimal'), and in research *with* the prospect of direct benefit they must be proportional to the expected benefit.(3, 5, 19) During the ethical review phase, RECs ensure that research protocols comply with these requirements for *all eligible children*.(2) Then, during the informed consent process, all persons concerned estimate whether participation is acceptable for *the individual child* concerned.(1) In the present analysis we suggest to also systematically check

during the trial whether the actual burden indeed can be regarded as minimal or as proportional for each participating child. The permitted levels of burden apply to all children and all children should be monitored, not only those who are too young to express dissent. The core question is: is the actual *experienced* burden indeed minimal (in research *without* the prospect of direct benefit), or proportional (in research *with* the prospect of direct benefit)? Figure 1 shows the existing protective measures related to the principle of non-maleficence, and how the principle should be operationalised during the course of the study. Thus our recommendations are well connected to the protective measures that are already in place.

Obviously, in practice it is not easy to judge whether the observed burden can be considered minimal or proportional. Recognising and interpreting signs of discomfort and relating them to the acceptable levels of burden are difficult tasks. Parents should play an important role in recognising and interpreting signs of discomfort. However the task of relating them to what is acceptable and permitted is more difficult, as the permitted levels of burden are usually not well enough defined. Lists exist in which research procedures are grouped into categories like 'minimal' and 'a minor increase over minimal', but those lists do not do justice to the subjective or personal component of burden; defined by the experience of the person concerned. Putting research procedures in categories like 'minimal burden', 'a minor increase over minimal burden' etcetera can provide direction for RECs, but should not be regarded as rigorous standards, as the actual experience of an individual child can be different. When a child shows signs of fear, distress, discomfort, panic and so on, the research team should be aware of the level of burden that was thought to be acceptable in the present setting. The team will then have to judge whether the observed level of discomfort can be considered to be within these limits. It would certainly help to develop a more operational definition of 'minimal burden'.

When an observed expression of burden is judged as being too high, lowering the burden for that child should be the first step, for example by comforting the child, by pain reducing interventions, by watching videos or listening to music, and so on.(20) However, if such interventions appear to have no, or insufficient effect, the child should be withdrawn from (that part of) the trial.

DISCUSSION

To date there is no sufficient guidance on how to deal with cases where the behaviour of a child raises doubts whether the child should be kept in a trial or should be withdrawn. We have identified two types of reasons for taking such behavioural signs very seriously: 1) respect for the growing autonomy of the child, in those cases where the child expresses a clear, explicit and persistent wish to be withdrawn from the study; and 2) the principle of non-maleficence, in those cases where the research burden for a specific child appears to exceed the level that was found acceptable during the ethical review process (for all eligible children) and was agreed to during the informed consent process (for the individual child). We recommend systematic monitoring of each child throughout the course of the study. We recommend such monitoring during the performance of research procedures both when the procedure can, and cannot directly benefit the participant. When a child shows signs of discomfort or distress it may be important to know whether there is any prospect of direct benefit. In cases of direct benefit the burden must be proportional to the expected benefit, and if no direct benefit can be expected, the burden must be no more than minimal.

The withdrawal of a child from a trial should remain an exception and should always be a last resort. The informed consent process should be carried out in such a way that in principle all children for whom participation is expected to be too burdensome, are excluded from participation. Minimising the burden before and during the trial is important, because it is not only an ethical requirement, but also the best way to prevent the need for withdrawal. Besides choosing the least burdensome procedures, this also includes providing a child friendly setting, good preparation, distraction and experienced research professionals. When despite such measures the actual burden for a particular child appears to be higher than acceptable, one should attempt to modify procedures in such a way that the child can stay in the trial. Unnecessarily withdrawing a child from a trial would mean that the former efforts of the child (including the exposure to risks and burden) were for nothing. In some cases it may also be possible to withdraw a child only from a certain part of the study, which is preferable over withdrawal from the entire study.

Exceptions ask for an individual and tailored approach. Children can experience and express their discomfort in rather different ways. Moreover, not all children feel equally confident in expressing their dissent. Research professionals should be sensitive to these differences. We are aware that the approach we present may

not provide a clear way forward in all possible situations. For example, what to do in situations in which the research burden seems unacceptably high for a certain child, but the child does not wish to stop? It is not possible to fully answer this question, because, as we just mentioned, a personal approach is needed. However, the first step is trying to lower the burden. Moreover, it is important to learn more about the child's motivation to continue. Vigilance to therapeutic misconceptions is essential here. If the child persists to continue because of an expected therapeutic benefit, where in fact there is no chance of a therapeutic benefit, it is important to uncover this wrong belief and to be sure that the child understands the purpose of the study.

CONCLUSION

In this chapter we addressed the importance of clarity and guidance on how to decide whether trial participation is still justified for a certain child. The failure to recognise and respect a child's dissent may harm the child as his developing autonomy is disrespected. Moreover, without clarity on this matter children may be kept in a trial for too long and may be harmed by the burden they experience, which means the child's well-being is insufficiently protected. Research ethics guidelines should be clear about the meaning of the used concepts. We recommend that terms like dissent and (deliberate) objection be reserved for those children who are capable of expressing a clear, explicit and persistent preference to stop participation. We also recommend that guidelines explicitly link the required monitoring of burden to the permitted levels of burden for the various kinds of research. We realise that our approach asks for some extra regulatory measures and a certain effort from research professionals, but we believe that when aiming to properly protect children in paediatric research against undue harm, these efforts are worthwhile.

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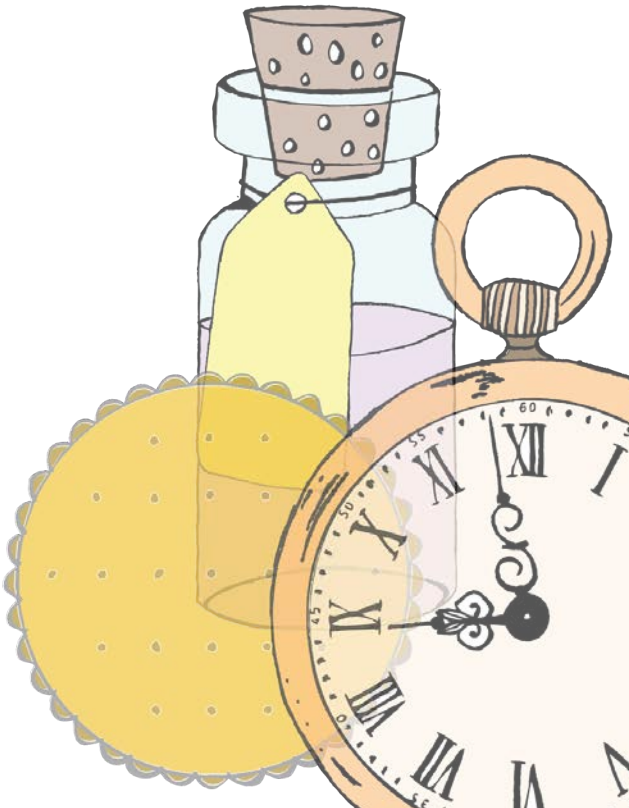
CHAPTER 9

GENERAL DISCUSSION



The ethical governance of clinical research with children is an ever-changing field. During the development of treatments for childhood diseases new challenges continually arise to which scholars, as well as law- and policymakers, have to react. The emergence of new technologies, new types of research, medical development, and new empirical data feed the ethical debate. The balance between the need for more paediatric research to facilitate medical-scientific innovation, and the need to protect children against possible harm associated with research participation, is dynamic.(1-5) Moreover, paediatric research practice shows that there are still certain ethical challenges in this field that deserve attention.(6) In this thesis we have identified some of those challenges, analysed them, suggested possible solutions and provided practical recommendations.

Our research project began with three main topics, each with their own research questions. These topics concerned the procedure-level approach to ethical review (chapter 6), the burden of research procedures for children (chapter 7), and the protection of children during the performance of paediatric research (chapter 8). The research questions on these three main topics will be answered in the next section. Along the way, other questions came up. The interesting case of a multinational trial on Duchenne Muscular Dystrophy (chapter 3) revealed that the ethical issues sketched in chapter 2 are still timely and relevant and that views on these matters can differ profoundly. In chapter 4 we have compared children with another group of vulnerable research subjects, namely dementia patients, to see which morally relevant characteristics these two groups share and how that is represented in legal and ethical guidelines. In chapter 5 we discuss the new European Clinical Trials Regulation, which was drafted and approved during the course of our research project. As the final version of the Regulation had us concerned about the quality of the risk-benefit assessment and the quality of research ethics committees (REC), we took the opportunity to write a critical analysis on the new Regulation. Apart from the results of our three main subprojects, the totality of our work lead me to evaluate the regulatory changes made in the last five years, and to sketch my view on the opportunities for future progress. I will discuss these two topics after an overview of our main conclusions.

MAIN CONCLUSIONS AND ANSWERS TO RESEARCH QUESTIONS

SUBPROJECT 1: A PROCEDURE-LEVEL APPROACH TO ETHICAL REVIEW

The primary aim of this subproject was to investigate the practical need and feasibility of a procedure-level approach to ethical review. To this end, we asked

the following research questions:

- *To what extent are there elements without direct benefit in paediatric studies with direct benefit and vice versa?*
- *What are the practical drawbacks for using a procedure-level approach to ethical review?*

Our study showed that a majority of paediatric intervention studies consist of a combination of both procedures *with*- and procedures *without* the prospect of direct benefit (68%). Of the protocols labelled *without* the prospect of direct benefit, 42% included an intervention that could possibly offer direct benefit. Vice versa, of the protocols labelled *with* the prospect of direct benefit, 94% also included one or more procedures *without* the prospect of direct benefit. Practical drawbacks that were mentioned during group discussions with REC-members concerned the extra time and special expertise that using this method would expectedly cost. Also the need for a clear format was put forward.

The percentages that we found need to be put in perspective. First, the protocols we analysed came from the archives of the Central Committee on Research Involving Human Subjects (CCMO) that supervises local committees and is responsible for the policy on ethical review, and from three local research ethics committees. In the Netherlands, the distinction between paediatric intervention studies *with*- and *without* direct benefit (the terminology used in practice in the Netherlands is 'therapeutic' and 'non-therapeutic') has organisational implications. The CCMO is the only Dutch research ethics committee qualified to review paediatric intervention studies *without* direct benefit. All other accredited research ethics committees are only qualified to review paediatric intervention studies *with* direct benefit.(7) The classification on protocol-level is based on this policy. That classification could partly explain the relatively high number of protocols *without* the prospect of direct benefit that nevertheless included an intervention that could possibly offer direct benefit. It could be the case that when RECs are in doubt about the direct benefit in a protocol, they send it to the CCMO to be on the safe side, thereby classifying it as '*without* direct benefit'. This could possibly explain the relatively high number of protocols that have a beneficial element in them. Still, this does not affect our general conclusion that a substantial majority of the paediatric intervention studies that we analysed, consisted of both procedures *with*- and *without* the prospect of direct benefit.

The high percentage (94%) of protocols *with* direct benefit that include at least one procedure *without* direct benefit is in itself not surprising. Administering an

investigational drug without properly testing the (side) effects would be bad science; therefore additional procedures to test the (side) effects are almost inevitable. Only in rare cases it is possible to test for effect without any extra blood draws or other procedures. The fact that procedures *without* direct benefit are included is not worrisome in itself. However it is worrisome that some studies include a very large amount of extra research procedures *without* the prospect of direct benefit, the so-called package deals.(8) Package deals are studies with an intervention that can possibly provide direct benefit, but that also contain a lot of extra research procedures that are done for data collection only. In some cases additional research questions are added to the protocol and extra measurements are done to answer these additional questions.

A procedure-level approach can help assess such package deals more precisely. The model we proposed in chapter 6 focuses on the distinction between procedures *with*- and procedures *without* the prospect of direct benefit.(9) However, a primary focus on procedures also provides the opportunity to ask other questions about each separate procedure, such as the purpose, the value and the relation to the various research questions within the protocol. For that reason our proposed model seems to be more versatile than other models that have been suggested, such as "component analysis" and the "net-risk test".(10, 11) Also it takes into account Wendler's concern about component analysis, namely that it is prone to accepting therapeutic but insignificant interventions. We have also proposed a more thorough definition of an intervention or procedure *with* direct benefit alongside our model. Our proposed definition is: *an intervention or other procedure that forms a valid therapeutic, diagnostic or preventive option for the participants in the study at stake.* By 'a valid option' we mean that it can expectedly compete with other available (therapeutic/diagnostic/preventive) options for the patient concerned, so that the patients will not receive inferior care. It also acknowledges that procedures can be distinguished based on whether they provide direct benefit or not, and we are convinced that this is a relevant distinction to make. The net-risk test was criticised by Weijer and Miller for unfoundedly regarding the therapeutic/non-therapeutic distinction as arbitrary.(12) By proposing our procedure-level approach we aim at a clean approach with a clear definition and enough space for dealing with complexities.

Several REC members whom we spoke to during our study mentioned that some procedures may not cause any therapeutic effect, but neither are they done solely for data collection purposes. For example, when administering an investigational

drug, the safety of the drug has to be monitored throughout the course of the study in order to protect the participants from undue harm. Given the fact that the participants receive the investigational drug, safety monitoring is by all means necessary. Indeed such procedures are not done solely for research purposes, but also for safety purposes within the setting of clinical research. However, that does not mean that these safety-monitoring procedures provide potential direct benefit, as some of the REC members claimed. They do provide protection, but only given the administration of the investigational drug. The monitoring procedure in itself does not provide any direct benefit. How, then, should these procedures be framed? We propose the following: safety-monitoring procedures should not be regarded as offering the prospect of direct benefit, but are connected to the study intervention that does offer the prospect of direct benefit as they provide protection within the context of receiving the study intervention. Safety-monitoring procedures with higher than minimal risks and/or burdens, can be acceptable if the study intervention has net-benefits. For example because it is a promising intervention that is expectedly much better than existing alternatives, or because it is a new drug for a disease for which no treatment yet exists. These net-benefits can compensate for the higher risks or burdens of the safety-monitoring procedures.

When approaching such complex protocols on the procedure-level, several questions need to be asked:

1. What is the purpose/are the purposes of each individual procedure (providing potential direct benefit, safety monitoring, data collection etc.)?
2. Which procedures relate to the primary and which to the secondary research questions?
3. What are the risks/burdens and the benefits (if any) of each procedure?
4. How do the risks and burdens of each procedure relate to the anticipated benefit (i.e. are they minimal or proportional, and are they minimised)?
5. How do the anticipated risks/burdens and benefits of the intervention relate to other available therapeutic/diagnostic/preventive options for the participants?

The approach that we propose is a flexible one. It does justice to the large diversity and complexity of research protocols. Assessing risks, burdens and benefits first on the procedure-level, rather than on the protocol-level, is the most promising way forward when aiming for fair, precise, clear and transparent ethical review.

SUBPROJECT 2: DOCTORS VIEWS ON RESEARCH BURDEN FOR CHILDREN

This subproject aimed to generate more empirical data on research burden for children. Such data are helpful for RECs when reviewing paediatric research protocols. Until now, not a lot is known on how burdensome certain research procedures are for children, especially not in relation to the categories often used by RECs; *minimal burden*, *a minor increase over minimal burden* and *more than a minor increase over minimal burden*.(13, 14)

The following research question was asked:

- *What is the burden of several research procedures for children, according to paediatricians?*

To answer this question we asked paediatricians to classify thirteen research procedures into the categories of *minimal burden*, *a minor increase over minimal burden* and *more than a minor increase over minimal burden*. The following research procedures were included; bronchial challenge test, a single venipuncture, repeated venipunctures (8x in 6 months), spirometry/pulmonary function test, muscle biopsy, insertion of a venous cannula, allergy skin test, lumbar puncture, buccal swab, bone marrow aspiration (sedated), 1 hour MRI scan unsedated, echocardiography and hospitalisation for two days.

Our questionnaire study showed that on some procedures there was more consensus than on others. For example a buccal swab was seen as minimally burdensome by a very large majority of the respondents, and also an echocardiography was classified thus by most respondents. A large majority classified a muscle biopsy and a lumbar puncture as more than a minor increase over minimal burden. However, on most procedures there was either only a small majority for one of the classifications, or no majority at all.

The spread in classifications may either have to do with actual differing experiences of the respondents, or with the content of the three classifications not being clear enough. With regard to the first issue; physicians might have differing experiences due to working with different age- and/or patient groups. To understand those differences it would help if more was known about how factors like age, the nature of the disease and prior experience with hospitals, influence children's experience of burden.(15, 16) Knowledge on burden experienced by various age- and patient groups is helpful for RECs while assessing the risks and burdens compared to the benefits of paediatric studies. With regard to the second issue; the content of the classifications, it could be the case that even with

similar experiences, physicians would categorise a procedure differently because the definitions of the categories are fuzzy. A clear and more operational definition of minimal burden may be helpful. Westra and colleagues have proposed such a definition, namely that the burden, or risk of discomfort, is minimal when: 'empirical data, expert opinions and/or the procedural characteristics (e.g. invasiveness; disturbance of normal routines) suggest that at most a quarter of the persons concerned will experience considerable discomfort'.(17)

SUBPROJECT 3: DISCOMFORT AND DISSENT

The starting point of this subproject was the evaluation of the Dutch Code of conduct related to expressions of objection by minors participating in medical research.(18) We collaborated with the core working group 'Guideline criteria for research with children', installed by the Paediatric Association of The Netherlands. While evaluating the Code, we found that the issue is broader than objection alone and that on an international scale guidance on this issue is inconsistent and incomplete. We therefore aimed to analyse the issue thoroughly and to provide the required clarity. To that end we set out to answer the following research question:

- *When, and on what ground should signs of discontent and dissent lead to withdrawing a child from a trial?*

A proper ethical review process together with a proper informed consent process provides a solid basis for including a child in a paediatric research study. Still, for a certain child participation can be harder or more burdensome than expected. The child may show signs of discomfort, discontent and dissent in a multitude of ways. Our analysis showed that there are two types of reasons to take such signs very seriously. These two types of reasons are related to two central ethical principles, namely: (1) respect for the growing autonomy of the child, in those cases where a child expresses a clear, explicit and persistent wish to be withdrawn from the study; and (2) non-maleficence, in those cases where the research burden for a specific child appears to exceed the level what was found acceptable during the ethical review process (for all eligible children) and was agreed to during the informed consent process (for the individual child).

We have recommended that during the course of a study all individual children should be monitored systematically. This monitoring should focus on the following two questions: (1) does the child still want to continue its participation?, and (2) is the level of burden that the child experiences still acceptable in relation to the

permitted level of burden for the study concerned? It is advisable to relate the last question to whether or not the research can provide direct benefit. Also in this case the focus should preferably be on the procedure-level.

We also provided practical recommendation to the working group 'Guideline criteria for research with children, for revising the current code of conduct. These recommendations are discussed more extensively later on in this chapter.

MISSED OPPORTUNITIES IN RECENT REGULATORY CHANGES

In the past years several laws and ethical guidelines concerning the regulation of biomedical research with humans have been revised or replaced, which brought changes in the governance of medical research with children. The European Clinical Trials Regulation (CTR), which regulates drug trials, repeals the European Clinical Trials Directive (CTD).(19, 20) With that replacement both the content and the legislative force were changed. The CTR will apply directly to all EU member states without the intervention of national laws, thereby having direct legislative force. In this section I will reflect on the recent regulatory changes and point out some opportunities that in my view were missed.

A RELATIVE STANDARD FOR RISK AND BURDEN

One of the changes with regard to the inclusion of children in drug trials concerned the acceptability of risk and burden. The CTD did not explicitly distinguish between research *with*- and *without* the prospect of direct benefit and as such it did not set any upper limit regarding the risk and burden in research *without* direct benefit. It only required (in article 4) that the research had 'some direct benefit for the group of patients' and that the risks and burdens were minimised in relation to the disease and developmental stage.(20) The CTD was the only document not to set any upper limit for risk and burden in paediatric research *without* direct benefit. The new CTR does set an upper limit, namely; minimal risk and minimal burden related to the standard treatment of the patient.(19) Whether this new standard is an absolute or a relative one depends on its interpretation.(21) However, the most obvious interpretation would be that it represents a relative standard, meaning that a higher level of risk and burden is allowed in research *without* direct benefit with patients who face higher risks and burdens in the context of their treatment, than for similar research with patients undergoing less severe treatments.

It is remarkable that a relative standard was adopted in the Clinical Trials Regula-

tion. There has been extensive debate in the United States about whether the definition of minimal risk used in the Federal Regulations (the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during routine physical or psychological examinations or tests) should be regarded as an absolute or a relative one.(17, 22-26) Obviously, the routine examinations and tests some patients undergo involve far more risk than the ones other patients, or even healthy children, usually undergo. In the context of that debate many scholars have convincingly argued that a relative standard is unjust, as it would mean that healthy children would receive a higher level of protection than patients.(27) By consequence, patients receiving the most severe treatments would receive the lowest protection (in terms of the acceptability of risk) in the context of research *without* direct benefit. Those in favour of a relative standard argue that this is justified because children who undergo risky and burdensome medical procedures in the context of standard care are more used to them and as such it would be less of a problem for them to also undergo them in the context of research.(28) This argument is problematic in two respects. First, while it might be correct that children can get used to certain procedures in terms of burden (or risk of discomfort), one cannot get used to the risks (of harm). Second, while some children do get used to certain procedures in terms of burden and by consequence experience *less* discomfort when undergoing them again, others have bad experiences with the same procedures and experience *more* discomfort the next time around.(27) Thus, children in the latter category would receive inferior protection with a relative minimal risk standard, as those children will likely experience more discomfort than what can reasonably be considered minimal. A counterargument would be to trust that these children and their parents, after being informed about the purpose, the design and the risks of a trial, would not consent to those trials, as they know it contains a procedure that the child is uncomfortable with. That argument is somewhat naïve, as therapeutic misunderstandings and sloppy informed consent practices have long been and still are prevalent.(29-31) Until those problems are solved, accepting more than minimal risk and burden for research *without* direct benefit should only be done with the greatest caution.

Adopting a relative standard for all paediatric drug research in the Clinical Trials Regulation does not demonstrate such caution. Apparently, the American debate on the minimal risk standard was not taken into account while drafting the CTR, which is a missed opportunity. It would have been better to clearly formulate an absolute standard of minimal risk and burden for research *without* direct benefit,

and to allow exceptions for extraordinary valuable research, while clearly stating in which situations, under which conditions and by which regulatory bodies such exceptions can justifiably be made.

PROCEDURE-LEVEL APPROACH

Alongside the drafting of the European Clinical Trials Regulation, the CIOMS guidelines (2015) and the Declaration of Helsinki (2013) were revised as well.(32, 33) The revised CIOMS guidelines have been drafted in 2015 and were approved by the General Assembly in 2016. The CIOMS guidelines are the only ethical guidelines in which a procedure-level approach to the risk-benefit assessment was explicitly adopted. Due to the lack of agreement among ethicists about which procedure-level approach is preferable (component analysis or the net-risk test), a more general approach was chosen in the revised guidelines.(10, 11) In paragraph 4 it is stated that *'it is essential not to directly judge the risks and potential benefits of studies as a whole in order to avoid missing potential concerns about individual interventions. Rather, the risks and potential benefits of each individual research intervention or procedure in the study must first be evaluated. Then, in a second step, the aggregate risks and potential benefits of the entire study must be assessed and must be considered appropriate'*.(33) This requirement grasps the mere basics of a procedure-level approach, but still emphasises why it is important to assess all procedures separately first.

Unlike the CIOMS guidelines, the Declaration of Helsinki and European Clinical Trials Regulation did not choose to adopt a procedure-level approach in their latest revision or drafting. This is unfortunate, as both are highly influential documents that could have taken the opportunity to incorporate recent developments in research ethics, thereby potentially contributing to improvement of ethical review practices.

WAYS FORWARD

The protection of children as subjects in biomedical research has been greatly improved ever since the drafting of the Nuremberg Code in which basic principles like voluntariness, the avoidance of unnecessary harm and the proportionality of risks were first declared in an internationally adopted document in the context of research with humans.(34) Since then, many other ethical guidelines and legal documents have started to govern medical research with human subjects on the national and international level, with the aim to foster ethical research conduct

and to properly protect research participants.(19, 20, 22, 35-39) Over time these documents got more specific. They started to focus on specific groups of subjects and have zoomed in on specific ethical challenges in research, such as the use of placebo and research in developing countries.(38, 40)

As I mentioned in the general introduction of this thesis, ethics stories rarely come with actual endings. Ethics is a philosophical discipline that aims to answer the question 'what should I do?'.(41) Medical ethics strives to know what is the right thing to do within the context of medical care, and in this case specifically, in the context of paediatric research. The context continually changes, develops and innovates and with that, new ethical challenges arise. Currently existing measures of protection leave space for strengthening and improvement and could be better directed to actual questions from this evolving context. With this thesis I aim to contribute to the strengthening of the existing protective measures. In this section I will propose several ways forward concerning this space for improvement, that follow from the results of my research project.

THE VALUE OF A PROCEDURE-LEVEL FOCUS BEYOND ETHICAL REVIEW

As was described in chapter 6, a procedure-level approach to the assessment of risks and benefits has the potential to seriously improve the ethical review of paediatric research protocols. I also shortly mentioned that such a procedure-level approach may benefit other steps in the research process as well. Ideally, all professionals involved in paediatric research are aware of the distinction between procedures *with-* and procedures *without* direct benefit and of the accompanying requirements concerning risk and burden.

The first step in which a procedure-level approach can be valuable is the **design** of research projects. A primary focus on procedures stimulates critical thinking about the intention and the value (for science only or also for treatment/diagnostics/prevention) of each separate research procedure. While designing a research project it seems helpful to ask the following questions about every single procedure; (1) what is the aim/are the aims of the procedure? (2) can the procedure provide therapeutic/diagnostic/preventive benefit to the participants themselves? and (3) what are the risks and the burdens of the procedure and are they minimised? Obviously, researchers know that paediatric research is subject to certain rules concerning the acceptability of risk and burden. However, they are not always exactly aware of the ethical considerations underlying these rules. This offers space for improvement and the opportunity to improve ethical research practices. It is not unlikely that more knowledge of the ethical principles on which

legal rules are founded, helps researchers to construe research designs that are better balanced in terms of risks, burdens and benefits, especially when combined with a procedure-level focus.

Second, a procedure-level approach will likely improve **ethical review** of protocols, as was described extensively in chapter 6. Summarising, a procedure-level approach has substantial advantages compared to the conventional approach that approaches protocols as a whole. In addition to a more precise and transparent risk-benefit assessment, it could account for an earlier identification of other ethical concerns, such as procedures that are unlikely to yield important data or procedures that can be replaced by a less risky or burdensome one.

Third, the process of **informed consent** may benefit from the awareness that a research protocol can consist of a combination of procedures that are done in order to collect data, and of procedures that can (also) benefit the participants themselves. Clearly, a valid informed consent requires a proper understanding of the research risks and burdens. In order to decide whether they accept the risks and burdens of a study, children and parents should know which risks and burdens relate to a beneficial procedure and which risks and burdens relate solely to the purpose of research. Proper, clear and honest information is more likely to lead to a durable decision.

Lastly, for the **monitoring of risk and burden during the course of the trial**, a procedure-level focus is important as well. The level of burden that a study is expected to impose on children, does not always align with the actual experienced burden of a specific child. This can lead to situations that raise doubt about whether it is still justified to keep a child in a trial.(42) A proposal for guidance on how to react to such situations was provided in chapter 8. While monitoring the actual burden a child experiences, a procedure-level focus can be helpful as it makes clear which level of burden is acceptable for the procedure concerned. Procedures that cannot offer any direct benefit for the participants should impose no more than minimal burden (as was argued in chapter 6). Otherwise, the burden of procedures that *can* offer direct benefit should be proportional in relation to the expected benefit. A clear and well thought out decision therefore relies on a clear view on the purpose and value of each procedure.

It could be helpful for both researchers and research ethics committees to use a clear format for the identification and assessment of separate procedures.

ALLOWING EXCEPTIONALLY VALUABLE, BUT HIGHER RISK RESEARCH

In the general introduction of this thesis I have described the long process of changing the Dutch national law on research involving human subjects, with regard to paediatric research. It had started with discontent among paediatricians about the restrictiveness of the law. They felt that the law did not provide enough possibility for doing paediatric research *without* direct benefit and that the Netherlands lagged behind other countries in terms of medical-scientific innovation.(43, 44) Around the same time the CCMO expressed the wish to be able to approve valuable studies that until that time laid beyond the scope of what the law permitted.(45) The Committee Doek then concluded that the 'negligible risk and minimal burden' requirement should be removed from the law altogether.(46) Yet, the advice of the Committee Doek was not adopted in the draft of the revised law. Instead, the American standard of 'a minor increase over minimal risk (and burden)' was chosen in the new proposal.(47, 48) However meanwhile the European Clinical Trials Regulation was drafted and approved, so the final version of the revised Dutch law was adjusted to the CTR, as the CTR would have direct legislating force. The new minimal risk requirement is therefore that research *without* the prospect of direct benefit may impose only 'minimal risk and minimal burden related to the standard treatment of the patient'.(19)

As argued before, expanding the leeway for paediatric research *without* direct benefit by replacing the absolute minimal risk standard for a relative one was irresponsible, as it gives too much space for research that is riskier than acceptable. The proposal of allowing a 'a minor increase over minimal risk' was less problematic, but it is doubtful whether it would have even been necessary. Regardless of the idea that exists among paediatric researchers that research *without* direct benefit is nearly impossible because of legal limitations, research by Westra et al shows otherwise. They studied all decisions by the CCMO about the 165 proposed paediatric research protocols *without* direct benefit between the years 2000 and 2007. Of these 165 protocols, 111 were observational studies and 54 were intervention studies. The analysis by Westra et al shows that the CCMO rejected only three protocols for the single reason that the risks or burdens exceeded the minimal level. Eight other protocols for which the minimal risk and burden requirement was a reason for rejection, also failed to meet other ethical requirements, like group relatedness. In 26 other cases protocols ultimately got

approved after modification related to the requirement of minimal risk and burden.(49)[1] It could be the case that researchers do not propose protocols they judge to be out of bounds, to research ethics committees, thereby leading to a 'proposal bias'. Unfortunately no data are available on how many protocols are not proposed to research ethics committees, or even not designed at all because of the expectancy that they will be rejected.(46) Still, the question remains whether changing the minimal risk and burden requirement is the best solution. The analysis by Westra et al showed that many protocols *without* direct benefit did get approval, either immediately or after modification.(49) Apparently, the CCMO is willing to work with researchers in order to adjust the proposed protocols towards an acceptable level of risk and burden. Maybe researchers are insufficiently aware of the possibilities of doing paediatric research *without* direct benefit, despite the legal restrictions. If this were the case, the solution would be to educate researchers on this matter, rather than to change the law.

Sometimes a higher-risk protocol *without* direct benefit is so promising and valuable, that the higher risks are justified for that specific case and it is important that there is a way to approve such protocols. The same study by Westra et al shows examples of valuable studies that should have been rejected when strictly following the legal framework. Still, because of their importance the CCMO approved them by stretching the notion of direct benefit.(49) Such regulatory detours are not a desirable and durable solution. But expanding the minimal risk standard itself gives space to *all* protocols *without* direct benefit to incorporate higher risks, not only the really promising ones. A much more elegant and far less cumbersome solution than changing the concerning law article, would be to grant the CCMO the discretion to make exceptions to the minimal risk and burden requirement in cases of exceptionally promising and valuable research, under the condition that the committee seeks expert advice and transparently reports how it came to the decision to deviate from the minimal risk requirement. Obviously, this is not possible as long as the European Clinical Trials Regulation requires otherwise.

[1] The CCMO uses its own interpretation of the national law for distinguishing between research with-, and research without direct benefit. It may be the case that following that interpretation, relatively many protocols are labelled as without direct benefit.

THE QUALITY OF RESEARCH ETHICS COMMITTEES

It has always been important to guarantee the quality of RECs. Yet, with the high number of RECs in some EU countries, it has been questionable whether all these committees have adequate (paediatric) expertise and experience. It seems that in several EU countries the number of RECs has somewhat decreased in past years, for example in the Netherlands and the United Kingdom.(50, 51) That could be a positive development, as individual committees will probably gain more reviewing experience with paediatric protocols.

The approval of the new Clinical Trials Regulation brought changes in the governance of paediatric drug research. All EU member states will be bound to the requirement of *minimal risk and burden in relation to the standard treatment of the patient* for paediatric drug research *without* direct benefit. For some EU member states that is a stricter requirement than before (e.g. Belgium), while for others it is a wider requirement (e.g. the Netherlands, that had a stricter version of the requirement before but chose to adjust the national law in accordance with the CTR). Whether stricter or wider than before, for all EU countries counts that quite a complex risk-benefit assessment needs to be carried out for paediatric drug research *without* direct benefit. This requires that committees that review such research have excellent paediatric expertise and sufficient experience.

On top of that, with the new CTR coming into force, more authority is granted to the so-called 'reporting member state' in multinational trials. The reporting member state, proposed by the sponsor, makes the final decision about the risk-benefit assessment. While the other participating member states are to be consulted about the risk-benefit assessment, this needs to be done in a rather limited time frame. Their main task is to assess local aspects such as the informed consent material, the qualifications of the investigators and the trial site.(19, 52) With these large responsibilities, the quality of the assessment should be guaranteed, but unfortunately it is not. The Clinical Trials Regulation includes no measures that can guarantee the quality of RECs. This was discussed in chapter 5.

An example of efforts to guarantee adequate experience and expertise is found in the Netherlands. The REC of the UMC Utrecht in the Netherlands has a dedicated and specialised chamber that reviews research with children.(53) Moreover, as mentioned before, the central committee (CCMO) is the only REC that is qualified to review paediatric intervention studies *without* direct benefit.(7) Lastly, the revised national law requires that at least one paediatrician should be part of every REC that reviews paediatric protocols.(54)

GUIDANCE FOR PROPER PROTECTION DURING THE PERFORMANCE OF RESEARCH

The ethics of including children in clinical research remains a topic of great interest and this is not surprising. It is easy to relate to the harm potentially inflicted by both the lack of proper treatments for childhood diseases, as well as by the risks of testing new interventions on children. This is the basic dilemma underlying all challenges in paediatric research ethics.(1) Some topics within this domain have been researched and discussed extensively, especially the legal requirements, the ethical review process and the informed consent process. Examples are the debates about the minimal risk standard and about the value of assent. Still, surprisingly little was written on how to properly protect children when they are already participating in the trial.(55, 56) Besides that, the relevant laws and ethical guidelines provide rather sparse and inconsistent guidance on how to guarantee the protection of children during trial participation. Although voluntariness has been a central value ever since the emergence of research ethics, during the performance of research studies it is safeguarded in a rather minimalist way. Looking at laws and ethical guidelines, it seems that requiring respect for dissent or objection of a child, is regarded as good enough protection. Yet, the exact content of concepts like 'dissent' and 'objection' remain quite vague, as do the consequences that should follow on dissent or objection. Such vagueness hardly contributes to proper protection.

Meanwhile, many research professionals are interested in protecting children during a trial. From a workshop we organised for research nurses and from discussions after presentations we gave, it became apparent that in practice it is very difficult to decide when to withdraw a child from a study. Many of the research nurses we spoke to, could name one or more examples of children having such a hard time undergoing research procedures that it raised doubt about whether the research should continue with that child.

In chapter 8 we proposed a more thorough view on how the protection of children during the performance of studies should be safeguarded. In that chapter we showed that respect for dissent should not be confused with protection against undue burden. Both the voluntariness of, and the degree of burden for each individual child should be closely monitored throughout the entire course of paediatric studies.

As a part of our study we evaluated the Dutch 'Code of conduct relating to expressions of objection by minors participating in medical research' and pro-

posed a revised version of the code.(18) Our recommendations for a revised code were, apart from the evaluation of the initial code, based on our conceptual analysis, our analysis of the most influential legal and ethical guidelines (chapter 8) and on feedback from research nurses during a focus group and a workshop. The revised code, which we co-wrote, is currently in the process of approval. We recommended that the following elements be included in the revised code:

- Instead of asking the question whether the child shows signs of objection, ask the question whether the child should be withdrawn from the study.
- When deciding about whether a child should be withdrawn from a study, distinguish between decisions based on high levels of experienced burden, and decisions based on the explicit wish of the child.
- Both the experienced burden and the voluntariness of the child should be closely monitored throughout the entire course of a study.
- While monitoring the degree of burden a child experiences, the purpose of the research procedure at stake should be kept in mind. The burden of procedures that can offer direct benefit for the child should be proportional in relation to the anticipated benefit. Procedures that do not offer any direct benefit, i.e. are done for research purposes only, should pose no more than minimal burden. Research professionals need to be vigilant that the experienced burden of each individual child does not exceed these permitted levels of burden. For example, research ethics committees usually assume that a single blood draw poses no more than minimal burden. Still, a child can be overly scared of a single blood draw and start to panic. In that specific case the burden is likely to exceed the minimal level, and that should be taken seriously. Also, research professionals should be sensitive to the various ways children show their discomfort. While the one child panics, the other child may feel less confident in expressing discomfort and remains relatively silent. However difficult it is to monitor such vague signs of discomfort, it is worthwhile to do it as well as possible.
- The research protocol should provide information on how the monitoring of burden is to be done. Standardisation of monitoring is not necessary.
- When monitoring reveals that the burden is too high for a certain child, the research team, together with the parents, should attempt to lower the burden. Comforting the child, distraction by music or a video, waiting for a little while and so on are examples of possible ways to lower the burden.

- The parents should be involved in the interpretation of the behaviour of the child.
- The burden of research procedures should always be minimised. Apart from choosing the least burdensome procedure, this also involves a child-friendly setting, experienced research professionals and proper information and preparation for the child concerned.
- When a child expresses an explicit wish to stop participating, this wish should be respected.
- At various points in time during the course of a study, a research professional should evaluate the research participation with the child and the parents. The research professional can remind the child and the parents that participation is voluntary and that the decision to stop can be made at any time.

SUGGESTIONS FOR FURTHER RESEARCH

We have argued why a procedure-level approach to ethical review is a promising way forward towards a more clear and precise risk-benefit assessment. We have proposed a clear and useful definition of direct benefit as well as a model of the various steps of the procedure-level approach. Research into the implementation of this method would be advisable and would ideally start with a pilot project, which is carefully evaluated afterwards to detect bottlenecks and opportunities for improvement. Attention should be given to the development of a format in which procedures *with*- and *without* direct benefit can be distinguished, as well as procedures related to the primary and the secondary research questions.

We have conducted an exploratory study on research burden for children as estimated by paediatricians. Simultaneously, a study on the self-reported burden of children was carried out.(15) An interesting follow up would be to compare the experiences or estimations by the various parties involved in the same trial. Ideally, the reviewing REC, the research professionals performing the study, the children undergoing the study and their parents are asked about the burden of the research. This way the viewpoints of the different parties can be meaningfully compared.

The revised code of conduct on objection, which we co-wrote, should be evaluated after several years of use. A code of conduct is only useful when it is readable and understandable; both content-wise and language-wise. Evaluation should

focus on this. It should be researched how the key concepts in the code are understood and how they are brought to practice. It would be interesting to see what monitoring strategies are used and how they could be improved. The improvement and/or development of monitoring strategies could also be an interesting and important research subject itself.

CONCLUDING REMARKS

Lewis Carroll taught us how to tell a story, but he taught us another lesson too. The right road to take depends a great deal on where we want to go.(57) Where I want to go in this case is a paediatric research context in which children are approached respectfully with regard to all their relevant characteristics. Children are vulnerable and they cannot (fully) consent to research participation. All protective measures for children as research participants evolve around this notion. But children are not *only* vulnerable and unable to consent.(2) They are persons, with experiences, with ideas and with opinions. Growth and development are essential and inherent characteristics of childhood. As such, children should be regarded partners in the research project, rather than subjects alone. Yes, children deserve the best protection, and that should include protection of their developmental growth and their emerging autonomy. That means that besides recognising what they cannot yet do, we also need to see and recognise what children *can* do. Whenever possible, we should strengthen the position of children by involving them in issues that concern them, encourage them to voice their wishes, questions and concerns and create an environment in which they can feel confident to do so.

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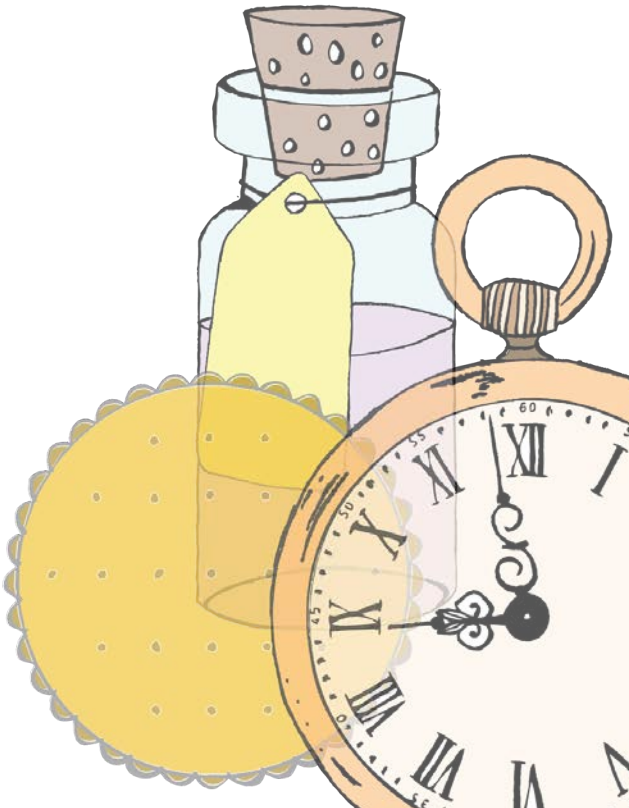
ADDENDUM



ENGLISH SUMMARY

In **chapter 1**, the general introduction, I sketch the central dilemma around which all questions in paediatric research ethics evolve. Either we accept that children who are ill cannot be properly treated or receive treatments that are not well researched, or we have to include children - who are vulnerable and unable to consent - in clinical research, which can possibly harm them. Children deserve to be protected against such harm, but they also deserve timely access to medical treatments. The large number of off-label and unlicensed prescriptions in paediatrics illustrates the need for more clinical research with children. The main challenge then is to find the most responsible way to regulate and perform research with children. While in general this is a much-discussed topic, there are specific questions that still need reflection and research.

Chapter 2 sketches the central ethical issues of clinical research with children. I give an overview of the regulatory landscape within the European Union. I specifically address two major ethical concerns; namely the acceptability of research risks and the informed consent process. The biggest challenges ahead are the implementation of legal requirements and the fostering of ethical research conduct in practice. By means of a short appendix I describe the repealing of the European Clinical Trials Directive by the European Clinical Trials Regulation, which was approved after the publication of our paper.

Then, after overviewing the regulatory framework and central ethical concerns, the thesis moves to an example from paediatric research practice in **chapter 3**. This chapter describes the case of a multinational paediatric research protocol on Duchenne muscular dystrophy that was approved in Belgium and Sweden but not in the Netherlands. All three countries are member states of the European Union and as such are subjected to the Clinical Trials Directive. The Directive aimed to harmonise the ethical review of multinational trials, but nevertheless ethical review outcomes differ. We took the case of this protocol to start a discussion on the acceptability of risk and burden. After illustrating the case, we asked the various parties involved in the case to reflect on whether and why the risks and burdens of this protocol were acceptable. Afterwards, two independent commentators reflected on the same question. Although the question we asked largely remained undiscussed, the discussion revealed some other questions that still need to be researched.

Chapter 4 focuses on the morally relevant characteristics of children as research subjects. Children are compared with another vulnerable group of subjects; namely dementia patients. These two groups of research subjects have certain characteristics in common and differ in others. The relevant characteristics of these two groups are not always well reflected in the regulatory framework. This chapter provides an overview of the relevant criteria and requirements in international legislation and ethical guidelines and identifies inconsistencies with respect to the two groups.

As mentioned before, during the course of our research project the new European Clinical Trials Regulation was drafted and approved. **Chapter 5** presents a critical analysis of the new regulation. The new regulation will replace the Clinical Trials Directive, which did not reach its goals of simplifying and harmonising the process of scientific and ethical review. However, the new Regulation also fails to guarantee the quality of the review process. Two main concerns described in this chapter are the quality of the risk-benefit assessment and the quality of ethics committees.

Chapter 6 presents the results of the first main subproject. This chapter discusses the need for a procedure-level approach to the risk-benefit assessment of paediatric research protocols. This means that research protocols are not primarily approached as *with*- or *without* the prospect of direct benefit as whole, but instead the first focus is on the separate procedures within the protocol. The theoretical advantages of a procedure-level approach, like a more fair and precise risk-benefit assessment, have been made clear already, but little empirical research has been done on the practical aspects. We showed that a majority of the research protocols consist of both procedures *with*- and *without* a prospect of direct benefit for the participants and that a rigid distinction on protocol-level is not tenable. Moreover, we discuss some related questions as well as practical concerns.

The second main subproject is presented in **chapter 7**. It describes paediatricians' views on research burden for children. Research with children is strictly regulated, and the permitted levels of burden for the participants are limited. For example, research that offers no possible direct benefit for the participants is usually considered acceptable when it, among other requirements, entails no more than (a minor increase over) minimal burden. The concept of burden therefore plays an important role in paediatric research ethics. This chapter presents the results of a questionnaire study among 86 physicians. The physicians were asked to put

thirteen common research procedures into the categories of 'minimal burden', 'a minor increase over minimal burden' and 'more than a minor increase over minimal burden'. Although some procedures are clearly put in the category of 'minimal burden' by a large majority of the respondents, and other procedures on the other end of the spectrum, there is disagreement among physicians about most of the procedures. This raises ethical questions. For example; given such disagreement, how can the concept of minimal burden be used in a meaningful way?

Chapter 8 presents the results of the third main subproject. It focuses on the protection of children *after* their inclusion in clinical research. However profound and precise the efforts of research ethics committees and research professionals are during the ethical review and the informed consent phase, they are no guarantees that participation is not harder than expected for a specific child. Adequately protecting children during the course of a study also means 'to react properly to signs of discomfort and dissent'. It needs to be clear in what kind of situations participation is still justified, and in what kind of situations it is not. In this chapter we show that guidance on this matter is scarce and inconsistent. We propose a more thorough approach as well as practical recommendations on how to safeguard the protection of children, also during this phase of the study. We argue that during research participation each child should be constantly monitored. Monitoring should focus on whether research participation of the child is still voluntary, and on whether the actual experienced research burden is not higher than acceptable.

Ultimately, practical proposals are needed for the improvement of ethical research conduct. In **chapter 9**, the general discussion, I present the main conclusions of our research project, but I also identify missed opportunities concerning the recent regulatory changes. Lastly, I present my ideas on the possible ways forward for the future of paediatric research ethics.

NEDERLANDSE SAMENVATTING

In **hoofdstuk 1**, de algemene inleiding, schets ik het centrale dilemma van de ethiek van medisch-wetenschappelijk onderzoek met kinderen. Ofwel we accepteren dat zieke kinderen niet goed behandeld kunnen worden of behandelingen krijgen die niet goed zijn onderzocht. Ofwel we moeten kinderen – die kwetsbaar zijn en niet zelfstandig kunnen beslissen - includeren in medisch-wetenschappelijk onderzoek dat risico's en belasting met zich mee brengt. Kinderen verdienen bescherming tegen zulke risico's en belasting, maar ze verdienen ook tijdige toegang tot medische behandelingen. Het grote percentage off-label gebruik van geneesmiddelen in de kindergeneeskunde illustreert de noodzaak om meer onderzoek te doen bij kinderen. De voornaamste uitdaging is om onderzoek met kinderen op de meest verantwoordelijke manier te reguleren en uit te voeren. Hoewel dit in het algemeen een veel bediscussieerd onderwerp is, zijn er specifieke vragen die onderzoek en reflectie verdienen.

Hoofdstuk 2 schetst de centrale ethische kwesties met betrekking tot medisch-wetenschappelijk onderzoek met kinderen. Ik beschrijf in dit hoofdstuk de wet- en regelgeving binnen de Europese Unie. In dit hoofdstuk noem ik twee belangrijke ethische kwesties; namelijk de aanvaardbaarheid van onderzoekrisico's en het informed consent proces. De grootste uitdagingen voor de toekomst zijn de implementatie van wettelijke vereisten in de praktijk en het bevorderen van ethisch onderzoeksgedrag in de praktijk. In een kort nawoord beschrijf ik dat de Europese Richtlijn Geneesmiddelen Onderzoek is vervangen door de Europese Verordening Geneesmiddelen Onderzoek, welke door het Europees Parlement werd aangenomen na de publicatie van ons paper.

Na het overzicht van het wettelijke kader en de centrale ethische kwesties, vervolgt mijn proefschrift in **hoofdstuk 3** met een voorbeeld uit de praktijk van onderzoek met kinderen. Dit hoofdstuk beschrijft een multinationale studie naar Duchenne spierdystrofie. Deze studie werd goedgekeurd in België en Zweden, maar niet in Nederland. Deze landen zijn alle drie lid van de Europese Unie en vielen daarmee destijds binnen het bereik van de Europese Richtlijn Geneesmiddelen Onderzoek. Deze Richtlijn had als doel de ethische toetsing van multinationaal onderzoek binnen de EU te harmoniseren, maar toch verschilde het besluit tussen deze landen. We hebben deze casus gebruikt om een discussie te beginnen over de aanvaardbaarheid van risico's en belasting. Na het beschrijven van de casus hebben we verschillende betrokkenen gevraagd om te reflecteren

op de vraag waarom de risico's en belasting van deze studie wel of niet aanvaardbaar waren. Daarna hebben we twee onafhankelijke commentatoren gevraagd om op dezelfde vraag te reflecteren. Hoewel onze vraag voor een groot deel onbeantwoord bleef, heeft de discussie wel een aantal andere vragen blootgelegd die verder onderzocht moeten worden.

Hoofdstuk 4 richt zich op de moreel relevante eigenschappen van kinderen als proefpersonen in onderzoek. Kinderen worden vergeleken met een andere groep van kwetsbare proefpersonen; namelijk mensen met dementie. Deze twee groepen van proefpersonen delen bepaalde eigenschappen maar verschillen in andere eigenschappen. De relevante eigenschappen van deze twee groepen zijn niet altijd terug te vinden in het wettelijke kader. Dit hoofdstuk geeft een overzicht van de relevante criteria en vereisten in internationale wetten en ethische richtlijnen en identificeert inconsistenties met betrekking tot de twee groepen.

Zoals eerder genoemd is tijdens de uitvoering van ons onderzoek de nieuwe Europese Verordening Geneesmiddelen Onderzoek opgesteld en aangenomen door het Europees Parlement. **Hoofdstuk 5** geeft een kritische reflectie op de nieuwe Verordening weer. De nieuwe Verordening neemt de plaats in van de Europese Richtlijn Geneesmiddelen Onderzoek, die het beoogde doel om het proces van wetenschappelijke en ethische toetsing te simplificeren en te harmoniseren, niet heeft waargemaakt. Toch lukt het ook de Verordening niet om de kwaliteit van het toetsingsproces te waarborgen. De twee voornaamste bezwaren zijn het niet waarborgen van de kwaliteit van de afweging van risico's en voordelen en van de kwaliteit van toetsingscommissies.

Hoofdstuk 6 geeft de resultaten weer van het eerste subproject. Dit hoofdstuk bespreekt de noodzaak van toetsing van onderzoek met kinderen op procedureniveau. Dat wil zeggen dat onderzoeksprotocollen niet primair benaderd worden als studie die in hun geheel wel of geen direct medisch voordeel voor de proefpersoon bieden. In plaats daarvan ligt de primaire focus bij de afzonderlijke procedures binnen het protocol. De theoretische voordelen van een benadering op procedureniveau zijn duidelijk; onder andere een eerlijkere en preciezere afweging van de risico's en de voordelen. Maar er is nog nauwelijks empirisch onderzoek gedaan naar de praktische aspecten. Onze resultaten laten zien dat de meerderheid van onderzoeksprotocollen bestaan uit een combinatie van procedures *met*- en procedures *zonder* direct medisch voordeel en dat daarom een rigide onderscheid op protocolniveau niet houdbaar is. Ook bespreken we in dit hoofdstuk een aantal gerelateerde vragen en praktische aspecten.

Het tweede subproject wordt beschreven in **hoofdstuk 7**. Hierin wordt besproken hoe kinderartsen de belasting van meedoen aan onderzoek voor kinderen inschatten. Onderzoek met kinderen wordt strikt gereguleerd en de toegestane mate van belasting voor de proefpersonen is beperkt. Bijvoorbeeld, onderzoek dat geen potentieel voordeel voor de proefpersonen biedt wordt over het algemeen acceptabel bevonden wanneer, naast andere vereisten, de belasting niet meer is dan minimaal. Het concept minimale belasting speelt daarom een belangrijke rol in de ethiek van onderzoek met kinderen. In dit hoofdstuk staan de resultaten van een vragenlijststudie onder 86 artsen. De artsen (overwegend kinderartsen) werden gevraagd om dertien onderzoeksprocedures te classificeren in de categorieën 'minimale belasting', 'in gerichte mate meer dan minimale belasting' en 'meer dan in geringe mate meer dan minimale belasting'. Een aantal procedures werden duidelijk geclassificeerd in de eerste of de laatste categorie door een meerderheid van de respondenten. Echter, voor veel procedures geldt dat de respondenten het niet eens waren over hoe belastend deze zijn voor kinderen. Dit roept ethische vragen op. Bijvoorbeeld, als men het niet eens is over de belasting van onderzoeksprocedures, hoe kan het concept minimale belasting dan op een zinvolle manier worden toegepast?

In **hoofdstuk 8** staat het derde subproject beschreven. Het hoofdstuk richt zich op de bescherming van kinderen *na* de inclusie in medisch-wetenschappelijk onderzoek. Hoe grondig en zorgvuldig de ethische toetsing en het informed consent proces ook worden uitgevoerd, het geeft geen garanties dat deelname aan onderzoek voor een specifiek kind niet zwaarder is dan verwacht. De adequate bescherming van kinderen tijdens de uitvoering van een onderzoek betekent ook dat er goed moet word gereageerd op signalen van ongemak en verzet. Het moet duidelijk zijn in welke situaties deelname van een kind nog verantwoord is, en in welke situaties niet. In dit hoofdstuk laten we zien dat het wettelijke en ethische kader erg weinig houvast geeft met betrekking tot dit onderwerp. Wij stellen een meer grondige en volledige benadering voor met daarbij praktische aanbevelingen over hoe ook tijdens de uitvoeringsfase van onderzoek de bescherming van deelnemende kinderen kan worden bewaakt. Wij beargumenteren dat ieder kind tijdens een onderzoek continu zou moeten worden gemonitord. Monitoring zou zich moeten richten op twee vragen; (1) is deelname van het kind nog steeds vrijwillig, en (2) is de werkelijk ervaren belasting voor een kind niet hoger dan acceptabel?

Uiteindelijk zijn er praktische voorstellen nodig om de bescherming van kinderen die meedoen aan onderzoek te waarborgen en te verbeteren. In **hoofdstuk 9**, de algemene discussie, presenteer ik de belangrijkste conclusies van mijn onderzoek. Daarnaast identificeer ik gemiste kansen bij recente wijzigingen van wetten en ethische richtlijnen. Tot slot presenteer ik mijn ideeën over mogelijke vooruitgang van de ethiek van medisch-wetenschappelijk onderzoek met kinderen.

SAMENVATTING VOOR KINDEREN

Dit boek gaat over kinderen die meedoen aan medisch-wetenschappelijk onderzoek. Zulk onderzoek is nodig om goed te begrijpen hoe een kinderlichaam werkt. Het is ook nodig omdat we willen weten hoe we zieke kinderen beter kunnen maken. Daarom worden er soms nieuwe medicijnen getest. In **hoofdstuk 1** staat wat er allemaal komt kijken bij dat soort onderzoek. Je mag kinderen niet zomaar gebruiken als 'proefkonijnen'. Een nieuw medicijn kan kinderen beter maken, maar ook zieker maken. Dat weten we niet van tevoren omdat het nog niet eerder is onderzocht. Er zijn daarom regels wanneer onderzoek doen bij kinderen wel en niet mag. Dit boek gaat over hoe die regels eruit moeten zien en hoe ze uitgevoerd moeten worden.

HOOFDSTUK 2: WETTEN EN REGELS

Wat we wilden weten: Wanneer mag een kind volgens de wet meedoen aan een medisch-wetenschappelijk onderzoek met kinderen? Kunnen deze regels beter?

Hoe we daar achter zijn gekomen: We lazen de wetten die er zijn in Europa goed. We hebben ook gelezen wat andere wetenschappers van de wetten vonden.

Welk antwoord we hebben gevonden: De belangrijkste regels zijn:

1. *onderzoek mag alleen bij kinderen worden gedaan als het echt niet bij volwassenen kan*
2. *kinderen moeten informatie krijgen over het onderzoek op hun eigen niveau (want ze moeten het kunnen begrijpen)*
3. *de ouders moeten toestemming geven en als het kan, het kind zelf ook*
4. *onderzoek mag niet te gevaarlijk of te vervelend zijn voor kinderen die eraan meedoen.*

Wat beter kan is ervoor te zorgen dat het niet blijft bij regels. Onderzoekers moeten zo goed mogelijk omgaan met kinderen die meedoen aan onderzoek.

HOOFDSTUK 3: EEN VOORBEELD

Wat we wilden weten: In 2008 hebben wetenschappers een onderzoek bedacht. Aan het onderzoek deden kinderen mee met een zeldzame spierziekte. Dit onderzoek mocht wel in België en Zweden worden gedaan, maar niet in Nederland. Was dit onderzoek nu wel of niet te gevaarlijk en vervelend voor kinderen?

Hoe we daarachter zijn gekomen: We vroegen aan de mensen die met het onderzoek te maken hadden waarom ze het onderzoek wel of niet te gevaarlijk en vervelend vonden. Ook vroegen we hetzelfde aan twee deskundigen die niets met het onderzoek te maken hadden.

Welk antwoord we hebben gevonden: we kregen helaas geen duidelijk antwoord op onze vraag. Dus eigenlijk weten we het nog steeds niet. We zijn wel iets anders te weten gekomen. Er zijn vragen waar mensen het niet over eens zijn en deze vragen moeten onderzocht worden. Bijvoorbeeld: mag je soms een uitzondering maken op de regels? Bijvoorbeeld als de ziekte heel erg is en een nieuw medicijn later misschien kan helpen?

HOOFDSTUK 4: KINDEREN ALS KWETSBARE PROEFPERSONEN

Wat we wilden weten: Kinderen kunnen nog niet goed zelf beslissen of ze mee willen doen aan een onderzoek. Mensen met dementie kunnen dat ook niet goed. Wat zijn de verschillen én de overeenkomsten tussen kinderen en mensen met dementie? Staan die verschillen en overeenkomsten ook in de wet?

Hoe we daarachter zijn gekomen: We lazen de Nederlandse, Europese en wereldwijde wetten over onderzoek doen met mensen. We onderzochten of de regels die daarin staan hetzelfde of verschillend zijn voor kinderen en voor mensen met dementie.

Welk antwoord we hebben gevonden: Sommige wetten hebben dezelfde regels voor *alle proefpersonen die niet zelf kunnen beslissen*. Andere wetten hebben verschillende regels voor *kinderen* en voor *volwassenen die niet zelf kunnen beslissen*. Die verschillen hebben bijvoorbeeld te maken met dat mensen met dementie vroeger wel nog konden beslissen over onderzoek. Ze konden dus 'vooruit' beslissen. Bij kinderen moet je juist rekening houden met wat zij er later van zullen vinden, als ze volwassen zijn.

HOOFDSTUK 5: DE NIEUWE EUROPESE WET

Wat we wilden weten: Is de nieuwe Europese wet beter voor kinderen die meedoen aan onderzoek?

Hoe we daarachter zijn gekomen: We lazen de nieuwe wet goed. We vergeleken de wet met wat wetenschappers zeggen over hoe je kinderen het best kunt beschermen.

Welk antwoord we hebben gevonden: De nieuwe wet is voor een deel beter geworden. Maar we maken ons ook zorgen. In de wet staat namelijk dat het beoordelen van de gevaren en de voordelen voor de kinderen die meedoen, niet hoeft te worden gedaan door een ethiekcommissie die hier veel verstand van heeft. Wij maken ons daar zorgen over omdat deze beoordeling heel belangrijk is, maar ook heel moeilijk. Alleen mensen die daar veel verstand van hebben, kunnen dat goed genoeg doen.

HOOFDSTUK 6: KIJKEN NAAR 'STUKJES' VAN HET ONDERZOEK

Wat we wilden weten: Soms kan een kind door mee te doen aan onderzoek beter worden. Er is ook onderzoek waar kinderen niet beter van kunnen worden. Bijvoorbeeld omdat alleen wordt onderzocht hoe snel het lichaam een medicijn opneemt. De regels zijn strenger voor onderzoek waar kinderen zelf niet beter van kunnen worden. Soms is niet helemaal duidelijk of kinderen wel of niet beter kunnen worden van een onderzoek. Wij hebben een idee om dat op te lossen. Vaak bestaat een onderzoek namelijk uit stukjes waar kinderen wel beter van kunnen worden en stukjes waar kinderen niet beter van kunnen worden. Wij wilden weten hoe vaak dit voorkomt.

Hoe we daarachter zijn gekomen: We zochten in ongeveer 75 onderzoeken naar stukjes onderzoek waar kinderen *wel* beter van kunnen worden, en stukjes waar kinderen *niet* beter van kunnen worden.

Welk antwoord we hebben gevonden: De meeste onderzoeken met kinderen bestaan uit beide soorten stukjes. Een speciale commissie moet altijd beoordelen of een onderzoek gedaan mag worden. Wij vinden dat zulke commissies beter eerst naar deze aparte stukjes kunnen kijken. De commissie kan dan beter bepalen of een onderzoek niet te gevaarlijk en te vervelend is voor kinderen.

HOOFDSTUK 7: BELASTING VAN ONDERZOEKSPROCEDURES VOOR KINDEREN

Wat we wilden weten: Hoe vervelend zijn onderzoeksprocedures (bijvoorbeeld een MRI scan of een allergietest) voor kinderen?

Hoe we daarachter zijn gekomen: We lieten een vragenlijst invullen door ongeveer 85 kinderartsen. De artsen moesten bij dertien procedures aankruisen hoe vervelend deze zijn voor kinderen.

Welk antwoord we hebben gevonden: Over sommige procedures waren de kinderartsen het helemaal eens. Bijvoorbeeld: met een borsteltje een beetje wangslijmvlies afnemen is bijna niet vervelend voor kinderen. Maar met een dikke naald een stukje spier wegnemen is wel heel erg vervelend voor kinderen. Ook waren er veel procedures waarover kinderartsen verschillend dachten. Bijvoorbeeld: hoe vervelend het is om een MRI scan te laten maken. Of hoe vervelend het is om een paar keer op een dag bloed te laten prikken. Daarover waren de kinderartsen het niet met elkaar eens.

HOOFDSTUK 8: ALS MEEDOEN AAN ONDERZOEK TEGENVALT

Wat we wilden weten: Wanneer moet een kind uit een onderzoek gehaald worden?

Hoe we daarachter zijn gekomen: We lazen de Nederlandse, Europese en wereldwijde wetten goed. Ook lazen we de 'Code Verzet'. Daarin staan regels waar onderzoekers zich aan moeten houden als een kind zich verzet tegen het onderzoek. We keken wat er goed en wat er niet goed aan is.

Welk antwoord we hebben gevonden: Ieder kind dat meedoet aan onderzoek moet goed in de gaten worden gehouden. Van tevoren bepaalt een commissie hoe vervelend een onderzoek mag zijn voor kinderen. Als een kind het veel vervelender vindt dan verwacht dan moet dat kind uit het onderzoek worden gehaald. Sommige kinderen zijn al oud genoeg zijn om duidelijk te zeggen dat ze niet meer mee willen doen. Als dat zo is moeten ze ook uit het onderzoek worden gehaald. De meeste wetten noemen wel één van deze twee dingen, maar niet allebei. Sommige wetten zijn niet duidelijk. In de wetten staat bijvoorbeeld niet wat er precies moet gebeuren als een kind zegt dat hij of zij niet meer mee wil doen.

De conclusie van het hele boek staat in **hoofdstuk 9**. Er staat ook in welke dingen in de toekomst beter kunnen. Bijvoorbeeld: de manier waarop de speciale commissies kijken of een onderzoek niet te gevaarlijk of te vervelend is. Volgens ons is er een manier om dat preciezer en eerlijker te doen. Namelijk door eerst te kijken naar de losse stukjes van het onderzoek. Ook moeten we meer te weten komen over hoe vervelend onderzoek eigenlijk is voor kinderen. Ons onderzoek heeft daar een begin voor gemaakt. Een andere onderzoeker heeft deze vraag aan kinderen zelf gesteld. Maar we weten het nog niet goed genoeg. Onderzoekers moeten ook goed weten hoe ze moeten omgaan met kinderen die meedoen aan

onderzoek. Het is belangrijk dat onderzoekers goed kunnen inschatten wanneer het beter is om een kind uit een onderzoek te halen. Wij hebben een voorstel gedaan over hoe onderzoekers dat moeten doen. Namelijk door alle kinderen die meedoen altijd goed in te gaten te houden. Ze moeten steeds controleren of kinderen wel door willen gaan en of kinderen het niet te zwaar vinden worden.

APPENDICES

Appendix 1: Case record form (chapter 6)

Case Record Form – Componentanalyse

Deel 1 – Algemene informatie

1. Onderzoeksnummer (uitsluitend voor eigen gebruik) …….

2. Type interventie-onderzoek:
   - o 0: Geneesmiddel onderzoek
   - o 1: Vaccinatie onderzoek
   - o 2: Voedingsmiddel onderzoek
   - o 3: Stamcel onderzoek
   - o 4 Onderzoek naar nieuwe vormen van diagnostiek

3. Initiatie:
   - o 0: Investigator-initiated
   - o 1: Door farmaceutische industrie

4. Doelstelling inclusief, indien van toepassing, naam geneesmiddel/vaccin/voedingsmiddel:
……
……

5. Bestaande kennis over het middel (uit adult studies/off-label gebruik), voor zover te vinden in het onderzoeksprotocol:
   - o 0: Geregistreerd voor deze groep (leeftijd en indicatie)
   - o 1: Geregistreerd, maar niet voor deze groep
   - o 1a: In de praktijk wel standaard behandeling voor deze groep (off label)
   - o 1b: In de praktijk wel af en toe gegeven aan deze groep, en/of wel geregistreerd voor vergelijkbare groep, en/of veel off label ervaring met middel bij vergelijkbare groep
   - o 1c: Helemaal nog geen ervaring nog met dit middel bij deze of vergelijkbare groep
   - o 2: Ook voor volwassenen nog niet geregistreerd
   - o 2a: Ook bij kinderen al een aantal studies gedaan
   - o 2b: Adult studies afgerond maar nog nooit aan kinderen gegeven.
   - o 2c: Adult studies lopen nog
   - o 3: Iets anders, namelijk: …….....

Extra informatie:
……
……

6. Fase (volgens protocol/onderzoekers):
   - 0: I
   - 1: II
   - 2: III
   - 3: IV
   - 4: nvt

7. Algemene beschrijving van het study design:
……
……

8. Proefpersonen:
   - Aantal: ……
   - Leeftijdsrange: ……
   - Wel/niet (at risk voor) de ziekte waar het om gaat: ……....
   - Overige relevante informatie: ……

9. Wat is de 'standard of care' voor deze ziekte (voor zover duidelijk wordt uit het protocol)?
- Therapie: ……
……
- Controles: ……....
……

10. Toedienen geneesmiddel/vaccin/voedingsmiddel/stamcellen/diagnostiek:
   - Controlegroep: ……....
   - Toedieningswijze: ……...
   - Duur: ……..
   - Dosering ……

11. Indien er therapie bestaat: wordt kinderen die behandeling in het onderzoek onthouden?
   - 0: Ja, op de volgende wijze: ……..
   - 1: Nee

12. Overige procedures (naast de te toetsen interventie):
……
……
……

13. Belang/nut van de studie (volgens onderzoekers):
……
……
……

14. Onderzoek door onderzoekers gezien als:
    - 0: Therapeutisch
    - 1: Niet-therapeutisch

Deel 2 – Beoordeling van de METC/CCMO

15. Onderzoek door METC/CCMO beoordeeld als:
    - 0: Therapeutisch
    - 1: Niet-therapeutisch
    -

16. Beoordeling:
    - 0: Positief
    - 1: Negatief, redenen:

      ……

      ……
    -

17. Opmerkingen over (niet-) therapeutische aard van de studie en/of over risico en belasting:

……

……

……

Deel 3 - Beoordeling Componenten

18. Vormt de interventie in het kader van dit onderzoek, voor deze groep proefpersonen, tevens (een deel van) de therapie of diagnostiek voor hun ziekte, of preventie van een ziekte die zij kunnen krijgen?
    - o Ja
    - o Nee
    - o Bij een deel van de groep wel, bij een ander deel niet

Appendix 2: Questionnaire (chapter 7)

Hoe belastend is het ondergaan van medische procedures voor kinderen?

Medisch wetenschappelijk onderzoek dat niet direct aan de deelnemende kinderen zelf ten goede kan komen (zogenoemd niet-therapeutisch onderzoek) mag alleen plaatsvinden als de risico's verwaarloosbaar zijn en de belasting minimaal. De achtergrond hiervan is dat kinderen niet in staat worden geacht om weloverwogen en vrijwillig te kiezen voor deelname aan dergelijk onderzoek. De toepassing van de begrippen “verwaarloosbaar risico” en “minimale belasting” blijkt in de praktijk echter erg lastig; toetsingscommissies worstelen er mee.

Daarom vragen we u om uw input. In het kader van het onderzoeksproject “Geneesmiddelen onderzoek bij kinderen: ethische kwesties in de praktijk” van de afdeling Medische Ethiek van het Erasmus MC, leggen wij u graag onderstaande vragenlijst voor over het begrip “minimale belasting”. Want de procedures waar de toetsingscommissies mee worstelen, worden ook buiten de setting van wetenschappelijk onderzoek vaak verricht. Waarschijnlijk heeft u als kinderarts (in opleiding) met de meeste wel te maken gehad in uw klinische werk. Onze vraag is dus: hoe schat u naar aanleiding van deze ervaringen, de belasting van onderstaande procedures in?

Ter ondersteuning: over het begrip minimale belasting staat in de toelichting op de Nederlandse wet (WMO) dat hetgeen de proefpersoon moet ondergaan: *“alles bij elkaar opgeteld niet ingrijpend is; de verstoring van het dagelijks leven die deelname met zich meebrengt, moet beperkt zijn en de belasting in de zin van pijn mag die van bijvoorbeeld een bloedprik niet overschrijden.”*

Bij voorbaat hartelijk dank voor uw deelname.

1. Wat is uw functie?

- ☐ algemeen kinderarts
- ☐ subspecialist (namelijk: _____)
- ☐ AIOS kindergeneeskunde
- ☐ ANIOS kindergeneeskunde
- ☐ co-assistent
- ☐ anders (namelijk: _____)

2. Hoeveel jaren ervaring heeft u in de kindergeneeskunde?

_____ jaren

3. Kruis in tabel 1 (z.o.z.) per procedure aan, hoe belastend deze in uw ogen is voor kinderen.

4. Zet in de meest linker kolom van tabel 1 de procedures op volgorde van <u>minst</u> belastend (1) tot <u>meest</u> belastend (13).

Tabel 1 Vraag 4		Vraag 3 Geen goed beeld van / niet te beoordelen	Minimale belasting	In geringe mate meer dan minimale belasting	Meer dan in geringe mate meer dan minimale belasting
	Histamine/metacholine provocatietest				
	Venapunctie				
	Herhaalde venapuncties (8x in 6 maanden)				
	Spirometrie / flow-volume meting				
	Spierbiopt				
	Infuusnaald inbrengen				
	Allergie huidtest op arm				
	Liquorpunctie				
	Wangslijmvliesafname (met borsteltje, 15 sec)				
	Beenmergpunctie (onder narcose)				
	MRI scan (zonder narcose, 1 uur lang)				
	Echo cor				
	2x dagopname				

5. Welke factoren zijn, volgens u, van invloed op de belasting van deze medische procedures voor kinderen (bijv. leeftijd, geslacht, ervaring met de procedure etc.)?

_____

_____

6. Ruimte voor verdere opmerkingen / toelichting:

_____

_____

DANKWOORD

Tijdens mijn sollicitatiegesprek voor de promotieplaats waarvan dit proefschrift het resultaat is, vroeg Inez de Beaufort mij of ik het wel zag zitten, zo'n soloproject. Het is toch een eenzaam proces, dat promoveren. Later in het gesprek vroeg ze me of ik wel een beetje sociaal was. Omdat het een afdeling is waar iedereen voor elkaar klaar staat als het moeilijk is of tegenzit. "Dus toch niet zo eenzaam?" vroeg ik. "Nee, in dat opzicht niet" antwoordde Inez. Ik heb in de jaren daarna mogen ondervinden dat het allebei waar was. Een soloproject, een klein beetje eenzaam, maar met veel hulp en ondersteuning waar dat nodig was.

Drie bijzondere en zeer verschillende personen waren in dit proces mijn begeleiders en (co-)promotoren; Inez de Beaufort, Suzanne van de Vathorst en Anna Westra. Met ieder hun eigen stijl hebben zij mij begeleid, ondersteund en mij vooral heel veel geleerd. Inez de Beaufort, hoofd van de afdeling Medische Ethiek, dank ik voor haar bijzondere persoonlijkheid, haar kennis en haar gave om te spelen met vorm en stijl, zonder af te doen aan de inhoud. Suzanne van de Vathorst dank ik voor haar zorgzaamheid en daadkracht, en voor hoe zij altijd de juiste bemoedigende woorden vindt. Van haar heb ik geleerd doelgericht te werk te gaan, hoofdzaken van bijzaken te onderscheiden en teksten te ontdoen van wat onnodig is. Met Anna Westra heb ik verreweg het meest intensief samengewerkt bij dit project en zelden heb ik zo goed met iemand kunnen samenwerken. Zowel qua werkwijze als op persoonlijk vlak klikten wij goed en dat heeft het proces soepel en aangenaam gemaakt. Ik ben haar zeer veel dank verschuldigd voor haar inzet voor dit onderzoek, haar betrokkenheid en haar uiterst zorgvuldige manier van werken. Van haar heb ik geleerd mijn eigen werk steeds te herzien en verder te structureren en verfijnen.

Graag dank ik professor van Dijk, professor Tiddens en professor Hennekam voor het lezen en beoordelen van mijn proefschrift en voor hun bereidheid zitting te nemen in de promotiecommissie.

De Onderzoeksschool Ethiek, later de Onderzoeksschool Wijsbegeerte, dank ik voor de vele cursussen, congressen, symposia en werkgroepen. Het was fijn een netwerk van medepromovendi en onderzoekers te hebben om ideeën uit te wisselen en ervaringen te delen. Te weten dat we met zo velen aan onze eigen soloprojecten werkten.

Tijdens mijn onderzoek heb ik veel hulp en input gekregen van verschillende Medisch-Ethische Toetsingscommissies. Graag bedank ik daarvoor de CCMO (in het bijzonder Monique Al), de NV-METC en de (secretariaten van) de METCs van het Erasmus MC, het LUMC, de MEC-U, het AMC en het UMC Utrecht.

Waardevol waren ook de gesprekken die ik voerde met, en de input die ik kreeg van de kinderartsen op de afdelingen kindergeneeskunde van het LUMC, het VUmc, de Isala Klinieken en het Juliana Kinderziekenhuis.

Enorm veel dank ben ik verschuldigd aan de vele researchverpleegkundigen die ik heb mogen ontmoeten gedurende mijn onderzoek. Met enkele van hen mocht ik een dagje meelopen in het Sophia Kinderziekenhuis, anderen sprak ik tijdens focusgroepen en workshops. Deze groep van zeer toegewijde (overwegend) dames staat midden in de praktijk, dichtbij de kinderen waar dit boek over gaat. Hun verhalen, ervaringen en inzichten zijn van grote waarde geweest voor dit proefschrift.

Liztophe Verhoeven wil ik graag bedanken voor het lezen en verbeteren van de inleiding en de samenvatting voor kinderen. Ik vind het heel leuk dat je dat wilde doen!

In 2012, less than a year after I started my PhD project, our department hosted the 11th World Congress of Bioethics in Rotterdam. On the first morning Inez introduced me to Hans-Jörg Ehni from Tübingen University, letting him assure her “to take good care of me as I was very young”. In the following days Hans-Jörg guided me through the wondrous world of bioethics and its people, all gathered then and there in Rotterdam. We kept in touch afterwards and I thank him for the many pleasant conversations, his useful feedback and reassuring words. I really hope we will manage to keep meeting from time to time.

Alle lieve en leuke collega’s van de afdeling Medische Ethiek ben ik dankbaar voor de fijne werkplek. Annemieke van Tintelen dank ik voor haar behulpzaamheid en voor het zorgen dat dingen altijd goedkomen. Hannie Aartsen dank ik voor haar tomeloze energie en passie voor het onderwijs. Karin Jongsma en Krista Tromp ben ik dankbaar voor, tsja, waarvoor niet eigenlijk. We zijn min of meer tegelijk begonnen aan dit avontuur dat promoveren heet. We hebben veel samen gewerkt en leuke dingen beleefd (de roadtrip naar Straatsburg bijvoorbeeld, en de high-tea met onze moeders). Ik dank Frans Meulenberg voor zijn betrokkenheid en voor wat hij kan met taal. Vele keren maakte hij mijn teksten beter, scherper, correcter en mooier. Ooit begonnen wij samen verhalen te schrijven. Nu mijn

proefschrift af is, moest dat maar eens snel een vervolg krijgen. Tineke Terpstra ben ik buitengewoon dankbaar voor haar wijsheid en haar bereidheid die met mij te delen. Wij hebben een aantal bijzondere gesprekken gevoerd waar zowel mijn proefschrift als ikzelf beter van zijn geworden.

Eline Bunnik en Hafez Ismaili M'Hamdi, ik vind het zo leuk dat jullie mijn paranimfen willen zijn. Ik ben blij dat ik jullie heb leren kennen, en dat wij elkaar nog steeds af en toe zien en spreken, ook al zijn we feitelijk geen collega's meer. Eline, dank voor jouw oprechte interesse, jouw bijzondere stijl die zachtheid en directheid zo mooi combineert en voor alle keren dat we samen naar het theater gingen (en dan vooral die keer dat ik met zwangere buik in jouw bakfiets mocht zitten en jij ons dwars door Amsterdam naar Frascati fietste). Hafez, dank voor jouw humor en jouw vele talenten, voor dat je zo'n gezellige kamergenoot was en zo'n goede gesprekspartner bent.

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I owe many thanks to Lisa Madlberger (and Jeroen Smith too), whose home I regularly got to use as my office and whose company and lunches made thesis writing a much more productive and much more enjoyable enterprise.

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en Sven steekt de BBQ aan (ongeacht het seizoen). Meer hebben we niet nodig. Wat fijn dat ik jullie heb, dank voor alles!

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CURRICULUM VITAE

Wendy Bos was born in Dordrecht, the Netherlands on September 9th 1984. She finished secondary school in 2001 and went to study production & stage management at the Amsterdam University of the Arts in 2002. In 2005 she switched to studying pedagogical sciences and philosophy at Utrecht University. She obtained a bachelor's degree in pedagogical sciences in 2008 and a bachelor's degree in philosophy in 2009. She continued studying philosophy and obtained her master's degree in 2010. After traveling South East Asia for several months she started her PhD project at the department of Medical Ethics and Philosophy of Medicine of Erasmus MC in Rotterdam in 2011, supervised by prof. dr. Inez de Beaufort and prof. dr. Suzanne van de Vathorst as her promotores. The project was funded by the ZonMw programme Priority Medicines for children. Wendy took several PhD courses and participated in symposia and working groups of the Dutch Research School of Philosophy (OZSW). She also participated in a summer school in Strasbourg (Ethical challenges in a European perspective). She taught classes to medical students on various topics in medical ethics and supervised minor students at Erasmus MC in Rotterdam. She published her work in international peer-reviewed journals and gave presentations at conferences, symposia, hospital departments and ethics committees. Wendy currently works at ZonMw as a programme officer.

LIST OF PUBLICATIONS

- Bos W, Tromp K*, Tibboel D, Pinxten W. Ethical aspects of clinical research with minors. Eur J Pediatr. 2013;172(7):859-66.
- Bos W, Westra A, Cohen A. Niet nog meer medicijntests kinderen. NRC Handelsblad 2014.
- Westra AE, Bos W, Cohen AF. New EU clinical trials regulation. BMJ (Clinical research ed). 2014;348:g3710.
- Bos W, Westra AE, Pinxten W, Mayer MP, Lantos JD. Risks in a Trial of an Innovative Treatment of Duchenne Muscular Dystrophy. Pediatrics. 2015;136(6):1173-7.
- Jongsma K, Bos W*, van de Vathorst S. Morally Relevant Similarities and Differences Between Children and Dementia Patients as Research Subjects: Representation in Legal Documents and Ethical Guidelines. Bioethics. 2015;29(9):662-70.
- Bos W, Westra A, de Beaufort I, van de Vathorst S. To stop or not to stop: dissent and undue burden as reasons to stop participation in paediatric research. J Med Ethics. 2016.

*shared first authorship

PHD PORTFOLIO

PERSONAL	
Name:	Wendy Bos
Department:	Erasmus MC – Department of Medical Ethics and Philosophy of Medicine
PhD period:	2011-2017
Promotors:	Prof. dr. I.D. de Beaufort and Prof. dr. S. van de Vathorst
Co-promotor:	Dr. A.E. Westra

PHD TRAINING		
PhD courses	**Year**	**Workload (ECTS)**
Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers (Erasmus MC)	2011	1,5
Systematisch literatuuronderzoek in PubMed (Erasmus MC)	2012	0,2
Systematisch literatuuronderzoek in andere databases (Erasmus MC)	2012	0,2
Endnote (Erasmus MC)	2012	0,2
Ethics of Care and Health (OZSE)	2012	6
Winter school: Ethical Theory and Moral Practice (OZSE)	2012	6
The Political Philosophy of Human Rights (OZSW)	2012	6
Summer school 'Ethical Challenges in a European Perspective' Strasbourg	2013	6
Integrity in research (Erasmus MC)	2013	2

Seminars and working groups	Year	Workload (ECTS)
PhD seminars of the Dutch Research School for Philosophy	2011-2013	3
Working group Ethics & Health Care (OZSW)	2011-2016	1
Research meetings ethics projects within the ZonMw Priority Medicines programme (Erasmus MC)	2012-2014	0,5
Conference Presentations	**Year**	**Workload (ECTS)**
IAB World congress Rotterdam	2012	1
Fourth Annual Dutch Conference on Practical Philosophy Eindhoven	2012	1
ZonMw congres 'Goed Gebruik Geneesmiddelen' Amsterdam	2016	0,5
ZonMw congres 'Goed Gebruik Geneesmiddelen' Amsterdam	2017	0,5
Invited Presentations	**Year**	**Workload (ECTS)**
Jaarsymposium Dutch Association of Bioethics	2012	0,3
ZonMw Priority Medicines for Children Den Haag	2013	0,1
Working group 'Guideline criteria for research with children' NVK Utrecht	2013	0,3
Workshop Research Ethics Rotterdam	2015	0,5
European working group Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population, Ministry of Health, Welfare and Sport Den Haag	2016	0,1
Sophia Children's Hospital (Erasmus MC) Rotterdam	2016	0,1
Other Presentations	**Year**	**Workload (ECTS)**
METC UMC Utrecht	2015	0,1

NVMETC Utrecht	2015	0,1
METC AMC Amsterdam	2015	0,1
LUMC Paediatrics department Leiden	2015	0,1
Isala Klinieken Paediatrics department Zwolle	2015	0,1
Juliana Chidren's Hospital Den Haag	2015	0,1
Workshop for research nurses Rotterdam	2016	0,1
TEACHING ACTIVITIES	**Year**	**Workload (ECTS)**
Classes on various topics concerning medical ethics to medical students in the bachelor and master programme	2012-2016	20
Supervision of minor theses	2012-2015	4
ADDITIONAL ACTIVITIES	**Year**	**Workload (ECTS)**
Ethics member of the core working group 'Guideline criteria for research with children' – Paediatric Association of The Netherlands	2012-2016	8
PhD day Erasmus MC	2016	0,5