

<http://hdl.handle.net/1765/115316>



General introduction



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

Mother, focus group (chapter 6)

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

ETHICAL DILEMMA IN PEDIATRIC CLINICAL RESEARCH

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

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

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

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

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

INFORMED CONSENT IN PEDIATRIC CLINICAL RESEARCH

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

LEGAL VALUE OF INFORMED CONSENT IN PEDIATRIC CLINICAL RESEARCH

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

and therefore cannot consent to research. Their parents (or legal guardians)ⁱⁱ need to consent for them, which is called proxy consent. In the Netherlands, proxy consent is arranged in the Medical Research (Human Subjects) Act (WMO), precisely art. 6:1.²¹

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

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

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

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

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

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

MORAL VALUE OF INFORMED CONSENT IN PEDIATRIC CLINICAL RESEARCH

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

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

INSTRUMENTAL VALUE OF INFORMED CONSENT IN PEDIATRIC CLINICAL RESEARCH

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

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

INFORMED CONSENT AND MOTIVATIONS IN PEDIATRIC CLINICAL RESEARCH

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

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

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

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

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

SCOPE OF THIS THESIS

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

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

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

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

RESEARCH AIMS

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

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

METHODOLOGICAL APPROACH

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

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

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

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

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

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

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

OUTLINE OF THIS THESIS

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

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

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

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

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

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

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

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

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

REFERENCES

1. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for health-related research involving humans, fourth edition. Geneva 2016.
2. World Medical Association. World medical association declaration of helsinki: Ethical principles for medical research involving human subjects. *JAMA* 2013;310(20):2191-2194.
3. Shirkey H. Therapeutic orphans. *J Pediatr* 1968;72(1):119-120.
4. Conroy S. Association between licence status and medication errors. *Arch Dis Child* 2011;96(3):305-306.
5. Turner S, Gill A, Nunn T, Hewitt B, Choonara I. Use of "off-label" and unlicensed drugs in paediatric intensive care unit. *Lancet* 1996;347(9000):549-550.
6. Proadhan P, Okhuysen-Cawley R, Imamura M. Central extracorporeal membrane oxygenation for refractory pediatric septic shock. *Pediatr Crit Care Med* 2011;12(5):606; author reply 606-607.
7. Shann F, Chiletto R. Neonatal herpes virus infection: Duration of extracorporeal support and the dose of acyclovir. *Pediatr Crit Care Med* 2011;12(5):605; author reply 605-606.
8. Johnson TN. The development of drug metabolising enzymes and their influence on the susceptibility to adverse drug reactions in children. *Toxicology* 2003;192(1):37-48.
9. Sutherland JM. Fatal cardiovascular collapse of infants receiving large amounts of chloramphenicol. *AMA journal of diseases of children* 1959;97(6):761-767.
10. European Parliament and the Council of the European Union. Regulation (ec) no. 1901/2006 of the european parliament and of the council of 12 december 2006 on medicinal products for paediatric use and amending regulation (eec) no. 1768/92, directive 2001/20/ec, directive 2001/83/ec and regulation (ec) no. 726/2004. *Off J Eur Union* 2006;49(L 378):1-19.
11. US Public Law. Best pharmaceuticals for children act, 2002.
12. Davies EH, Ollivier CM, Saint Raymond A. Paediatric investigation plans for pain: Painfully slow! *Eur J Clin Pharmacol* 2010;66(11):1091-1097.
13. Wimmer S, Rascher W, McCarthy S, Neubert A. The eu paediatric regulation: Still a large discrepancy between therapeutic needs and approved paediatric investigation plans. *Paediatr Drugs* 2014;16(5):397-406.
14. Kimland E, Odland V. Off-label drug use in pediatric patients. *Clin Pharmacol Ther* 2012;91(5):796-801.
15. Ceelie I, van der Starre C, Tibboel D, Stol K, Koren G, de Wildt SN. Evaluation of drug formularies for pediatric intensive care. *Pediatr Crit Care Med* 2011;12(1):e14-19.
16. Doherty DR, Pascuet E, Ni A, Stewart P, Splinter W, Vaillancourt R. Off-label drug use in pediatric anesthesia and intensive care according to official and pediatric reference formularies. *Can J Anaesth* 2010;57(12):1078-1088.
17. Bourgeois FT, Olson KL, Ioannidis JP, Mandl KD. Association between pediatric clinical trials and global burden of disease. *Pediatrics* 2014;133(1):78-87.
18. Lepola P, Needham A, Mendum J, Sallabank P, Neubauer D, de Wildt S. Informed consent for paediatric clinical trials in europe. *Arch Dis Child* 2016;101(11):1017-1025.
19. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The belmont report ethical principles and guidelines for the protection of human subjects of research. Washington D.C.: U.S. Government Printing Office, 1978.
20. Trials of war criminals before the nuremberg military tribunals under control council law no. 10. Washington D.C.: U.S. Government Printing Office, 1949:181-182.

21. Wet medisch-wetenschappelijk onderzoek met mensen [dutch medical research (human subjects) act]. Staatsblad 161: The Hague, the Netherlands, 1998.
22. Tait AR, Geisser ME. Development of a consensus operational definition of child assent for research. *BMC Med Ethics* 2017;18(1):41.
23. Hein IM, De Vries MC, Troost PW, Meynen G, Van Goudoever JB, Lindauer RJ. Informed consent instead of assent is appropriate in children from the age of twelve: Policy implications of new findings on children's competence to consent to clinical research. *BMC Med Ethics* 2015;16(1):76.
24. Grootens-Wiegers P, de Vries MC, van Beusekom MM, van Dijk L, van den Broek JM. Comic strips help children understand medical research: Targeting the informed consent procedure to children's needs. *Patient Educ Couns* 2015;98(4):518-524.
25. Committee Doek [Commissie Doek]. Advice medical scientific research with children [advies medisch-wetenschappelijk onderzoek met kinderen], 2009.
26. Ministry of Health Welfare and Sports. [wet van 26 oktober 2016 tot wijziging van de wet medisch-wetenschappelijk onderzoek met mensen in verband met het wijzigen van de mogelijkheden voor het verrichten van medisch-wetenschappelijk onderzoek met proefpersonen die de leeftijd van zestien jaar nog niet hebben bereikt of die wilsonbekwaam zijn]. The Hague: Staatsblad, 2016.
27. Hein IM, Troost PW, Lindeboom R, Benninga MA, Zwaan CM, et al. Accuracy of the macarthur competence assessment tool for clinical research (maccat-cr) for measuring children's competence to consent to clinical research. *JAMA Pediatr* 2014;168(12):1147-1153.
28. Pandiya A. Readability and comprehensibility of informed consent forms for clinical trials. *Perspect Clin Res* 2010;1(3):98-100.
29. Brehaut JC, Carroll K, Elwyn G, Saginur R, Kimmelman J, et al. Informed consent documents do not encourage good-quality decision making. *J Clin Epidemiol* 2012;65(7):708-724.
30. Foe G, Larson EL. Reading level and comprehension of research consent forms: An integrative review. *J Empir Res Hum Res Ethics* 2016;11(1):31-46.
31. Kent G. Shared understandings for informed consent: The relevance of psychological research on the provision of information. *Soc Sci Med* 1996;43(10):1517-1523.
32. Grootens-Wiegers P, De Vries MC, Vossen TE, Van den Broek JM. Readability and visuals in medical research information forms for children and adolescents. *Science Communication* 2015;37(1):89-117.
33. Chappuy H, Baruchel A, Leverger G, Oudot C, Brethon B, et al. Parental comprehension and satisfaction in informed consent in paediatric clinical trials: A prospective study on childhood leukaemia. *Arch Dis Child* 2010;95(10):800-804.
34. Chappuy H, Bouazza N, Minard-Colin V, Patte C, Brugieres L, et al. Parental comprehension of the benefits/risks of first-line randomised clinical trials in children with solid tumours: A two-stage cross-sectional interview study. *BMJ Open* 2013;3(5).
35. Tait AR, Voepel-Lewis T, Malviya S. Do they understand? (part i): Parental consent for children participating in clinical anesthesia and surgery research. *Anesthesiology* 2003;98(3):603-608.
36. Tait AR, Voepel-Lewis T, Malviya S. Do they understand? (part ii): Assent of children participating in clinical anesthesia and surgery research. *Anesthesiology* 2003;98(3):609-614.
37. Unguru Y, Sill AM, Kamani N. The experiences of children enrolled in pediatric oncology research: Implications for assent. *Pediatrics* 2010.
38. Grootens-Wiegers P, Hein IM, van den Broek JM, de Vries MC. Medical decision-making in children and adolescents: Developmental and neuroscientific aspects. *BMC Pediatr* 2017;17(1):120.

39. Giesbertz NA, Bredenoord AL, van Delden JJ. Clarifying assent in pediatric research. *Eur J Hum Genet* 2014;22(2):266-269.
40. Duffett M, Choong K, Hartling L, Menon K, Thabane L, Cook DJ. Randomized controlled trials in pediatric critical care: A scoping review. *Critical care* 2013;17(5):R256.
41. de Oliveira LLH, Vissoci JRN, Machado WL, Rodrigues CG, Limkakeng AT. Are well-informed potential trial participants more likely to participate? *J Empir Res Hum Res Ethics* 2017;12(5):363-371.
42. Caldwell PH, Butow PN, Craig JC. Parents' attitudes to children's participation in randomized controlled trials. *J Pediatr* 2003;142(5):554-559.
43. Waisel DB. Let the patient drive the informed consent process: Ignore legal requirements. *Anesth Analg* 2011;113(1):13-15.
44. Sugarman J. Examining provisions related to consent in the revised common rule. *Am J Bioeth* 2017;17(7):22-26.
45. Office of Human Research Protections. Federal policy for the protection of human subjects (common rule). *Federal Register* 2017;82(12):7149-7274.
46. Wangmo T, Hauri S, Gennet E, Anane-Sarpong E, Provoost V, Elger BS. An update on the "empirical turn" in bioethics: Analysis of empirical research in nine bioethics journals. *BMC Med Ethics* 2018;19(1):6.
47. Hurst S. What 'empirical turn in bioethics'? *Bioethics* 2010;24(8):439-444.
48. Borry P, Schotsmans P, Dierickx K. The birth of the empirical turn in bioethics. *Bioethics* 2005;19(1):49-71.
49. Miller FG, Wendler D. The relevance of empirical research in bioethics. *Schizophr Bull* 2006;32(1):37-41.
50. Salloch S, Vollmann J, Schildmann J. Ethics by opinion poll? The functions of attitudes research for normative deliberations in medical ethics. *J Med Ethics* 2014;40(9):597-602.
51. Editorial: Empirical ethics: A challenge to bioethics. *Medicine, Health Care and Philosophy* 2004;7(1):1-3.
52. Emanuel E, Grady C, Crouch R, Lie R, Miller F, Wendler D. The oxford textbook of clinical research ethics: Oxford University Press 2008.
53. Salloch S, Schildmann J, Vollmann J. Empirical research in medical ethics: How conceptual accounts on normative-empirical collaboration may improve research practice. *BMC Med Ethics* 2012;13:5.
54. Ives J, Dunn M, Molewijk B, Schildmann J, Bærøe K, et al. Standards of practice in empirical bioethics research: Towards a consensus. *BMC Medical Ethics* 2018;19(1):68.
55. Van Thiel GJ, Van Delden JJ. Reflective equilibrium as a normative empirical model. *Ethical Perspectives* 2010;17(2):183-202.
56. De Vries M, Van Leeuwen E. Reflective equilibrium and empirical data: Third person moral experiences in empirical medical ethics. *Bioethics* 2010;24(9):490-498.