THE INTEGRATION OF RESEARCH AND CARE IN PEDIATRIC ONCOLOGY: IMPLICATIONS FOR REVIEW AND CONSENT

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THE INTEGRATION OF RESEARCH AND CARE IN PEDIATRIC ONCOLOGY: IMPLICATIONS FOR REVIEW AND CONSENT

De vermenging van zorg en onderzoek in de kinderoncologie: gevolgen voor toetsing en toestemming

(met een samenvatting in het Nederlands)

Proefschrift

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General introduction

Background of pediatric oncology

In high-income countries, cancer is the leading cause of death from illness for children aged between 1 and 15 years.(1) Most children (>90%) receive treatment for their disease in specialized pediatric oncology treatment and research centers, where treatment protocols are developed and evaluated. Evaluation of treatments is highly necessary, as many drugs are prescribed off-label without sufficient knowledge on safety and efficacy.(2-5) In addition, childhood cancer is a rarity, and evidence from research in adult oncology cannot easily be generalized to children.(6)

In order to be able to obtain valid and valuable research data, the pediatric oncology community aims for systematic inclusion of children in medical research. Although recent numbers are difficult to find, it has been estimated that in high-income countries, 50%-70% of child cancer patients takes part in clinical trials.(7-9) Conduct of clinical trials and the participation of the majority of children with cancer on these trials have been linked to the significant increase in survival rates over the past decades.(10-12) The overall 5-year survival rate for children diagnosed with cancer is now approximately 80%, whereas this was 40% in the 1970s.(11;13;14)

Thus, many children with cancer receive their treatment in the context of research. Consequently, the strict distinction between research and care that is promoted in ethical guidelines (15-17) and research ethics literature,(18-20) does not apply to pediatric oncology. Yet, this on the surface seamless intertwinement of research and care can easily become problematic, as different activities entail different obligations and interests.(21) The field of pediatric oncology has received considerable scholarly attention, both from an ethical and an empirical perspective, indicating that the integration of research and care may introduce ethical complexities that warrant attention.(6;22-24)

However, both the challenges and advantages of the integration of research and in pediatric oncology have until now been insufficiently studied. It is essential to consider the moral implications of the integration of research and care in order to sufficiently protect the interests of patients and their families such an integrated research/care environment. Therefore, the main question of this thesis is: ‘How should the integration of research and care in pediatric oncology be morally evaluated?’ At least, two ethical issues arise from the integration of research and care. First, because many pediatric oncologists are involved in research, they include their own patients in pediatric cancer studies. That is, inclusion takes place within a relationship where parents and children depend on the treating physician for the necessary treatments. Inclusion within a dependent relationship may unduly influence parental decision making as they are reluctant to refuse when the informed consent procedure is performed by the child’s physician who provides him or her with the necessary care and treatments. Accordingly, the dependent relationship may compromise the voluntariness of informed consent of parents. Second, the integration of research and care also raises questions about the proper categorization of protocols that combine research and care, the type of ethical review that is warranted, and informed consent.

This second theme focuses on a particular type of pediatric oncology protocols: 'best available treatment protocols'. Thus, this thesis consists of two parts, that both address one of these two main themes, 'Dependent relationships and voluntary informed consent' and 'The distinction between research and care'.

Part I: Dependent relationships and voluntary informed consent

In the context of recruitment for (medical) research, several types of relationships exist in which potential participants are recruited for research by someone they are dependent on to receive something that is valuable to them. Accordingly, these relationships can be referred to as 'dependent relationships'. A variety of dependent relationships have been identified in the literature, such as those between students and teachers, between prisoners and prison authorities, and between patients and health care professionals.(25-29) In this thesis we focus on the relationship between patients and physicians, more particular on the relationship between pediatric oncology physician-investigators and parents of children with cancer.

We realize that in pediatric medicine at least three parties are involved in the decision making processes, that is the physician/investigator, (one of) the parents and the child him or herself. Therefore, the situation is different than in adult medicine, as the triangular relationship between children, parents and physician-researchers may shed a different light on voluntary informed consent. In theory, parents may perceive no compromise to their voluntary informed consent, when the child has the feeling that it is enrolled against its will. However, although we acknowledge the importance of the involvement of children in decisions that concern them, and support the further ethical and empirical analysis of assent, in this thesis we mainly study the voluntariness of parental consent. This is because in general parents are the ones to make the legal decision with respect to their child's research participation, and the criteria for informed consent (understanding, competence and voluntariness) do in first instance and more stringently apply to consent rather than assent.

In the general research ethics literature, several assumptions can be found that underlie the idea that inclusion for research within a dependent relationship may compromise the voluntariness of informed consent of potential participants (that is, competent adults who are patients and are invited to take part in research). These assumptions are all related to the interaction between patients and their physicians, resulting from the fact that in the treating relationship patients depend on their physician to receive the necessary care and treatments.(30) First, it may be difficult for patients to refuse a request for research participation from their physician, since patients may be concerned about the (medical) consequences of refusing. A second assumption is that when a patient is included by someone who is both the patient's physician and a researcher, the patient might conclude that there is no choice as to whether to enroll in the suggested study.(31) Third, an invitation by the treating physician may easily be interpreted as a recommendation to the preferred course

of action, based on trust in and respect for the doctor.(32) That is, based on their physician's suggestion, patients may think that enrollment is their best treatment option, and will therefore not refuse.(33-35) Fourth, patients see enrollment in research as a way to do something back for the care received and may therefore feel obliged to participate.(36;37) Fifth, due to their research focus and interests, physicians who act as researchers may (unconsciously) put pressure on patients to consent.(38) This enumeration of considerations is not meant to be exhaustive, but aims to give an idea of the different ways in which a dependent relationship could in general influence voluntary consent of patients.

In order to examine the advantages and disadvantages of inclusion for research within a dependent relationship, it is important to clarify when involvement of treating physicians with the recruitment process is potentially problematic. Based on the different roles and tasks the treating physician may have during the recruitment process,(35) three situations can be identified. In the first situation the physician only informs a patient about the existence of a study conducted by a colleague and explains that if the patient is interested the principal investigator can be contacted (referral). We regard this first situation as common recruitment practice and therefore it will not be one of the situations we refer to when we speak of inclusion within a dependent relationship. The second situation involves a treating physician who is personally involved with the study in question, either as principal investigator or as one of the other investigators. Here, the physician has a double role as clinician and investigator, which could influence the decision-making of patients, as they may be hesitant to refuse participation in a study their physician is involved with. A third situation occurs when the treating physician includes his own patients in someone else's study in which he himself is not officially involved. We contend that, at least for pediatric oncology, this third situation could also result in threats to voluntary informed consent, because virtually all pediatric oncologists are in some way involved and have interests in the studies that are performed. Even if they are not officially involved, research is part of their daily work and they have a professional and institutional interest in the amount and quality of research that is conducted in their field. Hence, in this thesis, when we speak of 'the dependent relationship', we mean one of the situations in which the physician is in some way (officially or not) involved with the study in question (that is, the second and third situations).

As mentioned previously, in the context of pediatric oncology many pediatric oncologists include their own patients in research and therefore similar dynamics may occur as described for research with adult patients. However, it is unclear whether parents indeed experience pressure to their voluntariness in giving informed consent to pediatric cancer studies due to the dependent relationship. Furthermore, thus far the discussion has concentrated on the conflicts that are created by inclusion for research by the treating physician. Perhaps being a physician and a researcher at the same time may also create opportunities.(39) One could argue that there are advantages of functioning in both roles. For example, the pediatric oncologists may know (medically) best whether it is in the interest of the child to participate in a particular cancer study.(6) In addition, guidelines allow exceptions to dependent

relationships, for example if an independent other obtains informed consent.(17) However, in pediatric cancer research, and possibly also in other parts of biomedical research, these solutions may function as window dressing, because independent others cannot guarantee voluntary informed consent when care and research are integrated. Currently, because the strategies that ethical guidelines suggest to minimize the influence of the dependent relationship have not been studied, we do not know whether these strategies are sufficient or whether alternative ways should be sought to safeguard voluntary informed consent.

Research questions of part I

- What are the approaches of the main ethical guidelines to safeguard voluntary informed consent in a dependent relationship and what are the strengths and weaknesses of these approaches?
- To what extent do actors in pediatric oncology (pediatric oncologists, research coordinators, Research Ethics Committee members, children with cancer, and their parents) experience the dependent relationship as a threat to voluntary informed consent, and what do they see as safeguards to protect voluntary informed consent within a dependent relationship?
- Does the intertwinement of research and care in pediatric oncology, where physicians include their own patients and where treatments are sometimes exclusively provided through research, compromise voluntary informed consent for research participation from a theoretical perspective? And if so, are these compromises to voluntary informed consent also morally problematic?

Part II: The distinction between research and care

In pediatric oncology, randomized phase III studies are considered as 'frontline treatment options'.(6) Some authors even state that in pediatric oncology it is the standard of care to enroll children in these clinical trials.(22;24;40;41) Physicians believe that state-of-the-art treatments can be accessed through participation in a clinical trial and that individual children benefit from participation in research.(6;42) This may indicate two different but related phenomena. First, this conviction of the pediatric oncology community may indicate that new treatments in the intervention arms of RCTs are often superior to the standard treatments in the control arm. However, it has neither been confirmed nor disproved whether new treatments in the intervention arm prove better than the standard treatment in the control arm.(43;44) Second, it is also frequently suggested that children benefit directly from participation in pediatric oncology trials, due to the high quality of care that is provided, such as close monitoring of response and toxicity, the rigorous process of protocol development, adherence to well-defined protocols, receiving full-doses of chemotherapy on a strict time schedule, more frequent blood tests, and the involvement of high-level laboratories.(45-47)

However the general perception in the research ethics literature has been that research and care should be distinguished, and that having a dual role for physician-investigators is problematic or even impossible.(18;48) Failing to appropriately separate medical research from medical care has been linked to a myriad of ethical problems, related to informed consent and risks and benefits for patients. However, recently, other views have been expressed, in response to new forms and methods of research, the rapid pace of innovations, and recognition of the importance of research to validate new and existing interventions. The paradigm that research and care are distinct practices is changing, suggesting that sometimes research and care need not be distinguished. This paradigm shift creates a variety of practical and ethical challenges, such as safeguarding interests of patients, establishing appropriate forms of consent, avoiding non-clinical risks and burdens to patients, and properly categorizing and regulating integrated activities.(24;49;50)

The second part of this thesis considers the implications of the integration of research and care in pediatric oncology. In particular, we focus on so-called 'best available treatment protocols', which combine research and treatment goals, and are therefore a clear example of the research and care integration in pediatric oncology. We will study questions around the proper categorization of this type of protocols, what type of ethical oversight is appropriate and which form informed consent should take. Also, we will explore the experiences of a variety of pediatric oncology stakeholders with the ways in which research and care are combined.

Research questions of part II

- Is the distinction between research and treatment morally relevant for pediatric oncology treatment protocols that are considered current best available treatment?
- What are the experiences of those involved in pediatric oncology with the intertwinement of research and care and the dual role of pediatric oncologists as researchers and treating physicians?
- What are the implications of best available treatment protocols for review and consent?
- What recommendations could provide guidance for pediatric oncologists and Research Ethics Committee with respect to best available treatment protocols?

Methods

In this thesis we use a mixed methods approach, combining empirical data with normative reflection. Such a combination of results from empirical research with normative thinking has become increasingly common in bioethics the past three to four decades.(51) Some scholars even speak of 'an empirical turn in bioethics',(52) whereas others question the meaning of such a turn.(53) Questions on how to combine empirical data with normative reflection still receive a lot of attention and it is doubtful whether the issue will ever be settled. The relevance of empirical results for normative reasoning has been questioned, mainly referring to the is-ought or fact-value distinction and the possible ways to overcome this gap and reconcile the different output of different disciplines.(51;52;54;55) Empirical findings can play various roles in bioethical research, and a variety of typologies regarding their interaction has been suggested, based on the assumed relationships between ethics and the empirical.(56-58)

Although combining empirical findings with normative reasoning introduces methodological challenges and should be performed with care and attention, we believe that it can provide proper normative guidance when supported by a sound methodology. Therefore, we use the method of the Reflective Equilibrium (RE), which provides a model for moral reasoning that can facilitate the integration of moral experience and empirical data. Our method is based on the Normative-Empirical Reflective Equilibrium (NE-RE).(59) Two key characteristics of this method have been implemented in our research project.

First, we take as a starting point that the moral intuitions of those involved in a certain practice (whether as professional or as patient/participant) have a certain value, as they are based on experience with morally difficult situations and the decision-making that needs to take place when confronted with moral dilemmas. This knowledge and experience with morally difficult situations resembles a form of moral wisdom, which is indispensable if one wishes to morally evaluate a certain practice. Second, to reach

a Reflective Equilibrium (that is, a coherent and comprehensive moral framework), relevance of moral intuitions is not determined 'at the gate', but this selection is made during the process of the RE itself. During the reasoning process all elements of the RE are critically assessed and 'adjusted, accepted or expelled'.(59) As such, one prevents simply taking over the moral intuitions of people from medical practice, as none of the elements that are morally relevant – from fact to background theories – has a preferential status over the others.

Practically, in this thesis, we use the results from our own empirical research and from a variety of empirical studies to broaden our set of morally relevant beliefs and experiences. We have collected morally relevant facts, amongst others by a review of ethical guidelines for research with human beings, and by a case study of pediatric oncology treatment protocols for children with leukemia. Moral intuitions have been studied in a qualitative study, conducting focus groups and interviews with physician-researchers, research coordinators, members of Research Ethics Committees, parents of a child with cancer and adolescents with cancer. Normative reflection involves moral principles (including conceptual analysis of voluntary informed consent and of the moral obligations of pediatric oncology physician-researchers) and relevant background theories. The empirical and normative elements have been put into Reflective Equilibrium in order to reach a coherent normative view. With this combination of topics and the methods used, we thoroughly evaluate the integration of research and care in pediatric oncology and aim to contribute to an ethically sound practice of pediatric oncology.

Outline of the thesis

Part I: Dependent relationships and voluntary informed consent

The three chapters that are related to the first theme of dependent relationships and voluntary informed consent are **Chapters 2, 3 and 4**. **Chapter 2** examines ethical guidelines for human subjects research and discusses the strategies these guidelines propose to minimize the influence of the dependent relationship on voluntary informed consent. Then, in **Chapter 3** we present the results of our qualitative study into the experiences of pediatric oncology stakeholders with voluntary informed consent in a dependent relationship. **Chapter 4** takes a more theoretical approach and discusses the concept of voluntary informed consent for pediatric oncology research, by combining findings from our own and other empirical studies with the account of voluntary consent from Nelson and colleagues.

Part II: The distinction between research and care

The integration of research and care raises concerns around the proper categorization of pediatric cancer drug studies (research or treatment), and thereby the need for ethical oversight. Other questions include how pediatric oncology investigators combine their dual roles and balance the sometimes diverging interests of patients

and research. We will take up these questions of theme 2 in **Chapters 5, 6, and 7**. In **Chapter 5** we discuss the moral relevance of the distinction between research and care, based on a case study of two Dutch pediatric oncology treatment protocols for Acute Lymphoblastic Leukemia (ALL). **Chapter 6** provides an overview of the experiences of a variety of actors in pediatric oncology with the intertwinement of research and care and the dual role of pediatric oncologists. Then, **Chapter 7** investigates review and consent for best available treatment protocols. **Chapter 8** provides three recommendations concerning best available treatment protocols, for pediatric oncology physician-investigators and Research Ethics Committees.

Finally, **Chapter 9** presents a general discussion of our findings, in which we suggest ideas about how in the (near) future the integration of research and care may be dealt with, by addressing several perspectives on the integration of research and care.

References

1. Kellie SJ, Howard SC. Global child health priorities: what role for paediatric oncologists? Eur J Cancer 2008 Nov;44(16):2388-96.
2. Conroy S, Newman C, Gudka S. Unlicensed and off label drug use in acute lymphoblastic leukaemia and other malignancies in children. Ann Oncol 2003 Jan;14(1):42-7.
3. Pandolfini C, Bonati M. A literature review on off-label drug use in children. Eur J Pediatr 2005 Sep;164(9):552-8.
4. Pinxten W, Nys H, Dierickx K. Frontline ethical issues in pediatric clinical research: ethical and regulatory aspects of seven current bottlenecks in pediatric clinical research. Eur J Pediatr 2010 Dec;169(12):1541-8.
5. van den Berg H, Tak N. Licensing and labelling of drugs in a paediatric oncology ward. Br J Clin Pharmacol 2011 Sep;72(3):474-81.
6. de Vries MC, Houtlosser M, Wit JM, Engberts DP, Bresters D, Kaspers GJ, et al. Ethical issues at the interface of clinical care and research practice in pediatric oncology: a narrative review of parents' and physicians' experiences. BMC Med Ethics 2011;12:18.
7. Bleyer WA, Tejeda H, Murphy SB, Robison LL, Ross JA, Pollock BH, et al. National cancer clinical trials: children have equal access; adolescents do not. J Adolesc Health 1997 Dec;21(6):366-73.
8. Fern L, Davies S, Eden T, Feltbower R, Grant R, Hawkins M, et al. Rates of inclusion of teenagers and young adults in England into National Cancer Research Network clinical trials: report from the National Cancer Research Institute (NCRI) Teenage and Young Adult Clinical Studies Development Group. Br J Cancer 2008 Dec 16;99(12):1967-74.
9. Tejeda HA, Green SB, Trimble EL, Ford L, High JL, Ungerleider RS, et al. Representation of African-Americans, Hispanics, and whites in National Cancer Institute cancer treatment trials. J Natl Cancer Inst 1996 Jun 19;88(12):812-6.
10. SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011, based on November 2013 SEER data submission, posted to the SEER website, April 2014. 2014.
11. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015 Jan;65(1):5-29.
12. Stiller CA, Kroll ME, Pritchard-Jones K. Population survival from childhood cancer in Britain during 1978-2005 by eras of entry to clinical trials. Ann Oncol 2012 Sep;23(9):2464-9.
13. Gatta G, Botta L, Rossi S, Aareleid T, Bielska-Lasota M, Clavel J, et al. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5--a population-based study. Lancet Oncol 2014 Jan;15(1):35-47.
14. Kaatsch P. Epidemiology of childhood cancer. Cancer Treat Rev 2010 Jun;36(4):277-85.
15. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Protection of Human Subjects. Institutional Review Board; Report and Recommendations. 1978.
16. Council for International Organizations of Medical Sciences (CIOMS). International Ethical Guidelines for Biomedical Research involving Human Subjects. 2002.
17. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013 Nov 27;310(20):2191-4.
18. Churchill LR. Physician-investigator/patient-subject: exploring the logic and the tension. J Med Philos 1980 Sep;5(3):215-24.
19. Katz J. Human experimentation and human rights. St Louis Univ Law J 1993;38(1):7-54.
20. Miller FG, Rosenstein DL. The therapeutic orientation to clinical trials. N Engl J Med 2003 Apr 3;348(14):1383-6.
21. Lewens T. Distinguishing treatment from research: a functional approach. J Med Ethics 2006 Jul;32(7):424-9.
22. Berg SL. Ethical challenges in cancer research in children. Oncologist 2007 Nov;12(11):1336-43.

23. Brody H, Miller FG. The clinician-investigator: unavoidable but manageable tension. Kennedy Inst Ethics J 2003 Dec;13(4):329-46.
24. Kass NE, Faden RR, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. The research-treatment distinction: a problematic approach for determining which activities should have ethical oversight. Hastings Cent Rep 2013 Jan;Spec No:S4-S15.
25. Appelbaum PS, Lidz CW, Klitzman R. Voluntariness of consent to research: a conceptual model. Hastings Cent Rep 2009 Jan;39(1):30-9.
26. Edens JF, Epstein M, Stiles PG, Poythress NG, Jr. Voluntary consent in correctional settings: do offenders feel coerced to participate in research? Behav Sci Law 2011 Nov;29(6):771-95.
27. Leentjens AF, Levenson JL. Ethical issues concerning the recruitment of university students as research subjects. J Psychosom Res 2013 Oct;75(4):394-8.
28. Miller FG. Recruiting Research Participants. In: Emanuel et al e, editor. The Oxford Textbook of Clinical Research Ethics.Oxford [etc.]: OUP; 2008. p. 397-403.
29. Moser DJ, Arndt S, Kanz JE, Benjamin ML, Bayless JD, Reese RL, et al. Coercion and informed consent in research involving prisoners. Compr Psychiatry 2004 Jan;45(1):1-9.
30. Hewlett S. Consent to clinical research--adequately voluntary or substantially influenced? J Med Ethics 1996 Aug;22(4):232-7.
31. Fiore RN, Cushman R. Informed consent and parental permission for research: rules, roles, and relationships. Am J Bioeth 2015;15(4):77-8.
32. Kass NE, Sugarman J, Faden R, Schoch-Spana M. Trust, The fragile foundation of contemporary biomedical research. Hastings Cent Rep 1996 Sep;26(5):25-9.
33. Cox K. Informed consent and decision-making: patients' experiences of the process of recruitment to phases I and II anti-cancer drug trials. Patient Educ Couns 2002 Jan;46(1):31-8.
34. Mueller MR. Involvement and (potential) influence of care providers in the enlistment phase of the informed consent process: the case of AIDS clinical trials. Nurs Ethics 2004 Jan;11(1):42-52.
35. Shah A, Porter K, Juul S, Wilfond BS. Precluding consent by clinicians who are both the attending and the investigator: an outdated shibboleth? Am J Bioeth 2015;15(4):80-2.
36. van Stuijvenberg M, Suur MH, de VS, Tjiang GC, Steyerberg EW, rksen-Lubsen G, et al. Informed consent, parental awareness, and reasons for participating in a randomised controlled study. Arch Dis Child 1998 Aug;79(2):120-5.
37. Wilson S, Draper H, Ives J. Ethical issues regarding recruitment to research studies within the primary care consultation. Fam Pract 2008 Dec;25(6):456-61.
38. Loh WY, Butow PN, Brown RF, Boyle F. Ethical communication in clinical trials. Issues faced by data managers in obtaining informed consent. Cancer 2002 Dec 1;95(11):2414-21.
39. Yanos PT, Ziedonis DM. The patient-oriented clinician-researcher: advantages and challenges of being a double agent. Psychiatr Serv 2006 Feb;57(2):249-53.
40. Haylett WJ. Ethical considerations in pediatric oncology phase I clinical trials according to The Belmont Report. J Pediatr Oncol Nurs 2009 Mar;26(2):107-12.
41. Lantos JD. The "inclusion benefit" in clinical trials. J Pediatr 1999 Feb;134(2):130-1.
42. Joffe S, Weeks JC. Views of American oncologists about the purposes of clinical trials. J Natl Cancer Inst 2002 Dec 18;94(24):1847-53.
43. Kumar A, Soares H, Wells R, Clarke M, Hozo I, Bleyer A, et al. Are experimental treatments for cancer in children superior to established treatments? Observational study of randomised controlled trials by the Children's Oncology Group. BMJ 2005 Dec 3;331(7528):1295.
44. Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. Lancet 2004 Jan 24;363(9405):263-70.
45. Caldwell PH, Murphy SB, Butow PN, Craig JC. Clinical trials in children. Lancet 2004 Aug 28;364(9436):803-11.

46. Ferrari A, Bleyer A. Participation of adolescents with cancer in clinical trials. Cancer Treat Rev 2007 Nov;33(7):603-8.
47. Murphy SB. Cancer clinical trials: risks and benefits. J Pediatr Hematol Oncol 2001 Dec; 23(9):564-7.
48. Sollitto S, Hoffman S, Mehlman M, Lederman RJ, Youngner SJ, Lederman MM. Intrinsic conflicts of interest in clinical research: a need for disclosure. Kennedy Inst Ethics J 2003 Jun;13(2):83-91.
49. Faden RR, Kass NE, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. An ethics framework for a learning health care system: a departure from traditional research ethics and clinical ethics. Hastings Cent Rep 2013 Jan;Spec No:S16-S27.
50. Largent EA, Joffe S, Miller FG. Can research and care be ethically integrated? Hastings Cent Rep 2011 Jul;41(4):37-46.
51. Miller FG, Wendler D. The relevance of empirical research in bioethics. Schizophr Bull 2006 Jan;32(1):37-41.
52. Borry P, Schotsmans P, Dierickx K. The birth of the empirical turn in bioethics. Bioethics 2005 Feb;19(1):49-71.
53. Hurst S. What 'empirical turn in bioethics'? Bioethics 2010 Oct;24(8):439-44.
54. Parker M. Two concepts of empirical ethics. Bioethics 2009 May;23(4):202-13.
55. 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.
56. Reiter-Theil S. What does empirical research contribute to medical ethics? A methodological discussion using exemplary studies. Camb Q Healthc Ethics 2012 Oct;21(4):425-35.
57. Kon AA. The role of empirical research in bioethics. Am J Bioeth 2009;9(6-7):59-65.
58. Molewijk B, Stiggelbout AM, Otten W, Dupuis HM, Kievit J. Empirical data and moral theory. A plea for integrated empirical ethics. Med Health Care Philos 2004;7(1):55-69.
59. van Thiel GJMW, Van Delden JJM. Reflective Equilibrium as a Normative Empirical Model. Ethical Perspectives 2010;17(2):183-202.

Part I:
Dependent relationships and voluntary informed consent

2

Strengths and weaknesses of guideline approaches to safeguard voluntary informed consent of patients within a dependent relationship

SAS Dekking, R van der Graaf, JJM van Delden. BMC Medicine. 2014 March 24;12:52

Abstract

Background

It is thought that a dependent relationship between patients and physicians who enroll their own patients in research compromises voluntary informed consent. Therefore, several ethical guidelines for human subjects research provide approaches to mitigate these compromises. Currently, these approaches have not been critically evaluated. In this chapter, we analyze the approaches of ethical guidelines to manage the influence of a dependent relationship between patients and physicians on voluntary informed consent and discuss the strengths and weaknesses of these approaches.

Methods

We performed a review of international ethical guidance documents on human subjects research, listed in the Oxford Textbook of Clinical Research Ethics and found through cross-referencing. We also searched GEOBs and the WHO website. Guidelines from all years were eligible for inclusion. Date last searched was December 2013.

Discussion

We identified two basic guideline approaches. 1. A process approach, which focuses on the person who obtains informed consent, i.e. an independent individual, such as a research nurse or counselor. 2. A content approach, emphasizing the voluntary nature of participation. Both approaches are valuable, either because the influence of the physician may diminish or because it empowers patients to make voluntary decisions. However, the approaches also face challenges. First, research nurses are not always independent. Second, physician-investigators will be informed about decisions of their patients. Third, involvement of a counselor is sometimes unfeasible. Fourth, the right to withdraw may be difficult to act upon in a dependent relationship.

Summary

Current guideline approaches to protect voluntary informed consent within a dependent relationship are suboptimal. To prevent compromises to voluntary informed consent, consent should not only be obtained by an independent individual, but this person should also emphasize the voluntary nature of participation. At the same time, dependency as such does not imply undue influence. Sometimes, the physician may be best qualified to provide information, e.g. for a very specialized study. Still, the research nurse should obtain informed consent. In addition, patients should be able to consult a counselor, who attends the informed consent discussions and is concerned with their interests. Finally, both physicians and research nurses should disclose research interests.

Background

Ethical guidelines for human subjects research assume that voluntariness of informed consent of patients for medical research could be compromised when their own treating physician obtains consent.(1) Guidelines are cautious with regard to dependent relationships between patients and physicians. When patients depend on physicians for care and treatment it is felt that patients may not feel free to refuse an invitation of their physician to take part in a study.(2;3) Patients may fear disappointing their physician or damaging the physician/patient relationship, which could influence their consent to research.(4;5) Several empirical studies have shown that treating physicians can have a considerable influence on the decision making of their patients with regard to research.(6-12) Many ethical guidelines for human subjects research have proposed strategies to safeguard voluntary informed consent of patients in the case of a dependent relationship.(13-21)

In this chapter we analyze the approaches mentioned in main ethical guidelines to safeguard voluntary informed consent in a dependent relationship and discuss the strengths and weaknesses of these approaches. Although some scholars have touched upon issues related to the guideline approaches, none of them has provided a systematic evaluation.(3;22-25) Ways to diminish threats to the voluntariness of informed consent deserve careful scrutiny, because of the widely acknowledged importance of voluntary consent.(1) In addition, implementing and executing those strategies will generally mean extra investments in terms of time and energy.(1) It is important to know whether this time is well spent.

Methods

This study is reported according to the Methods section of the PRISMA checklist 2009.

Protocol and registration

No review protocol exists for this study.

Eligibility criteria

We performed a review of ethical guidelines, reports and regulations on medical research with human subjects (henceforth referred to as 'guidelines'). We only selected main international guidelines and national guidelines that play a role in the international debate on medical research involving human beings. Further relevance of guidelines was determined on the basis of the presence of phrases that concerned the relationship between patients and physicians in the context of medical research, and the potential undue influence of this relationship on patient decision making with regard to research participation. First, guidelines that did not mention the potential influence of the relationship between patients and physicians on voluntary informed consent were excluded from our analysis and evaluation.

Second, guidelines that only mentioned dependent relationships and its influence, but did not provide an approach to diminish this influence were excluded. Third, national guidelines that were not substantially different from international guidelines were excluded, because they would have no added value to our evaluation. (See Figure 1).

Guidelines and regulations from all years were eligible for inclusion in our review, since also more historic regulations are generally considered to be of relevance for present-day analyses. Guidelines had to be written in the English language, in order to be accessible to and relevant for an international audience.

Information sources

We took the Oxford Textbook of Clinical Research Ethics as starting point.(26) Furthermore, we searched the databases of PubMed and EMBASE to find literature to conduct our ethical evaluation. We also searched the Global Ethics Observatory (GEOBs) database of UNESCO and the website of the WHO. Date last searched for all these databases was December 2013. We had no specific dates of coverage, since we considered all possible publication dates of potential relevance.

Search

We started with examining the main international ethical guidelines and national guidelines that play a role in the international debate on medical research involving human beings, based on the Oxford Textbook of Clinical Research Ethics which lists 16 ethical guidelines.(26) Of these ethical guidelines, eight did not mention the ethical issue of the influence of a dependent relationship between patients and physicians on voluntary informed consent and were excluded.(27-35)

Two guidelines did mention that voluntary informed consent could be compromised within a dependent relationship, but they both did not provide an approach to safeguard voluntariness of patient consent and were therefore excluded.(36;37) Two guidelines both mentioned dependent relationships and an approach to protect voluntary informed consent.(32;38) However, since these guidelines have adopted the principles of the *Declaration of Helsinki*, they were not substantially different from this major international guideline and were excluded.

The four remaining guidelines of the Oxford Textbook of Clinical Research Ethics referred both to the influence of a dependent relationship on voluntary informed consent and suggested an approach to diminish this influence. Hence, these guidelines were included in our analysis and evaluation: The WMA's *Declaration of Helsinki*;(21) the CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects*;(13) the Canadian *Tri-Council Policy Statement, Ethical Conduct for Research Involving Humans*;(20) and the Australian National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research*.(14)

The second part of our search was based on the method of searching for titles added by cross referencing, since there is no one database in which all ethical guidelines are included. To find these additional guidelines, we searched the references of other guidelines and of articles discussing ethical guidelines for human subjects research. This search provided us with four additional guidelines that conformed to our eligibility criteria: *Institutional Review Boards: Report and Recommendations* of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research of the United States;(18) *Ethical issues in clinical research in neurology: advancing knowledge and protecting human research subjects* of the Ethics and Humanities Subcommittee of the American Academy of Neurology (in neurology research and care are often combined, meaning that patients are frequently recruited within a dependent relationship);(17) *the Ethics Manual Sixth Edition* of the American College of Physicians;(19) and *Managing Conflicts of Interest in the Conduct of Clinical Trials* of the American Medical Association's Council on ethical and judicial affairs.(15)

To find further internationally important guidelines we performed a search in 'Database 4: Ethics Related Legislation and Guidelines' of the GEOBs database of UNESCO. The theme we searched within this website was 'Medical research with human beings' and we included all legal categories (i.e. treaties, constitution, domestic laws, authoritative case laws and guidelines). Finally, we searched the website of the WHO. Both the database and the website did not provide us with additional ethical guidelines that were of relevance for the international debate on voluntary informed consent and dependent relationships between patients and physicians.

In order to find (empirical) support for the conduct of our evaluation of the guideline strategies, we performed several searches in PubMed and EMBASE, using various combinations of the following search terms: 'dependent relationships', 'dependency', 'physician-patient relationship', 'clinician-patient relationship', 'medical research'. 'clinical research', 'research', 'clinical trials', 'ethical guidelines', 'guidelines', 'policy', 'ethical guidance', 'voluntariness', 'voluntary informed consent', 'informed consent', 'consent', 'influence', 'empirical', 'qualitative' and 'quantitative'.

Data collection process

All included guidelines were examined for an explicit description of an approach to protect voluntary informed consent for research when it is obtained within a dependent relationship between patients and physicians.

Synthesis of results

We selected the phrases of the eight included guidelines that expressed an approach to diminish the risk of compromised voluntariness due to the undue influence of the treating relationship with and dependence upon the physician. We derived the key aspects of each of these guideline phrases and compared them in order to infer

whether they contained similar approaches to safeguarding voluntary informed consent. We identified two basic approaches within these ethical guidelines, i.e. a process versus a content focused approach.

With regard to the evaluation of the two guideline approaches, we used empirical data from the studies that showed up in our PubMed and EMBASE searches. In addition, where empirical support was lacking our evaluation is based on rational argumentation applied to the particularities of the clinical research context.

Study selection; Data items; Risk of bias in individual studies; Summary measures; Risk of bias across studies; Additional analyses

N/A

Discussion

Defining dependent relationships, voluntary informed consent and vulnerability

Dependent relationships

Dependency is often mentioned as a critical feature of physician-patient relationships in clinical research, both in the ethical guidelines for medical research with human beings (13;14;20;21) and in literature.(39;40) A dependent relationship in the context of medical research can be defined as a pre-existing treating relationship between patients who are prospective participants and their physicians which carries the potential for undue influence due to the dependence of patients upon their physicians for care and treatment.(13-15;17;18;20;21) Although some national guidelines and legislations acknowledge that also in the clinical context undue influence by the physician should be avoided,(41-43) we will focus on the context of medical research.

Voluntary informed consent

All reviewed guidelines express the thought that dependent relationships should be considered carefully, due to the influence the treating physician can have on the consent of the prospective participant. Although this influence is not necessarily regarded as problematic, the potential for undue influence frequently is emphasized. The reason that undue influence is regarded undesirable is because it compromises voluntary informed consent. This is reflected in the definition of the Belmont Report, which states that voluntary informed consent 'requires conditions free of coercion and undue influence'.(28) Two recently suggested interpretations of voluntary informed consent also regard the concept of influence as key to their definition of voluntary informed consent, although they speak of 'illegitimate' (44) and 'controlling' (45) influences respectively.

Our working definition of voluntary informed consent is the one provided by the Belmont Report,(28) which has also been accepted by the majority of the guidelines from our analysis.(13;14;17;18;20;21) With this definition as starting point, we are able to evaluate the guideline approaches according to their capacity to diminish the undue influence of physicians on patients when they recruit them for participation in medical research.

Vulnerability

To understand why patients recruited by their own physician are in need of protection by ethical guidelines, we need to consider the concept of vulnerability. Three recent accounts of vulnerability acknowledge the importance of the situation or context of research participants for attributing vulnerability.(46-48) Based on these accounts we suggest that the context of a dependent relationship could add an extra layer or increased likelihood of vulnerability on patients who are recruited for research, due to the hierarchical structure that is present in a dependent relationship.(46;48) Vulnerability then can be seen as a claim to special protection,(46) which strengthens the assumption that additional safeguards for patients recruited by their own physician are sensible and deserve careful scrutiny.

For now we consider that dependent relationships are generally regarded as a potential source of undue influence, that undue influences compromise voluntary informed consent, and that a dependent relationship may render patients vulnerable and therefore in need of special protection.

Two basic guideline approaches

It appears that ethical guidelines for medical research with human beings suggest two different approaches to manage the impact of a dependent relationship on voluntary informed consent. The first approach focuses on the process of obtaining informed consent; the second approach focuses on the content of the information that is communicated to the patient (see Table 1). Most guidelines refer to only one of the two approaches,(15;17-21) two guidelines include both approaches.(13;14)

Process approach

The informed consent process concerns two primary activities: to inform patients on the study details and to obtain written informed consent.(21) The first guideline approach to diminish the influence of the dependent relationship on patients is to have an independent, qualified individual take over one or both of these two primary tasks of the physician-investigator.(13-15;17;18;21) First, this independent individual can carry out the informed consent procedure instead of the physician-investigator,(13-15;21) to separate the informed consent process from the therapeutic relationship:(4) ‘Where the researcher has a pre-existing relationship with potential participants, it may be appropriate for their consent to be sought by an independent person’.(14) This person, who could be a research nurse or any other health care professional not directly responsible for the usual care of the patient in question,

should be ‘completely independent’ (21) from the treating relationship patients have with their physician.

Second, the independent individual could explain the study details and possible alternatives to research participation to the patients-subjects and answer the questions patients have with regard to the provided information.(14;15;17;18) When fulfilling these tasks, the independent individual functions as a kind of counselor.

Content approach

The second guideline approach aims to safeguard voluntary informed consent within a dependent relationship by demanding that certain vital pieces of information are conveyed to patients. One guideline stresses that ‘the right to withdraw consent and discontinue participation at any time must be communicated’.(19) One reason why patients find it difficult to refuse participation in a study is because they fear their refusal will adversely affect the care they receive or the relationship with their physician.(49) Therefore, several guidelines require from physicians that they emphasize to their patients that they will not suffer any negative consequences from possible refusal or withdrawal from the study.(13;19;20)

Strengths and weaknesses of both approaches

Process approach

Some positive aspects of what we have called the process approach have been suggested in the literature. By conveying the task of obtaining informed consent to an independent individual, the informed consent procedure is made more formal and clearly distinct from the practice of caregiving.(22;50) The physician could thereby communicate an explicit message to the patient, emphasizing the difference between research and usual practice.(3;22)

To delegate the informed consent process to an independent individual is important to avoid that patients feel intimidated by their physician.(25) It is mentioned that research nurses (or other study coordinators) are considered to be more neutral than physicians and researchers, making them better suited to obtain patient informed consent,(11) since they are not directly involved with the usual care of the patients.(50) Their neutrality then arises because they are independent from the treating relationship between patients and physicians. Since guidelines regard dependent relationships as problematic, this initial neutrality of the research nurse is thought to diminish the potential undue influence of the physician on patient decision making.(2;50)

However, considerable demands are often placed upon research nurses to recruit and retain a high number of patients to meet the study targets,(51;52) and sometimes their employment depends upon their succeeding to complete trials in order to gain funding for subsequent studies. Therefore, it is questionable how neutral the position of research nurses actually is.

In addition, research nurses are frequently not as independent from the treating relationship with patients as is suggested. Although there is no generally accepted, standardized description of the tasks of the clinical research nurse,(53) an important aspect of their role is that in addition to their research related tasks, they are usually also involved in the care of the patients they have recruited for research.(52) Clinical research nurses monitor the participating patients, explaining additional details, providing support, and carrying out the distribution of medication.(54;55) Therefore, they must find a balance between the needs of patients and the demands of the research protocol.(56) Qualitative studies have shown that research nurses themselves experience such a role conflict,(51;52;55) although they generally feel that their role as patient advocate is their primary one.(55)

The caregiving role of research nurses entails ongoing interaction with patients, which could result in a relationship between research nurses and the patients they take care of,(51;55) similar to the dependent relationship between patients and physicians. A risk of such a relationship is that patients feel they are in some way dependent upon the research nurse, leading patients to think they should follow the nurse's recommendations.(55) This could in turn prevent them from withdrawing from the study, which is contrary to the demand that voluntary informed consent needs to be protected both at the start of the study and as the study progresses.(1)

In addition to factors specifically applying to the research nurse, several other challenges to the process approach can be assumed. The strategy to have an independent individual obtain informed consent instead of the treating physician starts from the assumption that such a person makes it easier to refuse for patients. However, two aspects of clinical research practice should be considered to assess the potential effectiveness of having a third person obtain consent.

First, the independent person is usually invited by the physician-investigator or appointed by the hospital where the patient is treated.(23) As a result, patients may not perceive this supposedly independent person as truly independent from the relationship they have with their physician. Therefore, this person could just as well unduly influence the consent of the prospective participant.

Second, even though an independent individual obtains the informed consent of patients, several situations exist in which the physician of these patients will also be notified of their decision. When patients express their refusal to the independent individual, their own physician who conducts the study in question will typically be informed of this decision,(23) since he or she needs to know whether the patient participates in the study or should receive standard treatment. In a dependent situation the treating physician will always know whether the patient declined or accepted research participation, because this physician is the one who both conducts the study and has the responsibility for the treatment of the patient. So, the influence of the dependent relationship is not removed, meaning that some patients may still consent against their wishes because their physician will know anyhow.

Furthermore, even when the treating physician is not involved with the study the patient is included in, it will in some situations still be necessary to inform the physician of the decision of their patient. For instance in case research participation influences the usual care or when during the trial clinical problems arise that should be dealt with by the physician.(23) Thus the decision whether a participant has given consent is always disclosed, irrespective of possible blinding of the physician for the study drug that a patient will receive if the patient has given consent. It is the disclosure of the decision to participate that is relevant in light of threats to voluntariness.

The use of counselors to support patients in decision-making and empower patients to choose their preferred option seems a useful way to improve voluntary consent,(55) since they should be able to ask relevant questions and provide support to patients.(25) However, a challenge for this approach emerges when counselors suffer from a lack of medical expertise.(25) This will especially be the case if the counselor is a friend or relative.(23)

Another challenge for the involvement of counselors is mainly practical. It will be difficult for many hospitals or other health care facilities to train and appoint a sufficient number of counselors to provide support for the large amount of patients that is recruited within a dependent relationship.

Support of counselors or of other kinds of representatives is not unique for the context of dependent relationships. Several ethical guidelines also propose advocates or counselors for patients with insufficient mental capacity to consent on their own.(13;14;20;21) A factor that is often mentioned is that these advocates should consider the interests and preferences of the prospective participant in question.(14;20)

Interestingly, in describing the role of the counselor who supports patients in dependent relationships, ethical guidelines merely state that these counselors should provide study details, be available for questions during and after the informed consent procedure and assess the advisability of further participation. As such, the guidelines do not explicitly mention that counselors should take the interests and preferences of patients into account.

Content approach

The rights to withdraw and refuse and the absence of negative consequences should always be communicated, also to patients recruited outside the context of a dependent relationship to emphasize the voluntary nature of research participation.(21;35) Without this information, not all patients will be aware of their rights to refuse and withdraw without any retribution, which would be an ethically undesirable situation and would mean an infringement upon the validity of informed consent.(57)

However, the positive effects of the content approach on patients in a dependent relationship have hardly been studied. We think that this results from the content approach not previously being identified as one of two approaches to protect voluntary informed consent in a dependent relationship: most scholars and studies

focus on introducing an independent individual in the informed consent procedure and more specifically on the role of the research nurse.

Therefore, advantages of the content approach are not readily supported by the literature. Although one study shows that some data managers (e.g. research nurses, research assistants, study coordinators) feel that presenting information in a non-coercive manner and making patients aware of their rights to refuse and withdraw could ensure voluntary participation,(25) it is unclear how patients perceive this. Arguably, conversations with a research nurse or some other member of the research team could provide patients with robust knowledge,(58) which could aid them with their decision making. Yet, at least two challenges remain for the content approach.

First, statements on the right to withdraw and the absence of negative consequences can easily become void expressions rather than effective ways to protect the voluntary informed consent. The disclosure of information is not sufficient to meet the requirements for informed consent,(25) since patients should also understand the information they receive.(59) The manner in which the physician communicates the information is of great importance for patient comprehension,(59) something that ethical guidelines currently do not incorporate.

Second, although a review by Mandava et al has shown that at least 75% of research participants are generally aware of their right to withdraw,(60) in certain contexts a gap exists between knowing something and acting upon it.(61) Understanding of information on voluntariness does not equal voluntary informed consent. A recent study by Horwitz et al tried to untangle comprehension and voluntariness in the informed consent process for a HIV trial in Haiti.(62) They found that even though the participants showed good understanding of the study details, including the voluntary nature of the study, 11% gave responses suggesting involuntary consent. One of these responses concerned the belief ‘that a “volunteer” is someone who makes an irreversible commitment to remain in the study’.(62)

This study shows that even patients who had understood the provided information did not realize that they were indeed free to withdraw at any moment. For patients within a dependent relationship the gap between knowing and acting upon may be even greater, since patients depend upon their physician for the provision of care and treatment. Thus, although patients know and understand their rights, they could be hesitant to withdraw from the study even though they know they have the right to, since they do not want to disappoint their treating physician.(22)

Moving forward

The approaches as suggested by ethical guidelines seem suboptimal safeguards with respect to the voluntariness of informed consent in a dependent relationship. First, the influence of the physician is not necessarily sufficiently diminished when someone else obtains informed consent. Second, the right to withdraw cannot sufficiently be protected by simply pointing at this right and this right may be difficult to act upon in a dependent relationship.

It is time that physicians, investigators and members of Research Ethics Committees acknowledge that current guideline approaches do not appropriately protect patients who are enrolled by their own physician. Moreover, we believe that quick and easy solutions to the problem of compromised voluntariness do not exist. At least, the two existing approaches should be combined. The content approach, although on its own not sufficient, is of pivotal importance. Patients should always be informed about the voluntary nature of research participation and about the absence of negative consequences when they refuse or withdraw. And as regards the process approach, it is not sufficient if obtaining informed consent is delegated to a presumed neutral third party, since these persons are often not independent, both of the treating relationship and of the study in question. At the same time, where feasible inclusion by the research nurse or an equally qualified person is preferred over inclusion by the treating physician, since this physician is the primary caregiver.

However, a dependent relationship does not always imply compromised voluntariness of informed consent of the patients who are recruited for research by their own physician. People are influenced by others all the time and not all influences necessarily pose a threat to voluntary informed consent.(24;45) Consequently, being in a dependent relationship does not imply that patients should make decisions about research participation completely independent from the physician. Moreover, in some dependent situations it can be preferable that the physician provided the patient with information instead of the research nurse, for instance if the research is the means through which treatment is delivered or if a study is too detailed and specialized for research nurses to explain. The informed consent can then be signed in the presence of a research nurse or an equally qualified colleague.

In the clinical context the relevance of social relationships for decision making has already been recognized, since ‘preferences developed independently are not necessarily better than treatment preferences developed in collaboration’.(63) One could argue that also in the context of medical research patients appreciate being informed by their own physician, if patients feel they know and trust this person and feel comfortable speaking to their physician. For instance, a review by McCann et al has shown that patients consider the interaction with their physician as key to their research involvement,(64) indicating that a supportive and active role of their physician is something that patients find valuable when deciding about research.

Although caution in the case of a dependent relationship is still required, an existing dependent relationship should not by definition prevent a supportive and engaged role of physicians, as long as they are aware of their potential influence and 'recognize how their interactions and relationships with patients can either enable or impair patients' autonomy'.(65) So, the challenge for physicians is to be engaged and supportive, without unduly influencing their patients. If physicians approach their own patients for research they should find a balance between undue influence at one end of a continuum and independent decision making on the other end. They should be honest and transparent about their research related interests and should give responsive support adapted to individual patients and their needs, preferences and abilities.(63) These requirements equally apply to research nurses who cannot be independent.

Where feasible, patients should be able to ask for additional protection by involving a counselor, also in case the research nurse obtains informed consent. Although some guidelines suggest that patients should be in the position to discuss research participation and the study details with someone else,(14;15;17;18) they do not elaborate on what his or her role exactly is. We suggest that this counselor should be independent (e.g. a regular nurse who works at a different department and is not involved in the study), specifically educated and be able to support patients in their decision making. Therefore, on the patient's request this counselor should be present during informed consent discussions. He or she should pay close attention to the preferences and views of patients, in order to enable them to make decisions that fit their goals and values. Also, the counselor should be available to answer any questions patients might have afterwards or during the proceedings of the trial.

Further research

In order to effectively reflect on the interaction between patients and their physicians during the informed consent procedure and develop an approach that respects medical research practice, more research is needed. First, we need to know whether patients indeed feel pressure to accept an invitation for research from their physician due to the prior therapeutic relationship. Second, if voluntary informed consent is compromised when obtained within a dependent relationship, it should be investigated how extensive the problem is and which factors contribute to it. Factors that could be of importance are whether physicians recruit patients for their own research or for someone else's.(15;17) Furthermore, the degree of dependency (20) can be of importance, which in turn can be influenced by the severity of the disease (40) and the length of the treating relationship.(17) Third, the merits of our new proposal, that is, a combination of the process and content approaches complemented by an upgraded version of the counselor, should be empirically studied taking the perspectives and experiences of patients and physicians into account.

Summary

Ethical guidelines try to manage the impact of a dependent relationship on voluntary informed consent in two ways. One approach focuses on the process of obtaining informed consent; the other on the content of the information that is communicated to the patient. Some guidelines include both approaches; other guidelines only articulate one of them. Our analysis shows that although both approaches could have some favorable impact on voluntary informed consent of patients, they also face challenges. Research nurses are not independent of the treating relationship patients have with their physician, since they frequently provide care to included patients. Also, they are not neutral with regard to the study they recruit patients for, as their job often depends on assuring high inclusion rates. Any other health care professional is likely to be regarded by patients as belonging to the team of the physician, which could also influence voluntary informed consent.

Furthermore, even if patients express their refusal to an independent individual, in many instances their own physician will be informed of this decision, which means that the influence of the physician on voluntary informed consent is still present. Making patients aware of their rights to refuse and withdraw at any time is important, but might not be convincing for patients who are enrolled by their own physician, because they depend on the physician for care and treatment.

At least the process and content approach should be combined. Patients in a dependent relationship should in all instances be informed of their rights to withdraw and refuse without any negative consequences with regard to their care or the relationship with their physician. Furthermore, inclusion by a research nurse is preferred over inclusion by the physician, since the physician is the primary caregiver of the patients. Deviations from this rule are conceivable in cases where research is part of the treatment or where a physician will be better able to explain the research protocol than the research nurse. After all, dependency as such does not imply undue influence. Patients need not make completely independent decisions in order for these decisions to be voluntary. In such cases, it is important that physicians are aware of their own influence and be transparent and honest about their existing research interests. This is also the case for research nurses who cannot be independent.

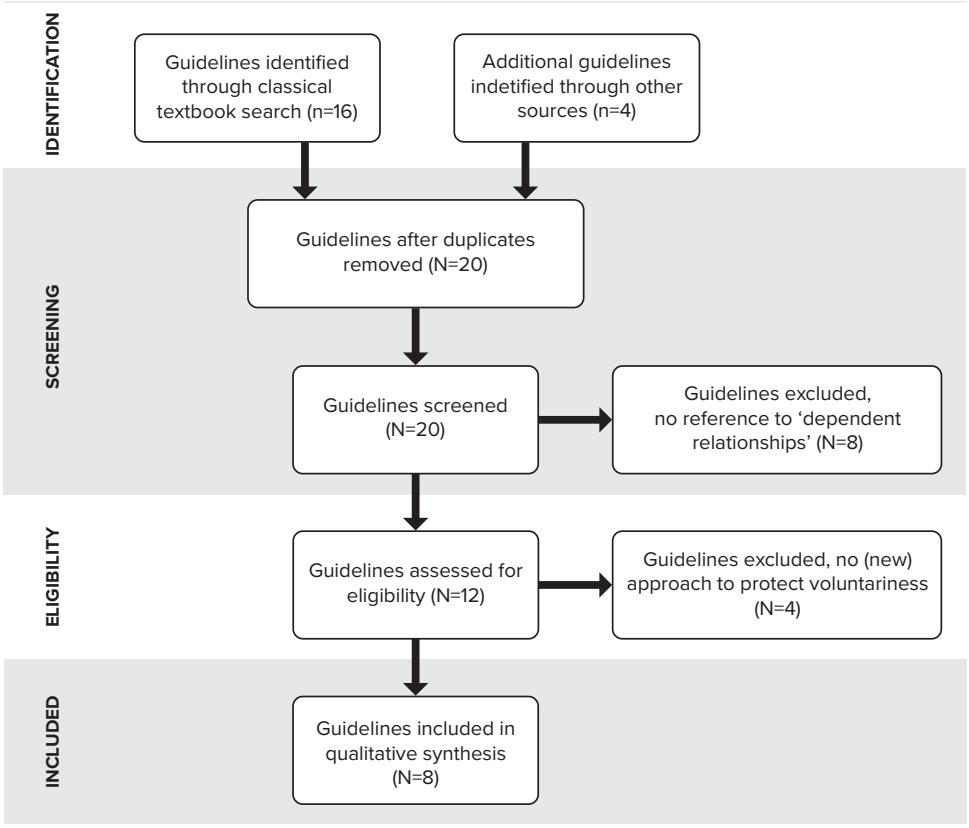
To further prevent undue influence patients should be able to ask for a specifically educated and independent counselor, who can attend the informed consent process. This should also be the case if the research nurse obtains informed consent. These counselors should be in the position to provide support to patients and optimally safeguard voluntary informed consent, if they actively take the values and preferences of patients into account.

Table 1: Guideline strategies to protect voluntary informed consent within a dependent relationship.

Declaration of Helsinki, 2013	World Medical Association	§27: 'When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.'
International Ethical Guidelines for Biomedical Research Involving Human Subjects, 2002	Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO)	Commentary on Guideline 6: 'The physician/investigator must assure [patients] that their decision on whether to participate will not affect the therapeutic relationship or other benefits to which they are entitled. In this situation the ethical review committee should consider whether a neutral third party should seek informed consent.'
Tri-Council Policy Statement, Ethical Conduct for Research Involving Humans, 2010	Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada	Article 3.1 a (Application): 'Pre-existing entitlements to care, education and other services should not be prejudiced by the decision of whether or not to participate in, or to withdraw from, a research project. Accordingly... a physician should ensure that continued clinical care is not linked to research participation.'
National Statement on Ethical Conduct in Human Research, 2007	National Health and Medical Research Council, Australia	4.3.2 'In the consent process, researchers should wherever possible invite potential participants to discuss their participation with someone who is able to support them in making their decision.' 4.3.10 'Where the researcher has a pre-existing relationship with potential participants, it may be appropriate for their consent to be sought by an independent person.'

Institutional Review Boards: Report and Recommendations, 1978	The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, United States	'In cases in which the investigator is responsible for the care of the subjects, the IRB may require that a neutral person, not otherwise associated with research or the investigator, be present when consent is sought, to explain the research to prospective subjects, or to observe the conduct of the research … Such a person may be designated to play a role in informing subjects of their rights and the details of protocols, assuring that there is continuing assent to participation, determining the advisability of continued participation, receiving complaints from subjects, and bringing grievances to the attention of the IRB as part of its continuing review of research.'
Ethical issues in clinical research in neurology: advancing knowledge and protecting human research subjects, 1998	The Ethics and Humanities Subcommittee of the American Academy of Neurology, United States	'[R]esearchers and IRBs may want to consider additional safeguards. For example, the IRB may request that an "uninterested" individual … discuss with prospective subjects the research study and other clinical or research alternatives.'
Ethics Manual Sixth Edition, 2012	Ethics, Professionalism, and Human Rights Committee, American College of Physicians, United States	'It should … be clear to patients that participation in research is voluntary and not a requirement for continued clinical care. The right to withdraw consent and discontinue participation at any time must be communicated.'
Managing Conflicts of Interest in the Conduct of Clinical Trials, 2002	The council on ethical and judicial affairs, American Medical Association, United States	'[T]he physician who has treated a patient on an ongoing basis should not be responsible for obtaining that patient's informed consent to participate in a trial that will be conducted by the physician. .. Instead … someone other than the treating physician should obtain the participant's consent. The non-treating health care professional also could remain available to answer additional questions during the trial.'

Figure 1. Flow diagram of the selection and inclusion of ethical guidelines



References

1. Appelbaum PS, Lidz CW, Klitzman R. Voluntariness of Consent to Research: A Preliminary Empirical Investigation. IRB: Ethics & Human Research 2009 Nov;31(6):10-4.
2. Black L, Batist G, Avard D, Rousseau C, Diaz Z, Knoppers BM. Physician recruitment of patients to non-therapeutic oncology clinical trials: ethics revisited. Front Pharmacol 2013;4:25.
3. Levine RJ. Clinical trials and physicians as double agents. Yale J Biol Med 1992 Mar;65(2):65-74.
4. Miller FG. Recruiting Research Participants. In: Emanuel et al e, editor. The Oxford Textbook of Clinical Research Ethics.Oxford [etc.]: OUP; 2008. p. 397-403.
5. Miller VA, Nelson RM. Factors related to voluntary parental decision-making in pediatric oncology. Pediatrics 2012 May;129(5):903-9.
6. Gammelgaard A, Mortensen OS, Rossel P. Patients' perceptions of informed consent in acute myocardial infarction research: a questionnaire based survey of the consent process in the DANAMI-2 trial. Heart 2004 Oct;90(10):1124-8.
7. Kass NE, Sugarman J, Faden R, Schoch-Spana M. Trust, the fragile foundation of contemporary biomedical research. Hastings Cent Rep 1996 Sep;26(5):25-9.
8. Kinney AY, Richards C, Vernon SW, Vogel VG. The effect of physician recommendation on enrollment in the Breast Cancer Chemoprevention Trial. Prev Med 1998 Sep;27(5 Pt 1):713-9.
9. Knifed E, Lipsman N, Mason W, Bernstein M. Patients' perception of the informed consent process for neurooncology clinical trials. Neuro Oncol 2008 Jun;10(3):348-54.
10. ACHRE Advisory Committee on Human Radiation Experiments Final Report. Washington, DC: U.S.: Government Printing Office; 1995.
11. Eggly S, Albrecht TL, Harper FW, Foster T, Franks MM, Ruckdeschel JC. Oncologists' recommendations of clinical trial participation to patients. Patient Educ Couns 2008 Jan;70(1):143-8.
12. Kleiderman E, Avard D, Black L, Diaz Z, Rousseau C, Knoppers BM. Recruiting terminally ill patients into non-therapeutic oncology studies: views of health professionals. BMC Med Ethics 2012;13:33.
13. Council for International Organizations of Medical Sciences (CIOMS). International Ethical Guidelines for Biomedical Research involving Human Subjects. 2002.
14. Australian Government National Health and Medical Research Council (NHMRC), National Statement on Ethical Conduct in Human Research. 2007.
15. Morin K, Rakatansky H, Riddick FA, Jr., Morse LJ, O'Bannon JM 3rd, Goldrich MS, et al. Managing conflicts of interest in the conduct of clinical trials. JAMA 2002 Jan 2;287(1):78-84.
16. Office of Inspector General. Department of Human and Health Services. Recruiting Human Subjects Pressures in Industry-Sponsored Clinical Research. 2000 Jun.
17. Ethical issues in clinical research in neurology: advancing knowledge and protecting human research subjects. The Ethics and Humanities Subcommittee of the American Academy of Neurology. Neurology 1998 Mar;50(3):592-5.
18. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Protection of Human Subjects. Institutional Review Board; Report and Recommendations. 1978.
19. Snyder L. American College of Physicians Ethics Manual: sixth edition. Ann Intern Med 2012 Jan 3;156(1 Pt 2):73-104.
20. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research council of Canada, Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. 2010 Dec.
21. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013 Nov 27;310(20):2191-4.
22. Brody H, Miller FG. The clinician-investigator. Unavoidable but manageable tension. Kennedy Institute of Ethics Journal 2003;13(4):329-46.
23. Hewlett S. Consent to clinical research--adequately voluntary or substantially influenced? J Med Ethics 1996 Aug;22(4):232-7.

24. Appelbaum PS, Lidz CW, Klitzman R. Voluntariness of consent to research: a conceptual model. Hastings Cent Rep 2009;39(1):30-9.
25. Loh WY, Butow PN, Brown RF, Boyle F. Ethical communication in clinical trials. Issues faced by data managers in obtaining informed consent. Cancer 2002 Dec 1;95(11):2414-21.
26. Emanuel EJ, Wendler D, Grady C. An Ethical Framework for Biomedical Research. In: Emanuel et al, editor. The Oxford Textbook of Clinical Research Ethics. OUP; 2008. p. 123-35.
27. The Nuremberg Code. Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10. Nuremberg, October 1946 to April 1949. Washington DC: US Government Printing Office; 1949-1953; 1949.
28. 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. 1978.
29. National Science foundation. 45 CFR Part 690: Federal Policy for the Protection of Human Subjects. Subpart A: The Common Rule for the Protection of Human Subjects. 1981.
30. National Health Council Brazil. Resolution 196/96: Rules on Research Involving Human Subjects, (1996).
31. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutical for Human Use. The ICH Harmonized Tripartite Guideline - Guideline for Good Clinical Practice. Geneva: ICH; 1996.
32. U.K. Medical Research Council Guidelines for Good Clinical Practice in Clinical Trials. London, England; 1998.
33. Uganda National Council of Science and Technology (UNCST). Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda. Kampala, Uganda: UNCST; 1998.
34. Indian Council on Medical Research. Ethical Guidelines for Biomedical Research on Human Subjects. New Delhi, India: Indian Council on Medical Research; 2000.
35. Council of Europe. Convention on Human Rights and Biomedicine (Oviedo Convention), Additional Protocol concerning Biomedical Research. 2005 Jan 25.
36. South African Medical Research Council. Guidelines on Ethics for Medical Research: General Principles. South Africa: South African Medical Research Council; 2002.
37. Department of Health, South Africa. Guidelines for Good Clinical Practice in the Conduct of Clinical Trials in Human Participants in South Africa. South Africa: Department of Health, South Africa; 2000.
38. Tanzania National Health Research Forum. Guidelines on Ethics for Health Research in Tanzania. Dar es Salaam, Tanzania: THNRF; 2009.
39. Pellegrino ED. Toward a reconstruction of medical morality. J Med Humanit Bioeth 1987;8(1):7-18.
40. Veatch RM. Assessing Pellegrino's reconstruction of medical morality. Am J Bioeth 2006 Mar;6(2):72-5.
41. Israel Patient's Rights Act, Israel Patient's Rights Act, (1996).
42. UK General Medical Council. Consent: patients and doctors making decisions together. 2008.
43. The New Zealand's Code of Health and Disability Services Consumers' Rights, The New Zealand's Code of Health and Disability Services Consumers' Rights, (1996).
44. Appelbaum PS, Lidz CW, Klitzman R. Voluntariness of consent to research: a conceptual model. Hastings Cent Rep 2009 Jan;39(1):30-9.
45. Nelson RM, Beauchamp T, Miller VA, Reynolds W, Ittenbach RF, Luce MF. The Concept of Voluntary Consent. The American Journal of Bioethics 2011 Aug 1;11(8):6-16.
46. Hurst SA. Vulnerability in research and health care; describing the elephant in the room? Bioethics 2008 May;22(4):191-202.
47. Lange MM, Rogers W, Dodds S. Vulnerability in research ethics: a way forward. Bioethics 2013 Jul;27(6):333-40.
48. Luna F, Vanderpoel S. Not the usual suspects: addressing layers of vulnerability. Bioethics 2013 Jul;27(6):325-32.

49. de Vries MC, Houtlosser M, Wit JM, Engberts DP, Bresters D, Kaspers GJ, et al. Ethical issues at the interface of clinical care and research practice in pediatric oncology: a narrative review of parents' and physicians' experiences. BMC Med Ethics 2011;12:18.
50. Alpert JE, Biggs MM, Davis L, Shores-Wilson K, Harlan WR, Schneider GW, et al. Enrolling research subjects from clinical practice: ethical and procedural issues in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. Psychiatry Res 2006 Feb 28;141(2):193-200.
51. Fisher JA. Co-ordinating 'ethical' clinical trials: the role of research coordinators in the contract research industry. Sociol Health Illn 2006 Sep;28(6):678-94.
52. Spilsbury K, Petherick E, Cullum N, Nelson A, Nixon J, Mason S. The role and potential contribution of clinical research nurses to clinical trials. J Clin Nurs 2008 Feb;17(4):549-57.
53. Hastings CE, Fisher CA, McCabe MA, Allison J, Brassil D, Offenhartz M, et al. Clinical research nursing: a critical resource in the national research enterprise. Nurs Outlook 2012 May;60(3):149-56.
54. Coulson S, Phelan L. Clinical research in paediatric oncology and the role of the research nurse in the UK. Eur J Oncol Nurs 2000 Sep;4(3):154-61.
55. Davis AM, Hull SC, Grady C, Wilfond BS, Henderson GE. The invisible hand in clinical research: the study coordinator's critical role in human subjects protection. J Law Med Ethics 2002;30(3):411-9.
56. McCabe M, Cahill Lawrence CA. The clinical research nurse. Am J Nurs 2007 Sep;107(9):13.
57. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? JAMA 2000 May 24;283(20):2701-11.
58. Gillies K, Entwistle VA. Supporting positive experiences and sustained participation in clinical trials: looking beyond information provision. J Med Ethics 2012 Dec;38(12):751-6.
59. Kaewpoonsri N, Okanurak K, Kitayaporn D, Kaewkungwal J, Vijaykadga S, Thamaree S. Factors related to volunteer comprehension of informed consent for a clinical trial. Southeast Asian J Trop Med Public Health 2006 Sep;37(5):996-1004.
60. Mandava A, Pace C, Campbell B, Emanuel E, Grady C. The quality of informed consent: mapping the landscape. A review of empirical data from developing and developed countries. J Med Ethics 2012 Jun;38(6):356-65.
61. Kennedy T, Regehr G, Rosenfield J, Roberts SW, Lingard L. Exploring the gap between knowledge and behavior: a qualitative study of clinician action following an educational intervention. Acad Med 2004 May;79(5):386-93.
62. Horwitz RH, Roberts LW, Seal DW, Joseph P, Maschke KJ, Verdier RI, et al. Assessing whether consent for a clinical trial is voluntary. Ann Intern Med 2013 Feb 5;158(3):222-4.
63. Entwistle VA, Cribb A, Watt IS. Shared decision-making: enhancing the clinical relevance. J R Soc Med 2012 Oct;105(10):416-21.
64. McCann SK, Campbell MK, Entwistle VA. Experiences of recruitment to clinical trials: a meta-ethnographic synthesis of qualitative studies. J Health Serv Res Policy 2013 Aug 28;18(4):233-41.
65. (65) Entwistle VA, Carter SM, Cribb A, McCaffery K. Supporting patient autonomy: the importance of clinician-patient relationships. J Gen Intern Med 2010 Jul;25(7):741-5.

3

A qualitative study into dependent relationships and voluntary informed consent for research in pediatric oncology

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Abstract

Background

In pediatric oncology, many oncologists invite their own patients to participate in research. Inclusion within a dependent relationship is considered to potentially compromise voluntariness of consent. Currently, it is unknown to what extent those involved in pediatric oncology experience the dependent relationship as a threat to voluntary informed consent, and what they see as safeguards to protect voluntary informed consent within a dependent relationship.

Aim

We performed a qualitative study among key actors in pediatric oncology to explore their experiences with the dependent relationship and voluntary informed consent.

Methods

We conducted 3 focus groups and 25 semi-structured, in-depth interviews with pediatric oncologists, research coordinators, Research Ethics Committee members, parents of children with cancer, and adolescents with cancer.

Results

Professionals regarded the dependent relationship both as a potential threat to and as a positive influence on voluntary decision-making. Parents and adolescents did not feel as though dependency upon the oncologist influenced their decisions. They valued the involvement of their own physician in the informed consent process. The professionals suggested three strategies to protect voluntariness: emphasizing voluntariness; empowering families; involvement of an independent person.

Conclusions

Thus, although the dependent relationship between pediatric oncologists, patients and parents may be problematic for voluntary informed consent, this is not necessarily the case. Moreover, the involvement of treating physicians may even have a positive impact on the informed consent process. Although we studied pediatric oncology, our results may also apply to many other fields of pediatric medicine where research and care are combined, for example pediatric rheumatology, neurology and nephrology. Clinical trials in these fields are inevitably often designed, initiated and conducted by medical specialists closely involved in patient care.

Introduction

Since in pediatric oncology the provision of treatment is closely combined with research, many oncologists are both clinicians and researchers and include their own patients in studies.(1) Guidelines for human subject research demand that physicians do not enroll their own patients in research.(2;3) The dependent relationship between them and their patients may compromise the voluntariness of the patient's consent, since this relationship may constitute an undue influence.(2-4) In ethical guidelines and literature, the presence of undue influence on patient decision making is considered to compromise voluntary informed consent for research.(2;5)

Currently, it is unknown to what extent actors in pediatric oncology experience the dependent relationship as a threat to voluntary informed consent, and what they see as safeguards to protect voluntary informed consent within a dependent relationship. In order to explore these two questions we conducted a qualitative study into the experiences of pediatric oncology actors with voluntary informed consent when the treating oncologist is involved in the informed consent process. Insight into these experiences is an important factor for the ethical evaluation of voluntary informed consent in pediatric oncology.(6)

Previous qualitative studies have not specifically investigated the experiences of those involved in pediatric oncology with voluntary informed consent within a dependent relationship, but have mainly described experiences of parents and physicians with the informed consent process for pediatric oncology trials in general. (7-17) Moreover, most studies focus on the disclosure and comprehension aspect of informed consent rather than on voluntariness, or they explore the satisfaction of families with the informed consent process and their suggestions for improvement. (7-10;12-17) A study by Miller et al addressed voluntary parental decision making, but discussed demographic and contextual factors that could affect parental perceptions of voluntariness rather than the influence of inclusion within the patient-physician relationship.(11)

Therefore, in this chapter we studied the dependent relationship in pediatric oncology and its potential influence on voluntary informed consent for research. We performed a qualitative study among key actors in pediatric oncology in which we explored their experiences with this relationship.

Materials and methods

A qualitative study design allows for in-depth exploration of a topic and is therefore most suited to capture the experiences of those involved in pediatric oncology. As a first exploration of the topic, we conducted three homogenous focus groups; one with Dutch pediatric oncologists, one with Research Ethics Committee (REC) members, and one with parents of children with cancer. To validate and deepen our insights, a second stage of in-depth interviews was performed.

We conducted 25 individual interviews with pediatric oncologists, research coordinators, parents of children with cancer, and adolescents with cancer.

Sample

The inclusion criterion for the pediatric oncologists, research coordinators, parents, and adolescents was to have been actively involved in inclusion for pediatric oncology trials. For the pediatric oncologists and research coordinators this means that they should regularly inform families about available studies and perform informed consent procedures. For parents and adolescents active involvement means to have been approached for a pediatric oncology study and to have had informed consent conversations, regardless of the final decision. That is, also parents and adolescents who refused one or more studies were eligible for the focus group or interviews. Also, for the parents and adolescents, the moment of being approached about participation in an oncology study, for their child or for themselves, should have been less than two years ago. The inclusion criterion for REC members was to be or have been member of an REC at a pediatric oncology center. All respondents had to be able to speak the Dutch language. In addition, for all respondents we aimed for a large variety in age, gender, types of cancer, and experience with research participation. See Table 1 for the characteristics of the professionals (pediatric oncologists, research coordinators and REC members), Table 2 for the parents and their children, and Table 3 for the adolescents. See Figure 1 for a flow chart of the different respondents.

Focus groups

Pediatric oncologists were recruited from the seven pediatric oncology centers in the Netherlands, one from each center. Our two pediatric oncology project advisors contacted the heads of the pediatric oncology centers, asking them to invite one of their physicians who were regularly involved in informed consent discussions to take part in our focus group. Six pediatric oncologists took part, one could not attend.

Also for the focus group with Research Ethics Committee members our goal was to include members from all seven Dutch pediatric oncology centers, but due to practical reasons five of them could not send a member to represent their center in the focus group. From one center one REC member attended, from another center two members were present. In order to increase the number of participants, we approached the central review committee of the Netherlands (CCMO), from which one person could participate. Thus, the focus group involved four participants from three different ethical committees.

Parents of children with cancer for the focus group were all recruited through one center for pragmatic reasons. We considered that organizing a meeting for parents situated at different centers would entail too much burden (in terms of travel time) and was therefore unfeasible. In principle, all parents were eligible whose child was participating in or had participated in a pediatric oncology study.

We aimed at maximal variation in the types of studies children (had) participated in for different kinds of malignancies. More specifically, we aimed for 2-3 patients taking part in a phase I-II study, 2-3 patients in a phase III study and 2-3 patients in a supportive care study, as the main study the child (had) participated in. In addition, children could have been invited for and involved in other studies. A research nurse contacted twelve parents of eight children by telephone, based on the child's study participation. These parents all accepted the invitation to participate in the focus group. In total nine parents of six children attended; four mothers and five fathers. Three parents could not attend due to practical reasons.

Interviews

Pediatric oncologists from the seven Dutch pediatric oncology centers were contacted via the heads of these centers and via two of our project advisors, who contacted their colleagues and provided them with a description of our study and its aims. Also, they indicated that the pediatric oncologists should contact SD if they were interested in taking part in an interview. Inclusion in the study was continuous via convenience sampling, all interested pediatric oncologists were considered eligible to take part as long as they had experience with including their patients in oncology studies and performing informed consent conversations. In addition, we asked participating pediatric oncologists whether they knew colleagues whom we could approach to take part in an interview. Research coordinators were recruited from two centers, since not all Dutch pediatric oncology centers employ research coordinators.

Parents and adolescents were approached through a call on the website of the Dutch Association for Parents, Children and Cancer (VOKK) and via physicians and research nurses of three pediatric oncology centers. Here also, inclusion in the study was continuous via convenience sampling, as all parents and adolescents with cancer were eligible who had been invited for research, regardless of type of study. In some cases, physicians recruited their own patients and parents of these patients for our study. In one case, the recruiting physician was also the investigator of a study the child was participating in. The physician approached a family about our study, gave them the information form and asked whether they were interested in participating. If so, the parent could contact the investigator of this study (first author SD), to make an appointment for the interview(s). Before each interview, informed consent was obtained by SD.

We interviewed nine pediatric oncologists from five different centers (three interested pediatric oncologists, from two different centers, were not interviewed in the end, due to logistic reasons), three research coordinators, eight parents of eight different children, and five adolescents. Four of these adolescents were the children of parents we interviewed. Of one adolescent the parents were not interviewed.

Data collection

Focus groups lasted two hours each. Topics were formulated after examination of the relevant literature and two one-week internships of SD at two Dutch pediatric oncology centers, where she attended consultations between physicians, parents and patients, and gathered expert knowledge from pediatric oncologists and research nurses.

Semi-structured, in depth interviews were conducted according to predefined topic lists (Table 4). All but one interview took place at a pediatric oncology center. One interview, with an adolescent boy, took place at home. Data collection took place from March 2013 to January 2015.

The study was approved by the Research Ethics Committee of the University Medical Center Utrecht. Parents and adolescents provided written informed consent for their participation and, if applicable, parents also provided written consent for their child's participation.

Data analysis

The analysis was carried out according to thematic analysis, a method for identifying, analyzing, and reporting themes within data.(18) Our themes were identified at the semantic level, meaning that we started with describing the experiences of the respondents followed by an interpretation in the light of the existing literature.(18) The focus groups and interviews were transcribed verbatim and the data were imported in the software program NVivo 10, in order to facilitate the process of analysis.

SD was the main analyst. SD, MK and RG independently read two interviews, selected fragments of the data that were relevant in relation to the study purpose, and coded these fragments with appropriate labels. During a first meeting, all findings were compared and contrasted, which resulted in the initial code tree. During two more team meetings, we compared our interpretations of fragments of two new interviews and identified the appropriate labels for these fragments. We worked towards reaching consensus between the different team members, and aimed to align our interpretations of the data. During this phase, we developed the code tree into a more conceptual code structure. Then, SD coded the focus groups and interviews in line with this shared interpretation of the first four interviews (that is, based on the conceptual code structure). The appropriate codes were grouped into conceptual categories or themes on the basis of their content, meaning, and interrelationships. SD described these themes, their characteristics, and the associations between them. To ensure reliability, these themes and accompanying descriptions were continuously discussed during team meetings, providing SD with a shared conceptual basis for the remainder of the coding process.

To enhance the validity of our findings, we held an expert meeting with pediatric oncologists in the last phase of data collection.

We discussed our preliminary results to assess whether these were an accurate representation of pediatric oncology practice and to obtain additional data. In general, the oncologists recognized our presentation of the informed consent process and of their experiences with including their own patients.

Results

The role of the dependent relationship

We identified three ways in which our respondents experienced the influence of the dependent relationship on voluntary informed consent, i.e. potentially problematic influence; minimal or no influence; positive influence. Representative quotations were chosen to illustrate the themes identified (Table 5).

Potentially problematic influence

The pediatric oncologists felt that patients and their parents are extremely dependent upon them for treatment and to safeguard the possibility of a cure. They thought that this dependency could compromise voluntary informed consent, because parents have an interest in maintaining a good relationship with their physician. (Quote 1 in Table 5)

Also research coordinators thought that sometimes parents were reluctant to say 'no' to one of the oncologists. In addition, a research coordinator who also had extensive caring tasks described situations in which she thought that parents felt guilty when their child decided not to participate. (Quote 2 in Table 5)

Only one father thought that the dependent relationship with the treating physician of his son may have been a factor in his deliberations about whether to consent to studies that were offered shortly after hearing their son's cancer diagnosis. (Quote 3 in Table 5)

One adolescent boy indicated that he had wondered what would happen if he refused to take part in the studies that were offered to him, and if it would affect his future care or the way his oncologist perceived him. When he asked the oncologists about this they told him that nothing would happen if he refused, and this sufficiently reassured him.

Minimal or no influence

Oncologists believed that they generally have no influence on decisions of parents about research. They thought that the majority of parents make these decisions completely or mainly independent, as a family, without feeling pressure from the oncologists or others.

Although parents recognized being and feeling strongly dependent on their oncologist, they said that this had no influence on their decisions about their child's research participation. They made their own decisions, based on criteria they considered important. They either hoped that a study could benefit their child or expected it would at least not have a negative influence on their child's general treatment. In addition, they considered studies with very low risk and burden, such as having some extra blood taken at regular blood drawing moments, as a simple way to contribute to improvement of therapy for children with cancer. (Quote 4 in Table 5)

Also, because of their experiences with their sick child, parents were even more motivated to contribute to the improvement of therapy for other patients. A father explained why they and their son wanted to take part in research. (Quote 5 in Table 5)

The adolescents reported to feel no pressure from their oncologist or others and felt free to refuse participation if they wanted to. They were motivated to participate in studies and contribute to improve treatment for future patients with their disease. If they had sensed that their oncologist would prefer for them to take part in a certain study, this generally had no influence on their decisions.

Positive influence

Pediatric oncologists explained that since they are the treating physician of the child, they are in the perfect position to guide families in their decision-making process. Because they know patients and their parents, they are able to provide information in an appropriate manner and to introduce the large number of studies in a way that it becomes feasible. They mentioned that protecting patients is necessary in order to maintain a positive treatment relationship. A person who is only a researcher does not have this interest in protecting the relationship. In addition, it was stated that if parents are clearly unable to make a decision about the research request, then the treating oncologist would decide not to enroll the child.

Parents mentioned that they appreciated the way the treating oncologist explained the research, which enabled them to make their own decisions. One mother said that if an unknown researcher would invite them in their study, she might even ask her son's treating oncologist for advice. For studies with a potential profound impact on their child's wellbeing parents said to prefer having the study explained by their own physician. (Quote 6 in Table 5)

Strategies to protect voluntariness of informed consent

Emphasizing the voluntary nature of participation

The health care professionals indicated trying to safeguard voluntary informed consent by stressing that research participation is a free choice, and that patients always have the right to withdraw. In addition, they emphasize that for them it does

not matter what parents decide and that refusal would not influence the treating relationship.

Parents and adolescents recalled being told that research participation was voluntary. Therefore, they felt that it really was their decision to make and that they need not consent to all the offered studies.

Empowering families

Both the pediatric oncologists and the REC members stressed the importance of ensuring that parents and older patients gain a sense of responsibility by making clear that they are the ones in charge. (Quote 7 in Table 5)

Diminishing the asymmetry in knowledge was also regarded as a way to empower families. Providing children with cancer and their parents with honest and objective information, both written and verbal, was often emphasized as a means to create optimal circumstances for making deliberate and well-balanced decisions. For the majority of parents it was very important to receive adequate information on a study, making clear what the impact on their child would be and in what way it could help to improve treatment.

An REC member suggested assigning a sort of 'medical coach' to families as a way to accomplish empowerment. This coach could advise them where to find certain information or who to approach for specific questions. The pediatric oncologists worried that letting a medical coach attend the informed consent conversations would disturb the dynamic between them and families.

Involvement of an independent person

Several pediatric oncology centers employ a clinical research team, which is responsible for the research logistics. The treating oncologist usually introduces the research, followed by a research nurse who further explains study details. The pediatric oncologists and research coordinators said to appreciate the different roles being more clearly separated this way. One oncologist was cautious with regard to research nurses obtaining informed consent, since these can be as influential as physicians.

The REC members recognized inclusion for pediatric oncology studies by the own treating oncologist as potentially problematic, but they were not convinced of the advantages of delegating this task to someone else. They regarded it as unnatural to try and separate the two roles in such a relatively small medical practice like pediatric oncology, where all health care professionals know all children and their families. (Quote 8 in Table 5)

Parents indicated that usually it did not matter for them which 'white coat' would provide information and obtain informed consent. One mother expressed that she was approached by an independent researcher a couple of days in a row to take part in a study. This made her feel a bit pressured and the researcher came across as too pushy.

For the adolescents it would have made no difference if an independent person such as a research nurse had obtained the informed consent. Especially in the beginning everyone is new to them and could be one of the doctors. Later on, they felt confident that their treating oncologist would accept their decision to refuse. They realized they were free to make their own choices about research, regardless of the person who would ask them to participate.

Discussion

We explored the experiences of pediatric oncologists, research coordinators, Research Ethics Committee members, parents of a child with cancer, and adolescents with cancer with voluntary informed consent for medical research within a dependent relationship. Our main finding is that although dependency is experienced as an aspect of the treating relationship, its influence on voluntary informed consent for research in pediatric oncology is not necessarily negative. In general both the professionals and patients and parents themselves did not regard inclusion by the own treating physician as problematic for voluntary informed consent. Moreover, professionals, parents and adolescents considered involvement of the own physician in the informed consent process as valuable. This finding is in contrast with ethical guidelines for medical research and bioethical literature, which mainly focus on potentially adverse effects of the dependent relationship on voluntariness of consent for research.(2;3)

An explanation for this difference between the experiences of our respondents and what is generally assumed in bioethical thinking may be as follows. Children with cancer who participate in research and their parents perhaps feel less "vulnerable" than is often thought with respect to decision-making on study participation,(10;12-14;19) even though their own physician is involved in the informed consent process. Patients are considered vulnerable when they are relatively or absolutely incapable of protecting their interests,(2) when there is an identifiably increased likelihood of incurring additional or greater wrong,(20) or when they are especially prone to harm or exploitation.(21) In research ethics guidelines, vulnerability is generally a label that is applied to groups of research participants, such as pregnant women or children.(22) Recently, Luna has proposed to look more closely to the situational aspects of potential research participants to assess whether certain characteristics or "layers" render them vulnerable.(23) As Luna argues, layers can be multiple; some may be related to social circumstances, while other layers may be related to problems with voluntary informed consent.(22)

On the one hand, children with cancer and their parents are subject to several layers of vulnerability, most notably a severe, potentially fatal disease, and a strong dependence on their treating physician, who is often also involved in the informed consent process. Obviously, the layer of the disease cannot be removed. Previously, we have argued that also the layer of the dependent relationship is difficult to resolve.(4) In pediatric oncology this may even be more difficult, since most pediatric oncologists are both involved in the treatment of children with cancer and informed consent discussions.(1) As such, the layer of the dependent relationship may influence those patients or parents who are vulnerable to the influence of authoritative figures such as physicians.

However, other aspects of the situation of children with cancer and their parents might render families less vulnerable when providing informed consent for research, which could reduce the influence of the two layers of a severe disease and inclusion for research by the treating physician. In general, despite being faced with the potentially fatal disease of their child, parents felt that they were able to manage requests for study participation, protect their own and their child's interests and make decisions based on their own preferences. Furthermore, we noticed that the experiences of parents and adolescents with their disease and that of others strongly shaped the way they perceived research, which increased their willingness to participate in research. Having the ability to help other children through research participation helped them to give meaning to their own illness or that of their child, since it enabled them to create something positive out of a primarily negative situation. Hence, our respondents' decisions regarding research participation appeared deliberate and voluntary, and not overly and directly influenced by the ideas and opinions of the pediatric oncology professionals.

Even though children with cancer who participate in research and their parents may be less vulnerable than expected, it remains necessary to critically reflect on ways to safeguard voluntary consent within a dependent relationship, since this relationship may still constitute an undue influence to some families.(24) Emphasizing the voluntary nature of participating appeared a good strategy to make children with cancer and their parents aware that they need not consent and can always withdraw their permission once enrolled in a study. However, on its own it may be insufficient to ensure voluntary participation. The availability of an independent medical counselor could be valuable for patients and their parents, as long as this person is specifically concerned with protecting their interests and available to provide advice and guidance.(4;24) The regular Dutch research practice offers patients and parents the option to deliberate with an independent doctor, of whom name and telephone number are regularly provided in the patient information form.(25) This procedure could be improved by actively approaching parents to offer them a consultation. As such, this is a way of empowering families.

A strong feature of our study is that we invited different groups of respondents, to assemble a variety of perspectives. A second strength is the combination of two different qualitative methods: focus groups and individual interviews.

This enabled us to receive answers to our questions both in a setting in which respondents could discuss different topics and in a more personal setting, allowing each respondent to elaborate on their experiences.

However, some limitations to our study also apply. First, although the total number of respondents is not particularly low for a qualitative study, the sample size does not permit drawing definite conclusions.

Second, since we could only study situations as experienced by the different respondents, we cannot rule out that despite the absence of direct, experienced influence or pressure, more implicit influences (such as trust and confidence in the treating physician) may have played a role in the research related decisions of parents and adolescents without them being aware of this.

Third, there may be a risk of bias in the interviewed parents and adolescent patients, due to five aspects of our study and its design. 1. Only those patients and parents could be approached who were well enough to participate rather than those who had difficulty with coping with the disease. 2. Two of the parents were recruited through the Dutch Association for Parents, Children and Cancer. This may have affected their views on pediatric oncology studies, since parents of this association are usually more actively engaged with research. However, one of these two parents had the most reservations with respect to the conduct of research. 3. The parents' educational level was above average, and therefore they may have been relatively well articulate and informed. These three aspects together may have increased the ability of our interviewed parents and adolescents to make decisions without feeling pressure from health care professionals. 4. Leukemia was the most common diagnosis in children in our study. In general, cure rates for leukemia are higher than for other types of cancer.(26) This relatively optimistic prognosis may have decreased feelings of dependence. Subsequently, this could have positively influenced the way the interviewed parents and adolescents regarded the informed consent procedure and their decision-making process. However, leukemia is also the most common form of cancer in children younger than 15 years old,(26) so in that respect our study provides an accurate reflection of the practice of pediatric oncology. 5. Some children were still under treatment, whereas others had already finished their treatment. The former group of children and their parents may not have a complete perspective on their experiences with the informed consent process and voluntariness. Consequently, their perspectives could have been different from those who have finished their treatment.

A fourth and final limitation is that we only reflect from within the Dutch pediatric oncology context. Therefore, ethical issues and their implications could vary, due to differences between the pediatric oncology contexts in different countries. Still, we believe that our study findings provide a valuable direction for future research on dependent relationships and voluntary informed consent.

Conclusion

The dependent relationship between pediatric oncologists, patients and parents need not be problematic for voluntary informed consent, since parents and adolescents did not experience pressure to participate and felt able to make well-considered decisions. Furthermore, involvement of the physician may even have a positive impact on voluntary informed consent. Yet, we should remain cautious, since in some cases dependency on the pediatric oncologists may influence more vulnerable patients and parents. To prevent compromises to voluntariness, the strategy to increase availability of an independent counselor could be a valuable option.

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Table 1. Characteristics of professionals

Pediatric oncologists	Focus group and expert meeting (N=7)	Interviews (N=9)	Total (N=16)
Gender			
Male	5	3	8
Female	2	6	8
Experience (years)			
5-10	2	3	5
11-15	1	4	5
16-20	1	1	2
>20	3	1	4
Areas of interest: clinical oncology [a]			
No specific	0	2	2
Solid tumors	5	4	9
Lymphomas	2	2	4
Leukemia	3	5	8
Stem cell transplantation	3	1	4
Histiocytosis	0	2	2
Myelodysplastic syndrome	1	0	1
Areas of interest: research [b]			
Clinical drug trials	6	6	12
Laboratory research	1	5	6
Supportive care	2	4	6
Palliative care	2	1	3
Stem cell transplantation	2	2	4
Research coordinators		Interviews (N=3)	Total (N=3)
Gender			
Male		1	1
Female		2	2
Experience (years)			
0-5		2	2
5-10		1	1
Research Ethics Committee Members	Focus group (N=4)		Total (N=4)
Gender			
Male	1		1
Female	3		3
Experience in REC (years)			
5-10	1		1
10-15	3		3
Background			
Medical ethics	1		1
Oncology	1		1
Pediatric rheumatology	1		1
Clinical pharmacology	1		1

[a] Pediatric oncologists could have various areas of interest in clinical oncology. Therefore, these numbers do not add up to 16.

[b] Pediatric oncologists could have various areas of interest in research. Therefore, these numbers do not add up to 16.

Table 2. Characteristics of parents and their children

Parents	Focus group (N=9)	Interviews (N=8)	Total (N=17)
Gender			
Male	5	2	7
Female	4	6	10
Age (years)			
34-39	2	3	5
40-44	1	3	4
45-50	5	3	8
Education			
Primary, lower secondary general, or lower vocational	2	0	2
Higher secondary general or intermediate vocational	3	4	7
Higher vocational or university	4	4	8
Children of these parents	**Focus group (N=6) [a]**	**Interviews (N=8) [b]**	**Total (N=14)**
Gender			
Male	6	4	10
Female	0	4	4
Age (years)			
0-4	0	2	2
5-9	2	0	2
10-14	2	4	6
15-19	2	2	4
Diagnosis			
Acute lymphoblastic leukemia	2	2	4
Acute myeloid leukemia	0	1	1
Leukemia (undefined)	0	1	1
Chronic myeloid leukemia	2	0	2
Rhabdomyosarcoma	1	0	1
Burkitt lymphoma	1	0	1
Hepatoblastoma	0	1	1
Osteosarcoma	0	1	1
Ewing sarcoma	0	1	1
Brain tumor (high grade glioma)	0	1	1
Medical situation			
Finished standard treatment, under control of the hospital	3	4	7
Under treatment within study protocol	3	3	6
Palliative care; only pain medication	0	1	1

[a] The nine parents of the focus group together had six children, since there were three parent couples.

[b] The interviewed parents were different parents than those from the focus group. There were no couples among the eight parents we interviewed, so these parents represent eight children. Four of these children were not interviewed themselves, and four of them (adolescents) were. The characteristics of these eight children are presented here. The characteristics of the four adolescents who were interviewed themselves are also separately presented in Table 3.

Table 3. Characteristics of adolescents

Adolescents	Interviews (N=5)
Gender	
Male	3
Female	2
Age (years)	
13	2
14	1
15	2
Diagnosis	
Acute lymphoblastic leukemia	1
Acute myeloid leukemia	1
Undefined leukemia	1
Brain tumor (high grade glioma)	1
Hodgkin lymphoma	1
Medical situation	
Finished treatment, under control of the hospital	3
Under treatment within study protocol	2

Figure 1. Flow chart of respondents

Numbers in bold added up = the total number of respondents = 45

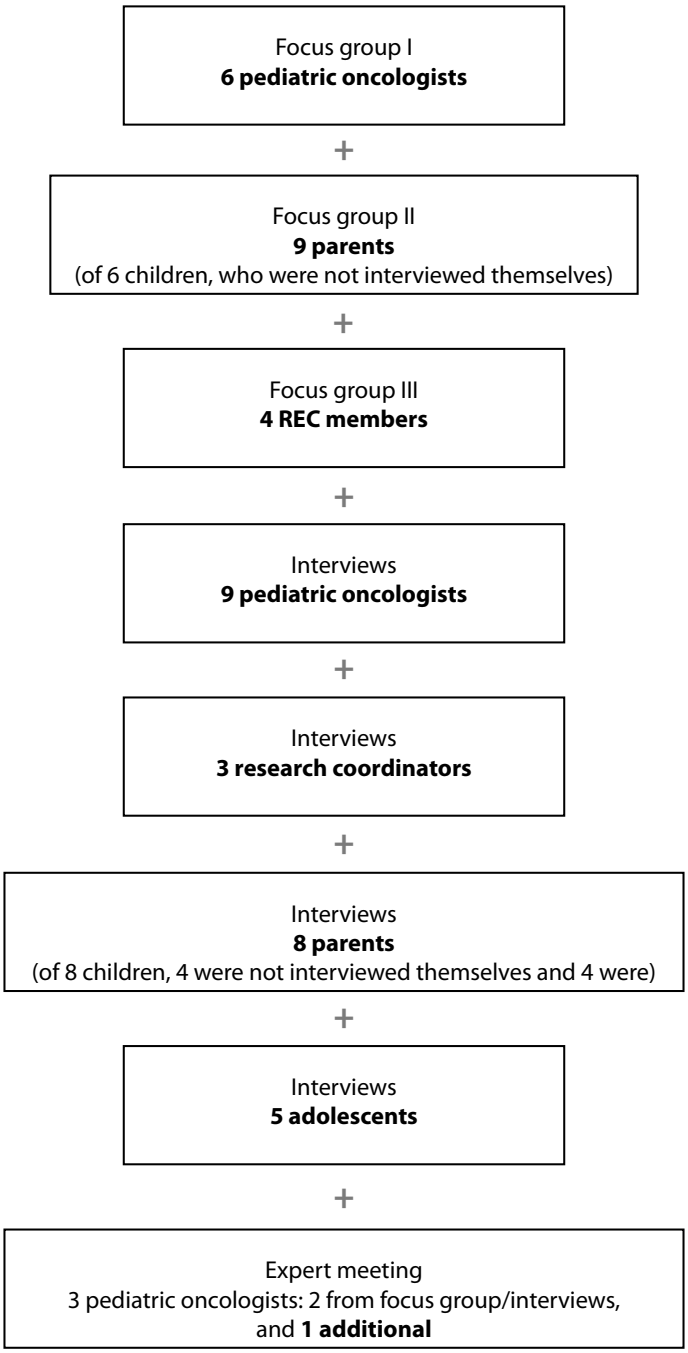

Table 4. Topic lists for the interviews and focus groups

Pediatric oncologists and research coordinators	Could you please introduce yourself and tell me something about your work as a pediatric oncologist/research coordinator?
	In what way are you involved with pediatric oncology research?
	Can you describe the informed consent process in your center? ◆ Who are involved? ◆ What is your own role?
	Which considerations do you think play a role for parents and children when deciding about research participation? ◆ Which influence do you think you have on decisions of parents and children to taken part in a study? ◆ To what extent do you consider your relationship with parents and children to be an influence on informed consent? ◆ In what way could voluntary informed consent be compromised? ◆ How do you react when parents refuse research participation for their child? ◆ Do parents 'buy' something when they consent to their child's research participation? And if yes, what do they 'buy'?
	Which differences do you see between safeguarding voluntary informed consent at the moment of inclusion and during the study? ◆ If parents decide to withdraw their child from a study, is there any ambition to persuade them not to?
	In what ways do you and your colleagues try to protect voluntary informed consent in your center? ◆ What do you think of having someone else, such as a research nurse, obtain informed consent? ◆ Which ways to protect voluntary informed consent in a dependent relationship have you encountered? ◆ Which other suggestions do you have for the protection of voluntary informed consent in a dependent relationship?
Research Ethics Committee members	Could you please introduce yourself and explain how you are or have been involved in reviewing pediatric oncology research protocols?
	Many children with cancer take part in pediatric oncology studies, either as part of or in addition to their treatment. ◆ Which considerations do you think are important for parents and patients to consent to research participation? ◆ Which considerations play a role for refusing research participation?
	Frequently, pediatric oncologists include their own patients in research ◆ What influence do you think pediatric oncologists have on decisions of parents or children? ◆ To what extent do you think that the dependent relationship between oncologists and families influences voluntary informed consent?
	What is the general policy of your REC when in a research protocol the treating oncologist is the same person as the investigator?

	What do you think of the solution to have someone else, such as a research nurse, obtain informed consent instead? Which ways to protect voluntary informed consent in a dependent relationship have you encountered? Which other suggestions do you have for the protection of voluntary informed consent in a dependent relationship?
Parents	Could you please introduce yourself and explain your child's diagnosis and treatment?
	Did your child take part in a pediatric oncology study that was part of his/her treatment? If so, how did you know about this? Did your child take part in any other a pediatric oncology studies?
	Can you describe the informed consent process for these studies? ◆ At which moment did you provide informed consent? ◆ What exactly did you provide consent for and to whom? ◆ Did you feel you have sufficient information at that moment? Why or why not?
	Which considerations were important for you to make the decision about your child's research participation? ◆ Which considerations did you have to consent? And which to refuse? ◆ Did you feel free to make your own decision? Did you feel any pressure to take part due to the dependence on the pediatric oncologist? Why (not)? ◆ Which reason was decisive for you?
	Which role did the treating oncologist play in your decision making process? ◆ To what extent was he or she involved with the decision? ◆ What was the attitude of the treating oncologists, did he/she express preference for a certain choice? ◆ What was the influence of the treating oncologist on your decision? ◆ To what extent did the dependent relationship between you, your child and the treating oncologist play a role in your decision making process? ◆ Did you have a discussion with the oncologist regarding the decision made?
	Were you asked during the study whether you still wanted to continue with your child's participation? If yes, who did this and how?
	Would it have made a difference for you if not the treating oncologist but someone else had performed the informed consent procedure? OR: Would it have made a difference for you if instead of the research nurse the treating oncologist had performed the informed consent procedure? What are your suggestions for safeguarding voluntary informed consent of parents and older patients in pediatric oncology?

Adolescents	When did you hear that you were ill and what happened next? What kind of treatment did you receive?
	Did you take part in research that was connected to your treatment? Did you take part in other types of research? What did this research involve for you?
	Can you describe the informed consent process? ◆ Who gave you the information about the research? ◆ At what moment did someone ask you whether you wanted to take part in research? ◆ Who asked you about this? ◆ At what moment? ◆ Did you feel you had enough information to make that decision? ◆ To what extent were you involved, by your parents and by the physicians?

Table 5 . Quotes from focus groups and interviews

Theme	Quote	Respondent
Potentially problematic influence	1	Pediatric oncologist: 'These people have a general interest in you as their physician; you have to make sure that their child survives. In oncology this is of course even stronger, since it is about life and death. So they have a certain interest in staying friends with the physician. Not everyone understands that, but most do. So there arises some sort of problem that people might think they have to say yes.'
	2	Research coordinator: 'One girl said that she did not want to take part because she did not want to come [to the hospital] an extra time. And then the mother said: "Sorry Jane, we really tried to talk her into it, but it didn't work out". And then I noticed that something went wrong, because they apologized to me, while I am supposed to be independent.'
	3	Parent: 'When you get a request in the first six weeks after diagnosis, you think like: "what if I say no now, will that have an influence on the chance that my child will get better?" In whatever way possible. Because then I would oppose the oncologist, while he wants to do a certain study and then he will regard you differently and will have less attention for you, because you do not take part in the study.'
Minimal or no influence	4	Parent: 'Your question seems to imply that as a parent you have more confidence in your treating oncologist than in another doctor or a research nurse. And that you feel some sort of social pressure to take part in the research. No ... you just consider what kind of research it is. What will it do to my child? Does the moment suit me etc.? You act very rationally, at least I do. Just considering whether the study is in line with what your child can handle. And not really with the person who introduces it.'
	5	Parent: 'For Jesse it had a large impact that a boy he became friends with passed away, which really depressed him and us of course. And then we thought, there is nothing we can do for this boy, he's not here anymore. So we said we will participate in all studies they ask us for, and he also wanted to take part in everything, just to be able to do something back.'
Positive influence	6	Parent: 'If it becomes life threatening, you just completely rely on your treating physician, your treating oncologist, because he shares your experiences from the beginning. And if some external person comes in who is also wearing a white coat, who might know even more, but I do not know this person, then I check the eyes of my treating oncologist, what they look like.'
Empowering families	7	REC member: 'It is also about the terminology you use. If you just say to parents that they are the ones who decide what happens to their child, not me. If you start with giving them the responsibility. They have to make the decisions.'
Involvement of an independent person	8	REC member: 'One of the really difficult aspects is that it is such a severe disease and that people are already extremely dependent upon the treating physician. And if you say: well then just say no to someone else, because that is what it comes down to, since the physician himself is often still the one to ask ... That you do not have the feeling that their situation is improved or that the child or the parents are better protected if you try to resolve it like that.'

References

1. de Vries MC, Houtlosser M, Wit JM, Engberts DP, Bresters D, Kaspers GJ, et al. Ethical issues at the interface of clinical care and research practice in pediatric oncology: a narrative review of parents' and physicians' experiences. BMC Med Ethics 2011;12:18.
2. Council for International Organizations of Medical Sciences (CIOMS). International Ethical Guidelines for Biomedical Research involving Human Subjects. 2002.
3. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013 Nov 27;310(20):2191-4.
4. Dekking SA, van der Graaf R, van Delden JJ. Strengths and weaknesses of guideline approaches to safeguard voluntary informed consent of patients within a dependent relationship. BMC Med 2014;12:52.
5. Hewlett S. Consent to clinical research--adequately voluntary or substantially influenced? J Med Ethics 1996 Aug;22(4):232-7.
6. van Thiel GJMW, Van Delden JJM. Reflective Equilibrium as a Normative Empirical Model. Ethical Perspectives 2010;17(2):183-202.
7. Chappuy H, Doz F, Blanche S, Gentet JC, Pons G, Treluyer JM. Parental consent in paediatric clinical research. Arch Dis Child 2006 Feb;91(2):112-6.
8. Chappuy H, Bouazza N, Minard-Colin V, Patte C, Brugieres L, Landman-Parker J, 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).
9. Eiser C, Davies H, Jenney M, Glaser A. Mothers' attitudes to the randomized controlled trial (RCT): the case of acute lymphoblastic leukaemia (ALL) in children. Child Care Health Dev 2005 Sep;31(5):517-23.
10. Kupst MJ, Patenaude AF, Walco GA, Sterling C. Clinical trials in pediatric cancer: parental perspectives on informed consent. J Pediatr Hematol Oncol 2003 Oct;25(10):787-90.
11. Miller VA, Nelson RM. Factors related to voluntary parental decision-making in pediatric oncology. Pediatrics 2012 May;129(5):903-9.
12. Stevens PE, Pletsch PK. Ethical issues of informed consent: mothers' experiences enrolling their children in bone marrow transplantation research. Cancer Nurs 2002 Apr;25(2):81-7.
13. Levi RB, Marsick R, Drotar D, Kodish ED. Diagnosis, disclosure, and informed consent: learning from parents of children with cancer. J Pediatr Hematol Oncol 2000 Jan;22(1):3-12.
14. Simon C, Eder M, Raiz P, Zyzanski S, Pentz R, Kodish ED. Informed consent for pediatric leukemia research: clinician perspectives. Cancer 2001 Aug 1;92(3):691-700.
15. Woodgate RL, Yanofsky RA. Parents' experiences in decision making with childhood cancer clinical trials. Cancer Nurs 2010 Jan;33(1):11-8.
16. Eder ML, Yamokoski AD, Wittmann PW, Kodish ED. Improving informed consent: suggestions from parents of children with leukemia. Pediatrics 2007 Apr;119(4):e849-e859.
17. Baker JN, Leek AC, Salas HS, Drotar D, Noll R, Rheingold SR, et al. Suggestions from adolescents, young adults, and parents for improving informed consent in phase 1 pediatric oncology trials. Cancer 2013 Dec 1;119(23):4154-61.
18. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology 2006;(3):77-101.
19. Berg SL. Ethical challenges in cancer research in children. Oncologist 2007 Nov;12(11):1336-43.
20. Hurst SA. Vulnerability in research and health care; describing the elephant in the room? Bioethics 2008 May;22(4):191-202.
21. Lange MM, Rogers W, Dodds S. Vulnerability in research ethics: a way forward. Bioethics 2013 Jul;27(6):333-40.
22. Luna F, Vanderpoel S. Not the usual suspects: addressing layers of vulnerability. Bioethics 2013 Jul;27(6):325-32.

23. Luna F. Elucidating the Concept of Vulnerability. Layers not Labels. Int J Fem Approaches Bioethics 2009;1:120-38.
24. Pinxten W, Nys H, Dierickx K. Regulating trust in pediatric clinical trials. Med Health Care Philos 2008 Dec;11(4):439-44.
25. Dutch Medical Research involving Human Beings Act, 2006.
26. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015 Jan;65(1):5-29.

4

Voluntary informed consent in pediatric oncology research

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Abstract

In pediatric oncology, research and treatments are often closely combined, which may compromise voluntary informed consent of parents. We identified two key scenarios in which voluntary informed consent for pediatric oncology studies is potentially compromised due to the intertwinement of research and care. The first scenario is inclusion by the treating pediatric oncologist, the second scenario concerns treatments confined to the research context. In this chapter we examine whether voluntary informed consent of parents for research is compromised in these two scenarios, and if so whether this is also morally problematic. For this, we employ the account of voluntary consent from Nelson and colleagues, who assert that voluntary consent requires substantial freedom from controlling influences. We argue that, in the absence of persuasion or manipulation, inclusion by the treating physician does not compromise voluntariness. However, it may function as a risk factor for controlling influence as it narrows the scope within which parents make decisions. Furthermore, physician appeal to reciprocity is not controlling as it constitutes persuasion. In addition, framing information is a form of informational manipulation and constitutes a controlling influence. In the second scenario, treatments confined to the research context qualify as controlling if the available options are restricted through manipulation of options. Although none of the influences is morally problematic in itself, a combination of influences may create morally problematic instances of involuntary informed consent. Therefore, safeguards should be implemented to establish an optimal environment for parents to provide voluntary informed consent in an integrated research-care context.

Introduction

Whereas in ethical guidelines and in research ethics literature, care and research are separated based on their different objectives, pediatric oncology is a classic example of a field in which research and care are closely intertwined.(1;2) As has frequently been emphasized, the high participation of children with cancer in pediatric oncology studies has been a significant factor in the improvement of survival rates for children with cancer.(3-5) However, the intertwinement of research and care also raises normative issues, such as the moral obligations of pediatric oncologists as physician-investigators, appropriate ethical oversight of pediatric oncology treatment protocols, and protection of the interests of patients and their parents.(1;2;6) In addition, it creates challenges specifically related to the voluntariness condition of informed consent of parents for their child's research participation. Due to both contextual influences and influences during the informed consent process, their freedom to choose may be restricted.(2;7) Insight into these potential compromises is essential in order for various stakeholders, such as pediatric oncologists and Research Ethics Committees, to be able to assess whether voluntariness is compromised, which safeguards are warranted and how to implement these.

In this chapter we aim to answer the following research questions: does the intertwinement of research and care in pediatric oncology, where physicians include their own patients and where treatments are sometimes exclusively provided through research, compromise voluntary informed consent for research? And if so, are these compromises to voluntary informed consent morally problematic? Although general barriers to valid informed consent in pediatric oncology have been extensively documented,(8-15) currently no systematic conceptual evaluation of voluntary informed consent for pediatric oncology studies has been provided in the context of the intertwinement of research and treatment.

We focus on consent of parents for their child's research participation, rather than the consent or assent of children and adolescents themselves. This is because in general parents are the main decision makers concerning their child's participation in cancer research, both legally, and in practice. Indeed, most children diagnosed with cancer are relatively young, with a median age below 6 years, and their capacity for decision-making has thus not yet sufficiently developed to make fully voluntary, competent and autonomous choices.(2;16) This is reflected in the law: minors, including adolescents, are generally not allowed to consent to research for themselves.(17)

We will first define voluntary informed consent in order to critically analyze potential threats to voluntariness of consent in pediatric oncology. Next, we will provide a description of two key scenarios in which voluntary informed consent of parents for pediatric oncology trials is potentially compromised, due to the intertwinement of research and care. These two scenarios are, to our knowledge, characteristic for pediatric oncology. Last, we will evaluate to what extent these two scenarios of potential threats compromise voluntary informed consent of parents, by both a

conceptual analysis and incorporation of empirical studies that address the informed consent process as experienced by a variety of pediatric oncology stakeholders.

Defining voluntary informed consent

Several disciplines such as theology, philosophy and most recently, neurology, have questioned the existence of a free will and subsequently the possibility for voluntary decision-making.(18) Neurologic experiments seem to suggest that our actions are not really under our control and that we do not consciously make decisions.(19) In addition, all kinds of situational clues can influence our choices, such as previous experiences, smells, words, and a variety of associations that are unconsciously constructed.(20) More overt influences, such as beliefs or pressures from loved ones, may also heavily affect our choices and decisions. Yet, in this chapter, we shall assume that our decisions are voluntary, since we are able to control our behavior and make choices within existing circumstances.(21) Beginning with this assumption, we now need a way to decide which influences compromise voluntariness and which ones do not. More specifically, we need a way to determine to what extent consent of parents for their child's enrolment in medical research should be considered voluntary, when it is obtained in an integrated care-research environment.

Different accounts of voluntariness from the bioethical literature and guidelines provide different suggestions, but they all conclude that a certain type or level of influence renders consent involuntary.(22-24) For the purpose of this chapter we will employ the interpretation of the concept of voluntary consent of Nelson and colleagues, because they clearly separate questions about voluntariness from questions about moral acceptability. Although their account is primarily meant to study voluntariness in general, they also present it as useful for the conceptual analysis of voluntary informed consent in biomedical research.(24) Importantly, they make a distinction between objective voluntariness ('that which is voluntary *in fact*') and subjective voluntariness ('that which is *perceived* as voluntary by the person who decides or acts') (italics in original).(24) Objective voluntariness focuses on actual influences and how these affect voluntary informed consent. In contrast, subjective voluntariness measures the way patients or other participants perceive the consent process and whether they experience controlling influences. The difference is made because sometimes actual influences are not experienced by the patient as such (for example in the case of deception), while in other instances influences are perceived as controlling whereas no actual influence was exerted.(24) Arguably, for a complete assessment of voluntary informed consent for research the subjective component of voluntariness is also of relevance. Consequently, we need empirical data reflecting experiences of participants to evaluate potential threats to voluntariness, besides a conceptual analysis.(25-27)

According to Nelson et al., voluntariness requires the two necessary and jointly sufficient conditions of intentionality and substantial freedom from controlling influences ('non-control').(24) The first condition, that of intentionality, means that the person consciously willed the action, as opposed to accidentally performing it,

such as dropping a pen.(24) Conceptually, 'intentional action' is closely associated with 'intentions' and 'intending to do something', which both raise questions around desires, passions, and motivations.(28;29) However, in its most basic form, which we will employ here, doing something intentionally requires that an agent has chosen to do it.(24) Thus, a decision need not be deliberate, considered, thoughtful or well-balanced to be intentional. In the case of informed consent for research, the condition of intentionality can be interpreted to minimally require that participants are aware that they make a decision regarding research participation.(27)

In pediatric oncology, informed consent for research is often required shortly after families have received the child's cancer diagnosis, while they are still in shock and disbelief and time to make a decision is limited.(2;10;14;15;30) Consequently, in these situations, parent's decisions to enroll their child in research may not always be intentional, if they are not aware that they consent to research but believe their decision applies to care as usual. In that case, their consent is automatically non-voluntary, because one of the necessary conditions of voluntariness, that of intentionality, is not fulfilled. At the same time, solutions have been offered to increase parental understanding of the distinction between participation in an RCT and off-study treatment, such as a staged informed consent process.(31) These solutions potentially increase intentionality of parents' decisions for research and thereby promote voluntary informed consent.

Moreover, the difficult choice environment of pediatric oncology will not inevitably have an impact on parental capacity to make intentional decisions. Although parents may not always be able to make deliberate decisions based on a careful weighing of all the risks and benefits, they will in general be aware that they make a decision for their child and that this decision concerns research. Several studies into parental comprehension of pediatric oncology research and informed consent show that 80-85% of parents realized they had consented to research and not to care as usual,(32-34) which seems to suggest that their consent for research was intentionally provided. More data regarding the intentionality condition in pediatric oncology would be valuable. For now, in what follows, we will assume that the majority of parents of a child with cancer are able to provide their consent to research intentionally.

The second condition of voluntariness, that of non-control, requires that a person's decisions or actions should be substantially free from controlling influences.(24) As such, there exists a continuum of influences, ranging from influences that are completely in line with voluntariness from those that completely negate voluntariness. Nelson and colleagues describe three categories of influences on this continuum and the extent to which these influences exert control over the autonomous person. These three categories are persuasion, manipulation, and coercion, with persuasion being a completely non-controlling influence and coercion being completely controlling (and therefore not compatible with voluntariness). Persuasion involves a rational way of exerting influence over an agent's decisions, by reason and arguments. Coercion occurs when a person's choices are unfavorably narrowed through a credible threat

of harm expressed by another person. Manipulation occupies the middle position on the continuum. It involves an agent who aims to change the way another person perceives a situation to motivate him or her to follow a certain course of action. Two broad categories of manipulation can be identified: manipulation of information and manipulation of options. Manipulation of information involves a large variety of communicational actions, such as withholding critical information, lying, deceiving, and the way risks and benefits are disclosed. Manipulation of options includes financial incentives or controlling access to treatments.(24;35-38) Although Nelson et al. acknowledge that it is 'notoriously difficult' to determine and evaluate the level of influence that is exerted in specific circumstances, they suggest that the majority of forms of manipulation are controlling and therefore incompatible with voluntary decision-making.(24)

Since most influences on our decisions will be somewhere in the middle of the continuum, a large grey area of influences exists for which it is not immediately clear whether they constitute a substantially controlling influence on voluntary decision-making. In the next section, we describe two scenarios from pediatric oncology practice, and we will determine where the influences in these scenarios should best be placed on the continuum of voluntariness. Assuming that the occurrence of coercion will be very exceptional in pediatric oncology, we examine whether any of the two scenarios should be categorized as a form of persuasion or manipulation. If a scenario qualifies as a form of manipulation, we will evaluate whether it also constitutes a substantially controlling influence.

Scenario 1. Inclusion by the treating pediatric oncologist

Description of scenario 1

Inclusion for research by the treating physician may pose a threat to voluntary informed consent of parents in three different ways, which we describe, and analyze subsequently.

1a. The dependent relationship

First, since the majority of pediatric oncologists have a dual role, as a clinician and as a researcher, they frequently invite their own patients in research.(2) Ethical guidelines for medical research with human beings suggest that physicians should not enroll their patients in research, because of the dependent relationship between them.(39;40) Inclusion for research within the dependent relationship between patients and physicians is considered as a potential undue influence or undue pressure on voluntary informed consent.(41) Due to their dependence on the pediatric oncologist, parents may be reluctant to decline an invitation to enroll their child in clinical research, since they may be concerned whether this will negatively affect their child's treatment or the relationship with the physician.(2;42)

1b. Physician appeal to reciprocity

Second, pediatric oncologists may sometimes encourage patients and their parents to enroll in medical research, by emphasizing to parents that their child reaps the benefits from previous research and the children who took part in this research.(6;43;44) For example, in a study into parental experiences in decision-making for childhood cancer clinical trials, parents noted that they 'were made well aware that the success of the treatment of childhood cancer to date was the direct result of past clinical trials'.(44) As such, pediatric oncologists refer to 'an ethic of reciprocity',(43) implying that parents should consider to do something back for what families before them have contributed to the success of current treatments.

1c. Framing of information

Third, the behavior and attitudes of pediatric oncologists could play a large role in the way parents perceive their decisions and freedom of choice.(45;46) Specifically, the way pediatric oncologists present, or frame, study-related information can have considerable impact on the choices parents make.(34;47;48) Framing of information can be defined as 'the key considerations [that are] emphasized in a speech act'.(49) On the one hand, framing is ultimately unavoidable and an inherent part of human communication.(50;51) On the other hand, framing has been depicted as a distinct form of conveying information, in which the speaker puts emphasis on specific aspects of the content, usually in order to influence the listener to do or believe something.(52) This normative interpretation incorporates the idea that even if framing is unavoidable, we can still choose which frame to use.

Moreover, the frame we choose depends on our background situation and education. For physicians, the 'prevailing medical culture' in which they are trained has an impact on their ideas and opinions.(50) Notably, from its outset, pediatric oncology has had an environment favoring research.(53) Consequently, the majority of pediatric oncologists has a positive outlook on research, something they convey during informed consent sessions.(6;54) Thus, due to their background and training, pediatric oncologists may tend to provide an overly optimistic presentation of the risks and benefits of research participation for the individual child.(46)

Analysis of scenario 1

1a. The dependent relationship

If treating physicians would put pressure on the decision making process this may aggravate feelings of dependence. There is no evidence that pediatric oncologists pressure parents to consent to research participation and therefore the dependent relationship does not qualify as either persuasion or manipulation. However, interestingly, parents may experience a compromise to voluntary informed consent even without actual influence of the physician. Some studies from pediatric oncology show that consent sometimes is provided in order to maintain a positive relationship with the physician or to secure optimal treatment for the child.(2;14;27) In addition, in one study a substantial part of parents felt pressure from the physician to enter their

child in medical research.(55) In contrast, other parents do not experience pressure when the treating oncologist of their child obtains their consent for research and they even regard the involvement of their own physician as valuable.(56) Most likely, it will vary considerably between families to what extent they feel free to refuse or consent to medical research to their child's pediatric treating oncologist.

In short, although the dependent relationship does not constitute a controlling influence on voluntary informed consent of parents, it narrows the scope within which parents can make their decisions. As such, it may function as a risk factor for controlling influence.

1b. Physician appeal to reciprocity

Referring to prior research contributions of other families may make it harder for parents to refuse enrolling their child; it may make them feel as though they too need to fulfil their duty. It has even been argued that appealing to reciprocity in pediatric oncology constitutes a form of 'moral coercion', since 'participation is presented as in some sense owed or obligatory'.(57) Pediatric oncologists are aware that an emphasis on ways in which research has improved treatments might make parents feel obliged to consent to research participation for their child.(6) As explained before, and following from the definition of coercion, using the notion of coercion here is not appropriate, as no threat of harm is involved and parents' choices are not narrowed by the pediatric oncologists. Instead, since they offer parents rational motivations to enroll their child, appealing to reciprocity should be considered a form of persuasion.(58) Persuasion is an influence that is in line with voluntary decision-making, since no form of pressure is involved. Instead, influence is exerted through reason and argument.

However, even though objective voluntariness is not compromised as a result of persuasion, subjective voluntariness may be compromised for those parents who experience the emphasis on reciprocity and mutual benefit as a controlling influence. Parents have reported to feel an obligation to consent, or even guilt when declining to enroll their child in a clinical study, while they realized their child benefited from previous research.(14;44) Yet, other parents present the desire to reciprocate as something positive.(6;59)

1c. Framing of information

The influence of framing information on decision-making is seen as a form of persuasion, since it may be employed to encourage parents to enroll their child.(46) However, persuasion demands influencing by rational arguments. Since framing involves the presentation of information, for example the way the aims, risks and benefits of clinical trials are presented, we do not consider framing a form of persuasion.(35)

We believe that framing of information more closely resembles manipulation.(60;61) More specifically, although the framing of information in pediatric oncology is considerably subtler than provision of lies or withholding information, it can still

qualify as informational manipulation, since it 'involves the use of non-persuasive means to alter a person's understanding of a situation';(24) indeed, pediatric oncologists influence parents' perception of the content and importance of a study. As mentioned before, manipulation is a broad category that occupies a middle position on the continuum of controlling influences. Furthermore, although most instances of manipulation are controlling, this is not necessarily the case. Since the account of Nelson and colleagues does not provide further conceptual tools to assess when manipulation is controlling, we need a subtler taxonomy to distinguish, and analyze different forms of manipulation.

One such taxonomy is provided by Blumenthal-Barby who suggests two adaptations to the general category of manipulation. First, the notion of manipulation is replaced by the more neutral term Non-argumentative Influence. Second, to provide more refinement in the analysis of the middle part of the voluntariness continuum, Non-argumentative Influence can be divided in the Reason-Bypassing Type and the Reason-Countering Type.(35) According to Blumenthal-Barby, framing falls in the category of Reason-Bypassing influences, since it circumvents a person's reasoning capacities, often without that person's awareness. As such, exactly because framing happens without their awareness, it diminishes the extent to which parents have control over their decisions.(62) Therefore, it seems to qualify as a controlling influence on voluntary informed consent,(35;63) especially for those parents who have little knowledge on cancer or medical research, as they have not yet developed a robust frame of their own.(64)

However, physician influence on the decision-making process of parents is difficult to avoid, since whatever 'frame' they use, this will always affect parents' choices to some extent.(51) Therefore, a distinction should be made between choices that are intentionally shaped and those that are not. For example, research examining pediatric oncologists' perspectives on consent for phase I trials, demonstrate that they are reluctant to influence patients' and parents' decisions.(65) Consequently, only if pediatric oncologists deliberately frame information in an effort to have parents enroll their child, this constitutes a controlling influence.(63;66) However, even if the physician has not deliberately chosen a frame, parents may still experience certain ways of explaining and informing as controlling. In that case, their subjective voluntariness is compromised, even though their objective voluntariness is not.

Scenario 2. Treatment contingent on research participation

Description of scenario 2

In pediatric oncology, cancer treatment is sometimes made contingent on research participation. We describe two different examples of this scenario.

2a. New treatments as part of an RCT

Menikoff reports that the pediatric oncology community has collectively decided that sometimes new treatments are not made available outside the research context.(7) These new treatments frequently involve modifications of treatment regimens already used to treat children or adults with cancer rather than a completely new drug that has not yet received market authorization. Thus, the pediatric oncologists would be legally allowed to prescribe the modified treatment regimen to children outside the research context, for example based on an individual assessment of what is in the child's medical interest or on request of the parents. Since it is likely that a substantial part of the parents would prefer the new treatment over the standard one,(7) this may be the reason for parents to enroll their child in the randomized controlled trial, whereas they would prefer to receive the new intervention outside the research context.

2b. Treatment protocols with an inherent research component

A second example concerns treatment protocols with an inherent research component, following from modifications compared to the previous protocol. These modifications result in a considerable level of uncertainty regarding the risks and benefits of a new protocol. However, based on a variety of scientific evidence and expert opinion, a new protocol is considered as the best available treatment for children with cancer.(6) As such, these "treatment optimisation studies"(67) are thought to provide current best treatment to individual patients, while they are simultaneously designed to answer study questions by collecting and evaluating treatment results.(68) Examples are protocols for the treatment of Acute Lymphoblastic Leukemia in the Netherlands, such as the DCOG ALL-10 protocol.(68)

Importantly, the previously used treatment protocol is considered outdated and no longer offered as a treatment option. For parents, it is not possible to consent to the treatment without also consenting to the research component of the protocol, as these two are completely interwoven. Even though any additional research procedures (such as data collection, blood draws or keeping a diary) will only be performed if parents explicitly provide their consent, the inherent research component of the protocol cannot be refused.

Analysis of scenario 2

In order to determine whether treatment confined to the research context poses an actual threat to voluntary informed consent, we have to consider the type of influence. First, it is an external influence rather than an internal one, since it originates from outside the person and not from internal processes, such as addiction or mental illness. Second, external influences can be divided in those resulting from the influence of other persons and influences due to the situation or circumstances (such as poverty or limited access to health care).(23;24) The potential threat of treatment that is only available in the research context should be considered a situational influence.

Debate exists whether situational influences compromise voluntariness, or that they are morally problematic in other ways.(23;24;69) Nelson and colleagues distinguish situations that have come about unintentionally, from those that have been deliberately created by other persons. Only situations that are the result of the intentional actions of other persons potentially constitute a controlling influence on voluntariness of informed consent. In our case, in both examples, pediatric oncologists have created the choice situation. As such, treatment that is made dependent on research participation can be considered a form of manipulation of options, because the pediatric oncologists have deliberately altered the choices available to parents.(24;35)

Classifying treatment that is only available in the research context as manipulation of options does not in itself determine whether it is controlling, since manipulation does not necessarily compromise voluntariness. A further issue to explore is that for consent to be voluntary 'the refusal to participate will involve no ... loss of benefits to which the subject is otherwise entitled'.(70) The benefits that patients are entitled to constitute that what we believe they should receive no matter what.(71) If we consider these benefits as the normative baseline situation of patients, then we can determine whether actions of others make patients better or worse off compared to this baseline. If the choice options of parents and children have been broadened due to the decisions of the pediatric oncology community they can be said to be made better off, whereas a restriction of options makes them worse off.(38;62) As such, a situation in which patients are made worse off compared to their normative baseline concerns a controlling influence on their decisions. In contrast, making patients better off by broadening their options is not substantially controlling.

To determine whether children are entitled to the research-dependent treatment, we need to question what the normative baseline for these children with cancer is. We may assume that they are entitled to receive approved treatments for their condition, even though patients do not have a legally enforceable right to demand any treatment. Thus, their normative baseline situation should be one in which they receive treatment for their disease that is primarily aimed at promoting their welfare and interests.

2a. New treatments as part of an RCT

With that baseline, the first example -when a new and promising intervention is only available within a randomized study- does not make children with cancer, or their parents, worse off. Indeed, they are not limited by the number of options to choose from, as they were never 'entitled' to the new intervention in the first place; moreover, the new intervention broadens the options available to them, compared to the baseline of only the standard treatment. Although parents may prefer their children to receive the intervention outside the research context, the absence of this possibility does not make them, or their children, worse off. Thus, this first example of making treatment contingent on research participation is not a controlling influence, as long as a treatment is made available which is 'compatible with optimal medical care'.(72)

2b. Treatment protocols with an inherent research component

When a treatment is only available in the research context, because the merits of new elements of a treatment protocol are uncertain, parents and their children are undeniably made worse off compared to the baseline situation; for the baseline situation is having a treatment for the child's disease without necessarily also having to participate in research. The decision to no longer offer the previous treatment protocol is understandable, as the pediatric oncologists regard this old protocol as inferior to the new one,(68) which is generally based on a robust evidence base. However, as long as the new treatment regimen has not proven to be superior, it appears too early to consider it 'the standard of care'. Therefore, in theory it would be sensible to provide parents with the opportunity to choose the older, more established protocol, with which the pediatric oncologists have more experience. Yet, since the previous treatment protocol is no longer offered to children and their parents, only the treatment protocol with a research component remains as an option. Thus, in this case, manipulating the options decreases the available options and therefore qualifies as a substantially controlling influence on voluntary consent of parents.

Summarizing, if new treatments are only made available in randomized studies, this does not qualify as a controlling influence because it does not restrict, but rather broadens the options available to patients and their parents. Therefore, patients are not made worse off. Treatment protocols with an inherent research component can be considered as a controlling influence, since they limit the options available to patients and their parents, and make them worse off compared to the normative baseline situation.

Discussion

We examined whether two scenarios that pose a potential threat to voluntariness of parental consent for pediatric oncology studies constitute a controlling influence on their decisions. The first scenario, inclusion within the treating relationship, consists of three different ways in which voluntariness may be compromised.

First, although the dependent relationship in itself does not constitute a controlling influence on voluntary informed consent, it does qualify as a risk factor for controlling influence as it defines the conditions within which decisions have to be made. Second, appeal to reciprocity is a form of persuasion and hence not controlling. Third, intentional framing of information is a form of informational manipulation, and therefore constitutes a controlling influence. Of the second scenario, only the example of treatment protocols with an inherent research component qualifies as controlling, since the options available to patients and their parents are restricted through manipulation of options.

Here it is important to also address the distinction between subjective and objective voluntariness. On the one hand, even though some scenarios do not constitute objective controlling influences on voluntary consent of parents, these may qualify as subjective controlling influences, based on parents' experiences. That is, if some parents experience an influence as controlling, their subjective voluntariness is undermined. We have suggested that this may be the case with the dependent relationship, appeal to reciprocity, and unintentional framing of information. On the other hand, if an influence is objectively controlling, but not experienced as such by parents, voluntariness of their consent it still compromised. This happens for example when pediatric oncologists deliberately frame information in an overly optimistic way, while parents do not realize the information is framed. Empirical studies into parental experiences with voluntary informed consent are essential to shed further light on subjective voluntariness with these and other influences.

So far, we have separated the assessment of voluntariness from the assessment of the moral acceptability of the different scenarios. That is, although our conceptual analysis in the previous section provides some hints about moral permissibility of the different potential threats to voluntary informed consent, it does not in itself determine the acceptability of consent.(24;35) Only two situations were analyzed as objective controlling forms of manipulation. To assess their moral acceptability we will weigh the infringement upon parental voluntariness of informed consent with the child's interests (risk versus benefit) and scientific progress (see Table 1 for the outcome of this evaluation).(66)

The first situation with a controlling influence, that is framing of study-related information by pediatric oncologists during informed consent meetings, should not be considered morally problematic. The language that is used reflects the norms and values of a practice, and research has a prominent place in pediatric oncology. As has been described in a variety of studies, off-label use is common both in pediatrics in general(73;74) and in pediatric oncology in particular,(75;76) and evidence for use of treatments in children is badly needed. Accordingly, the important goal of developing new safe and effective treatments for children with cancer seems to override the compromise to parental voluntariness.(77)

The second controlling situation involves treatment protocols with an inherent research component. For its moral evaluation, we should critically scrutinize the

conditions under which it is permissible for physicians to make treatment conditional upon participation in research.(69) This is a substantially complex issue, but several conditions have been identified, such as whether the research concerns a fair transaction, the risks to the welfare of patients, and the importance of the research to advance medicine.(69;78) It can be argued that whether treatment protocols with an inherent research component involve a fair transaction depends on whether the available option (that is, the treatment as laid down in the protocol), has a favorable risk-benefit ratio for the children involved.(66) Therefore, the risks and burdens should be scrutinized, and weighed against the benefits, to establish whether making treatment depend upon the child's research participation is morally problematic.

Importantly, any extra research procedures such as blood draws are optional. Therefore, the risks and burdens of these procedures do not have to be taken into account to assess the moral acceptability of the controlling influence of these kinds of protocols. The additional research-related risks and burdens associated with the introduction of new elements of a treatment protocol are difficult to establish, as the risks and burdens of childhood cancer treatments are considerably high in itself. In general, as robust data are used to establish the new treatment regimen, and pediatric oncologists have strong confidence in its value for the treatment of patients, risks due to the modified treatment regimen may be justified by the prospect of direct benefit to the child. Another important consideration concerns that fact that best available treatment protocols not only aim to provide benefit to the children involved, but also for the group of children. That is, pediatric oncologists have additional reasons to pursue these studies, such as increasing knowledge on childhood cancer and improving treatments for future children with cancer. Therefore, it seems that, all things considered, for these types of protocols making treatment dependent on research participation is morally acceptable.

However, this does not mean that morally problematic situations are foreign to pediatric oncology informed consent discussions. Rather, we suggest that the combination of different factors could create morally problematic situations in which parental informed consent is no longer sufficiently voluntary. That is, if the child's treating physician performs the informed consent procedure for research that is connected to treatment, emphasizes the reciprocal nature of research, and frames study-related information in an overly positive manner, the cumulative influence on parents may become fully controlling and tip the scale towards morally impermissible consent. Here again, the experiences of parents can be of additional value. That is, if some influences or combination of influences are experienced as controlling by a significant number of parents, this provides further reason to consider these influences as morally problematic.

This combination of factors equal the layers of vulnerability as described by Luna. (79;80) She proposes that instead of labeling whole groups, such as children or patients with severe illness, as vulnerable, we should look closely to the situational aspects of the context in which a study is conducted. 'If vulnerability is viewed as layered and dynamic then there is no single feature that in and of itself defines

vulnerability; … Instead, there is a set of layers that render a person vulnerable'.(80) Layers can be related to several characteristics, both of persons themselves and of the circumstances.(81) Since vulnerability is not a 'stand-alone concept', persons must always be vulnerable to something.(82) In the case of parents of a child with cancer, there is a set of layers that makes them vulnerable to compromises to their voluntary informed consent, 'consent-based vulnerabilities' so to say.(82) Although none of the scenarios we analyzed leads to morally problematic informed consent in itself, each factor may add a layer of vulnerability to participating children and their parents, increasing the risk that voluntariness of informed consent is no longer morally acceptable.

Although the exact tipping point of the scale is difficult to determine, it is possible to remove or diminish the impact of existing layers.(80;82) Awareness among pediatric oncologists and other health care professionals of these different influences could enhance voluntary decision-making if it is used as a basis to implement specific safeguards that aim to minimize the influence of each of the layers. Based on the literature, several suggestions can be provided as to the type of systematic safeguards that may be implemented. The voluntary nature of participation and the right to withdraw at any time should be clearly and repeatedly communicated to parents.(83) Introduction of reconsideration or time-out as part of the informed consent process may also be helpful. This means that patients and their parents should be asked whether they wish to continue with a study, to increase voluntary participation in medical research.(56;84) Although such an approach is not necessary for all study types that are conducted within pediatric oncology, there is a variety of studies, such as randomized controlled trials, for which reconsideration could mean an improvement of the informed consent process. Finally, an independent counselor for parents who wish to discuss a study with someone who is not involved with their child's care may help them making a balanced decision whether enrolment is an appropriate decision for them as a family.(42) This independent counselor does not need to have full knowledge of pediatric oncology research, but should function as a guide, who discusses parents' values and considerations, without any conflicting interests related to research. Implementation of these different safeguards will contribute to the creation of an optimal environment for parents to provide voluntary informed consent in an integrated research-care context.

Table 1. Outcome of analysis and moral evaluation of pediatric oncology scenarios

Scenarios	Controlling	Morally problematic
1a. Dependent relationship	NO	NO
1b. Physician appeal to reciprocity	NO	NO
1c. Intentional framing of information	YES	NO
2a. New treatments as part of an RCT	NO	NO
2b. Treatment protocols with an inherent research component	YES	NO

Conclusion

We conclude that influences due to the intertwinement of research and care in pediatric oncology do not necessarily compromise voluntary informed consent of parents. However, a combination of influences may create morally problematic instances of involuntary informed consent. Implementation of systematic safeguards will contribute to the creation of an optimal environment for parents to provide voluntary informed consent in an integrated research-care context.

References

1. Brody H, Miller FG. The clinician-investigator: unavoidable but manageable tension. Kennedy Inst Ethics J 2003 Dec;13(4):329-46.
2. de Vries MC, Houtlosser M, Wit JM, Engberts DP, Bresters D, Kaspers GJ, et al. Ethical issues at the interface of clinical care and research practice in pediatric oncology: a narrative review of parents' and physicians' experiences. BMC Med Ethics 2011;12:18.
3. SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011, based on November 2013 SEER data submission, posted to the SEER website, April 2014. 2014.
4. Pritchard-Jones K, Dixon-Woods M, Naafs-Wilstra M, Valsecchi MG. Improving recruitment to clinical trials for cancer in childhood. Lancet Oncol 2008 Apr;9(4):392-9.
5. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin 2014 Mar;64(2):83-103.
6. Dekking SA, van der Graaf R, Kars MC, Beishuizen A, de Vries MC, van Delden JJ. Balancing research interests and patient interests: a qualitative study into the intertwinement of care and research in paediatric oncology. Pediatr Blood Cancer 2015 May;62(5):816-22.
7. Menikoff J. Full disclosure: telling patients when not being a research subject is a good choice. Perspect Biol Med 2005;48(1 Suppl):S139-S149.
8. Baker JN, Leek AC, Salas HS, Drotar D, Noll R, Rheingold SR, et al. Suggestions from adolescents, young adults, and parents for improving informed consent in phase 1 pediatric oncology trials. Cancer 2013 Dec 1;119(23):4154-61.
9. Berg SL. Ethical challenges in cancer research in children. Oncologist 2007 Nov;12(11):1336-43.
10. Eiser C, Davies H, Jenney M, Glaser A. Mothers' attitudes to the randomized controlled trial (RCT): the case of acute lymphoblastic leukaemia (ALL) in children. Child Care Health Dev 2005 Sep;31(5):517-23.
11. Kodish E. Informed consent for pediatric research: is it really possible? J Pediatr 2003 Feb;142(2):89-90.
12. Kodish ED, Pentz RD, Noll RB, Ruccione K, Buckley J, Lange BJ. Informed consent in the Childrens Cancer Group: results of preliminary research. Cancer 1998 Jun 15;82(12):2467-81.
13. Kupst MJ, Patenaude AF, Walco GA, Sterling C. Clinical trials in pediatric cancer: parental perspectives on informed consent. J Pediatr Hematol Oncol 2003 Oct;25(10):787-90.
14. Levi RB, Marsick R, Drotar D, Kodish ED. Diagnosis, disclosure, and informed consent: learning from parents of children with cancer. J Pediatr Hematol Oncol 2000 Jan;22(1):3-12.
15. Simon C, Eder M, Raiz P, Zyzanski S, Pentz R, Kodish ED. Informed consent for pediatric leukemia research: clinician perspectives. Cancer 2001 Aug 1;92(3):691-700.
16. Martenson EK, Fagerskiold AM. A review of children's decision-making competence in health care. J Clin Nurs 2008 Dec;17(23):3131-41.
17. Joffe S, Fernandez CV, Pentz RD, Ungar DR, Mathew NA, Turner CW, et al. Involving children with cancer in decision-making about research participation. J Pediatr 2006 Dec;149(6):862-8.
18. Soon CS, Brass M, Heinze HJ, Haynes JD. Unconscious determinants of free decisions in the human brain. Nat Neurosci 2008 May;11(5):543-5.
19. Magni SF. Brain Determinism and Free Will. Ethica & Politica / Ethics & Politics 2009;11(2):57-67.
20. Kahneman D. Thinking, Fast and Slow. London: Penguin Books; 2012.
21. Wall E. Voluntary Action. Philosophia 2001;28(1-4):127-36.
22. 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. 1978.
23. Appelbaum PS, Lidz CW, Klitzman R. Voluntariness of consent to research: a conceptual model. Hastings Cent Rep 2009 Jan;39(1):30-9.

24. Nelson RM, Beauchamp T, Miller VA, Reynolds W, Ittenbach RF, Luce MF. The concept of voluntary consent. Am J Bioeth 2011 Aug;11(8):6-16.
25. Dugosh KL, Festinger DS, Marlowe DB, Clements NT. Developing an index to measure the voluntariness of consent to research. J Empir Res Hum Res Ethics 2014 Oct;9(4):60-70.
26. Miller VA, Ittenbach RF, Harris D, Reynolds WW, Beauchamp TL, Luce MF, et al. The decision making control instrument to assess voluntary consent. Med Decis Making 2011 Sep;31(5):730-41.
27. Miller VA, Nelson RM. Factors related to voluntary parental decision-making in pediatric oncology. Pediatrics 2012 May;129(5):903-9.
28. Frankfurt HG. Necessity, volition, and love. New York: Cambridge University Press; 1999.
29. Wasserman R. Intentional Action and the Unintentional Fallacy. Pac Philos QI 2011;92(4):524-34.
30. Kodish E, Eder M, Noll RB, Ruccione K, Lange B, Angiolillo A, et al. Communication of randomization in childhood leukemia trials. JAMA 2004 Jan 28;291(4):470-5.
31. Angiolillo AL, Simon C, Kodish E, Lange B, Noll RB, Ruccione K, et al. Staged informed consent for a randomized clinical trial in childhood leukemia: impact on the consent process. Pediatr Blood Cancer 2004 May;42(5):433-7.
32. Chappuy H, Doz F, Blanche S, Gentet JC, Pons G, Treluyer JM. Parental consent in paediatric clinical research. Arch Dis Child 2006 Feb;91(2):112-6.
33. Chappuy H, Bouazza N, Minard-Colin V, Patte C, Brugieres L, Landman-Parker J, 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).
34. Petersen I, Spix C, Kaatsch P, Graf N, Janka G, Kollek R. Parental informed consent in pediatric cancer trials: a population-based survey in Germany. Pediatr Blood Cancer 2013 Mar;60(3):446-50.
35. Blumenthal-Barby JS. Between reason and coercion: ethically permissible influence in health care and health policy contexts. Kennedy Inst Ethics J 2012 Dec;22(4):345-66.
36. Faden R, Beauchamp T. A history and theory of informed consent. New York: Oxford University Press; 1986.
37. Hawkins JS, Emanuel EJ. Clarifying confusions about coercion. Hastings Cent Rep 2005 Sep;35(5):16-9.
38. Wertheimer A. Coercion. Princeton, New Jersey: Princeton University Press; 1987.
39. Council for International Organizations of Medical Sciences (CIOMS). International Ethical Guidelines for Biomedical Research involving Human Subjects. 2002.
40. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013 Nov 27;310(20):2191-4.
41. Miller FG. Recruiting Research Participants. In: Emanuel et al e, editor. The Oxford Textbook of Clinical Research Ethics.Oxford [etc.]: OUP; 2008. p. 397-403.
42. Pinxten W, Nys H, Dierickx K. Regulating trust in pediatric clinical trials. Med Health Care Philos 2008 Dec;11(4):439-44.
43. Simon C, Eder M, Kodish E, Siminoff L. Altruistic discourse in the informed consent process for childhood cancer clinical trials. Am J Bioeth 2006 Sep;6(5):40-7.
44. Woodgate RL, Yanofsky RA. Parents' experiences in decision making with childhood cancer clinical trials. Cancer Nurs 2010 Jan;33(1):11-8.
45. Knibbe ME, Maeckelberghe EL, Verkerk MA. Confounders in voluntary consent about living parental liver donation: no choice and emotions. Med Health Care Philos 2007 Dec;10(4):433-40.
46. Miller VA, Cousino M, Leek AC, Kodish ED. Hope and persuasion by physicians during informed consent. J Clin Oncol 2014 Oct 10;32(29):3229-35.
47. Deatrick JA, Angst DB, Moore C. Parents' views of their children's participation in phase I oncology clinical trials. J Pediatr Oncol Nurs 2002 Jul;19(4):114-21.
48. Simon CM, Siminoff LA, Kodish ED, Burant C. Comparison of the informed consent process for randomized clinical trials in pediatric and adult oncology. J Clin Oncol 2004 Jul 1;22(13):2708-17.
49. Chong D, Druckman JN. Framing Theory. Annu Rev Polit Sci 2007;10:103-26.

50. Kirklin D. Framing, truth telling and the problem with non-directive counselling. J Med Ethics 2007 Jan;33(1):58-62.
51. Brooks T. Should we nudge informed consent? Am J Bioeth 2013;13(6):22-3.
52. Will KE, Decina LE, Maple EL, Perkins AM. Examining the relative effectiveness of different message framing strategies for child passenger safety: Recommendations for increased comprehension and compliance. Accid Anal Prev 2015 Jun;79:170-81.
53. Unguru Y. The successful integration of research and care: how pediatric oncology became the subspecialty in which research defines the standard of care. Pediatr Blood Cancer 2011 Jul 1;56(7):1019-25.
54. Joffe S, Weeks JC. Views of American oncologists about the purposes of clinical trials. J Natl Cancer Inst 2002 Dec 18;94(24):1847-53.
55. Read K, Fernandez CV, Gao J, Strahlendorf C, Moghrabi A, Pentz RD, et al. Decision-making by adolescents and parents of children with cancer regarding health research participation. Pediatrics 2009 Sep;124(3):959-65.
56. Soto C, Tarrant C, Pritchard-Jones K, Dixon-Woods M. Consent to tissue banking for research: qualitative study and recommendations. Arch Dis Child 2012 Jul;97(7):632-6.
57. Hester DM, Hackler C. Improving medicine through research and the constitutive nature of altruism. Am J Bioeth 2006 Sep;6(5):51-2.
58. Ladd RE, Forman E. Altruistic motives reconsidered. Am J Bioeth 2006 Sep;6(5):55-6.
59. Dixon-Woods M, Wilson D, Jackson C, Cavers D, Pritchard-Jones K. Human Tissue and 'the Public': The Case of Childhood Cancer Tumour Banking. BioSocieties 2008;3:57-80.
60. Nelson TE, Oxley ZM, Clawson RA. Toward a psychology of framing effects. Political Behavior 1997;19(3):221-46.
61. Vishwanath A. Using frames to influence consumer willingness to pay for the patient health record: a randomized experiment. Health Commun 2009 Jul;24(5):473-82.
62. Saghai Y. Salvaging the concept of nudge. J Med Ethics 2013 Aug;39(8):487-93.
63. Hausman DM, Welch B. Debate: To Nudge or Not to Nudge. Journal of Political Philosophy 2010;18(1):123-36.
64. Druckman JN. The implications of framing effects for citizen competence. Political Behavior 2001;23(3):225-56.
65. Yap TY, Yamokoski AD, Hizlan S, Zyzanski SJ, Angiolillo AL, Rheingold SR, et al. Informed consent for pediatric phase 1 cancer trials: physicians' perspectives. Cancer 2010 Jul 1;116(13):3244-50.
66. Miller FG, Wertheimer A. The fair transaction model of informed consent: an alternative to autonomous authorization. Kennedy Inst Ethics J 2011 Sep;21(3):201-18.
67. Pritchard-Jones K. Clinical trials for children with cancer in Europe - still a long way from harmonisation: a report from SIOP Europe. Eur J Cancer 2008 Oct;44(15):2106-11.
68. Dekking SA, van der Graaf R, de Vries MC, Bierings MB, van Delden JJ, Kodish E, et al. Is a New Protocol for Acute Lymphoblastic Leukemia Research or Standard Therapy? Pediatrics 2015 Aug 17.
69. Wertheimer A. Voluntary consent: why a value-neutral concept won't work. J Med Philos 2012 Jun;37(3):226-54.
70. 45 CFR 46.118a8, 45 CFR 46.118a8, (2015).
71. Buchanan T. Coercion, harm, and complicity in research integrated with mandatory public health programs. Am J Bioeth 2004;4(1):57-9.
72. Largent EA, Joffe S, Miller FG. Can research and care be ethically integrated? Hastings Cent Rep 2011 Jul;41(4):37-46.
73. Lindell-Osuagwu L, Korhonen MJ, Saano S, Helin-Tanninen M, Naaranlahti T, Kokki H. Off-label and unlicensed drug prescribing in three paediatric wards in Finland and review of the international literature. J Clin Pharm Ther 2009 Jun;34(3):277-87.
74. Pandolfini C, Bonati M. A literature review on off-label drug use in children. Eur J Pediatr 2005 Sep;164(9):552-8.

75. Conroy S, Newman C, Gudka S. Unlicensed and off label drug use in acute lymphoblastic leukaemia and other malignancies in children. Ann Oncol 2003 Jan;14(1):42-7.
76. van den Berg H, Tak N. Licensing and labelling of drugs in a paediatric oncology ward. Br J Clin Pharmacol 2011 Sep;72(3):474-81.
77. Menikoff J. The hidden alternative: getting investigational treatments off-study. Lancet 2003 Jan 4;361(9351):63-7.
78. Orentlicher D. Making research a requirement of treatment: why we should sometimes let doctors pressure patients to participate in research. Hastings Cent Rep 2005 Sep;35(5):20-8.
79. Luna F. Elucidating the Concept of Vulnerability. Layers not Labels. Int J Fem Approaches Bioethics 2009;1:120-38.
80. Luna F, Vanderpoel S. Not the usual suspects: addressing layers of vulnerability. Bioethics 2013 Jul;27(6):325-32.
81. Schroeder D, Gefenas E. Vulnerability: too vague and too broad? Camb Q Healthc Ethics 2009 Apr;18(2):113-21.
82. Coleman CH. Vulnerability as a regulatory category in human subject research. J Law Med Ethics 2009;37(1):12-8.
83. Dekking SA, van der Graaf R, van Delden JJ. Strengths and weaknesses of guideline approaches to safeguard voluntary informed consent of patients within a dependent relationship. BMC Med 2014;12:52.
84. Roth-Cline M, Nelson RM. Parental permission and child assent in research on children. Yale J Biol Med 2013 Sep;86(3):291-301.

Part II:
The distinction between research and care

5

Balancing research interests and patient interests: a qualitative study into the intertwinement of care and research in pediatric oncology

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Abstract

Background

Traditionally, in ethical guidelines and in research ethics literature, care and research are clearly separated based on their different objectives. In contrast, in pediatric oncology, research and care are closely combined. Currently, it is unknown how relevant actors in pediatric oncology perceive this combination of research and care. We conducted a qualitative study into the experiences of those involved in Dutch pediatric oncology with the intertwinement of research and care and the dual role of pediatric oncologists as researchers and treating physicians.

Procedure

A qualitative study approach, using 2 focus groups and 19 semi-structured, in-depth interviews with pediatric oncologists, research coordinators, parents of children with cancer, and adolescents with cancer.

Results

Four themes characterize how actors experience the intertwinement of research and care in pediatric oncology. First, research is considered of major importance, and pediatric oncology professionals convey this message to patients and their parents. Second, there is ambiguity about categorization of studies into cancer therapy as either research or treatment. Third, role conflicts appear within the work of the pediatric oncologists. Finally, the various benefits of combining treatment with research are emphasized.

Conclusions

Research is regarded as a fundamental and indispensable characteristic of pediatric oncology practice. Pediatric oncology professionals, parents, and patients have a very positive outlook on combining research and care, but may not reflect sufficiently critical on its potential conflicts. Increased reflection on how to optimally combine research and care could serve as an important protection of the interests of children with cancer and their parents.

Introduction

From the outset pediatric oncology has been constructed as a practice that strongly combines research and care,(1) which has helped to improve survival rates for children with cancer in the past few decades.(2;3) However, combining research and care also leads to normative issues such as the moral obligations of pediatric oncologists as physicians and researchers, and the question of whether pediatric oncologists should serve the interest of individuals or groups of patients.(4)

De Vries and colleagues assert that pediatric oncologists 'continuously need to be aware of the potential conflict between research and treatment goals' (4) in order to be able to serve interests of current patients as well as those of future patients through research. It is currently unknown how relevant actors experience pediatric oncology practice, the intertwinement of research and care, and the double role of pediatric oncologists as researchers and treating physicians. Insight into these experiences is valuable for the evaluation of the close relationship between research and care in pediatric oncology.(5)

Qualitative research on the ways in which actors in pediatric oncology experience the intertwinement of research and care is limited. Most previous qualitative studies focus on the ethical issues of pediatric oncology trials as such,(6-16) rather than on issues related to the combination of research and care and the dual role of pediatric oncology physician-investigators. A study by Byrne-Davis and colleagues observed informed consent discussions between pediatric oncologists and families specifically for trials 'that are closely embedded into practice'.(17) They noticed that during these conversations the physicians switched between their clinical role and their investigator role, mainly by the language they used.(17) However, Byrne-Davis and colleagues did not investigate how the pediatric oncologists themselves perceived their double role. Furthermore, although they interviewed parents on their experiences with the informed consent process, they did not address how the parents experienced that their child's treatment was part of a clinical trial.(17)

In this chapter we present our qualitative study into the experiences of those involved in pediatric oncology with the intertwinement of research and care and the dual role of pediatric oncologists as researchers and treating physicians.

Methods

A qualitative study design allows for in-depth exploration of a topic and is therefore most suited to capture the experiences of pediatric oncology actors. As a first exploration of the topic, we conducted two focus groups; one with Dutch pediatric oncologists and one with parents of children with cancer. To validate and deepen our insights, a second stage of in-depth interviews was performed. We conducted 19 individual interviews with pediatric oncologists, research coordinators, parents of children with cancer, and adolescents with cancer (13-18 years old).

Parents and adolescents provided written informed consent for their participation and, if applicable, parents provided written informed consent for the participation of their child. The study was approved by the Research Ethics Committee of the University Medical Center Utrecht.

Sample

The inclusion criterion for all groups of respondents was to have experience with the combination of research and care. Parents and adolescents had to be able to speak the Dutch language. Also, the moment of inclusion in research should have been at most two years ago. In addition, we aimed for a large variety in types of cancer, age, gender, and experience with research participation. See table 1 for the characteristics of the professionals (pediatric oncologists and research coordinators) and table 2 for the parents and children. See figure 1 for a flow chart of the different respondents.

Focus groups

Pediatric oncologists were recruited from the seven university pediatric oncology centers in the Netherlands, one from each center. Six pediatric oncologists took part, one oncologist could not attend.

Parents of children with cancer for the focus group were recruited through one center for pragmatic reasons. We considered that organizing a meeting for parents situated at different centers would entail too much burden (in terms of travel time) and was therefore unfeasible. A research nurse contacted twelve parents of eight children by telephone, who all accepted the invitation to participate in the focus group. In total nine parents of six children attended; four mothers and five fathers. Three parents could not attend due to practical reasons.

Interviews

Pediatric oncologists from the seven Dutch pediatric oncology centers were contacted via two of our project advisors and the heads of the university pediatric oncology centers. Inclusion in the study was continuous via convenience sampling. Research coordinators were recruited from two different centers, since not all Dutch pediatric oncology centers employ research coordinators.

Parents and adolescents were approached via physicians and research nurses of three pediatric oncology centers and through a call on the website of the Dutch Association for Parents, Children and Cancer (VOKK).

We interviewed nine pediatric oncologists, three research coordinators, five parents of five different children and two adolescents. One adolescent was the daughter of a mother we interviewed.

Data collection

Focus groups lasted two hours each. Topics were formulated after examination of the relevant literature.

We conducted semi-structured, in depth interviews according to a predefined topic list (table 3). All but one interview took place at a pediatric oncology center. One interview took place at home. Data collection took place from March 2013 to March 2014.

Analysis

The analysis was carried out according to thematic analysis, a method for identifying, analyzing, and reporting themes within data.(18) The focus groups and interviews were transcribed verbatim and the data were imported in the software program NVivo 10, in order to facilitate the process of analysis. SD was the main analyst. She selected fragments of the data that were relevant in relation to the study purpose and coded these fragments with appropriate labels. MK and RG independently coded four interviews and all findings were compared and contrasted. The codes were grouped into conceptual categories or themes on the basis of their content, meaning, and interrelationships. These themes were regularly discussed during team meetings. Our themes were identified at the semantic level, meaning that we started with describing the experiences of the respondents followed by an interpretation in the light of the existing literature.(18) To enhance the validity of our findings, we held an expert meeting with pediatric oncologists in the last phase of data collection. We discussed our preliminary results with them, to assess whether these were an accurate representation of pediatric oncology practice and to obtain additional data.

Results

All respondents reflected on their respective experiences with the situation in which research and care are intertwined and with the dual role of pediatric oncologists as researchers and treating physicians. Four themes characterize how actors experience the intertwinement of research and care in pediatric oncology. Representative quotations were chosen to illustrate the themes identified (see Table 4).

Importance of research

The pediatric oncologists emphasized the large role of research in their daily work and that every treatment includes a research component. (Quote 1 in Table 4)

All pediatric oncologists and research coordinators expressed a strong desire to improve their field. To achieve this improvement, it was regarded as natural to try to include all eligible patients in research. One oncologist said that she felt uncomfortable about approaching families about research in the beginning of her career.

After a while, when she had realized what research is able to bring, she had lost this insecurity.

Pediatric oncologists and research coordinators stated they emphasize to families the importance of research and that research has helped to improve treatments and increase survival rates. They acknowledged that these statements could influence parents and older patients, who are generally not aware of medical research before their cancer diagnosis. According to both the health care professionals and parents themselves, parents are in a state of shock and disbelief and their only objective is to cure their child. Some pediatric oncologists thought that the existent emphasis on research might make parents feel obliged to consent to research participation of their child. (Quote 2 in Table 4)

Parents themselves were motivated to contribute to the improvement of therapy for other patients, as long as a study would not require too much of their child or themselves in terms of time or physical burden or if the research could also benefit their child. (Quote 3 in Table 4)

Parents were told by the hospital staff that their child is treated in a university hospital, where research is an important part of daily practice. Therefore, parents realized that they can be invited to enroll their child, which they considered as no more than reasonable. Several parents pointed at feelings of reciprocity: they should contribute what they can, since their child benefits from research in the past and from the participation of other children. Also adolescents were aware of the large role of research in pediatric oncology and were willing to contribute. (Quote 4 in Table 4)

Ambiguity about categorization of studies

The pediatric oncologists distinguished different types of studies, based on whether a study investigated the effects of cancer therapy itself or something else (Table 5). If studies did investigate cancer therapy, these were regarded as integral to the treatment options of patients, which in turn rendered it difficult to separate the roles of physician and researcher. For all other types of studies, such as laboratory research or supportive care studies, the oncologists considered it easier to separate conversation about these studies from conversation about treatment.

Furthermore, the pediatric oncologists considered it difficult to categorize the studies into cancer therapy as either research or treatment. This difficulty in particular concerned best available treatment protocols. According to the pediatric oncologists, these protocols form a grey area between research and treatment, since they call these protocols state-of-the-art treatment, while these are simultaneously designed to evaluate whether the protocol's modifications of previously used treatment regimens have improved survival rates. It was mentioned that with this type of treatment the pediatric oncology community primarily aims to prove that they were right to consider such a modified treatment protocol as best available treatment. (Quote 5 in Table 4)

Parents also made a distinction between different types of studies based on the extent to which a study could benefit their own child. As such, studies into cancer therapy were perceived as providing treatment rather than research. (Quote 6 in Table 4)

Role conflicts

In general, pediatric oncologists stated that they functioned both as a clinician and as a researcher. Some had this dual role because they obtained informed consent, others because they also designed and conducted their own studies. With regard to which role had priority, they gave different answers. On the one hand, they indicated that being the treating doctor of their patients would always prevail over their researcher role. On the other hand, pediatric oncologists described situations in which research interests had played a large role. An example of such a situation concerned a patient with refractory disease, who did not fulfil the eligibility criteria for a certain phase I/II trial. Instead of giving him some other treatment, the oncologists decided to wait until the patient would become eligible and could be treated within the trial, while taking into account whether it was safe for the patient to have his treatment postponed. (Quote 7 in Table 4)

Furthermore, pediatric oncologists reported the wish to include all patients in a study, leading to a conflict between their two roles in the context of informed consent. First, when informing families about research they sometimes felt a tension between motivating and being too persuasive. (Quote 8 in Table 4)

Second, both pediatric oncologists and research coordinators mentioned that they had included patients in a trial while they thought that parents had not really understood the study details, mainly right after hearing their child's cancer diagnosis. (Quote 9 in Table 4)

Parents and adolescents felt that the treating oncologist of their child acted as a physician and not as a researcher. In their experiences, their child's wellbeing and interests prevailed over other interests of the pediatric oncologists. One father reported a moment where the researcher role of their pediatric oncologist took precedence over his care giving role: as a family they had decided to stop the experimental medication for their son, because no sign of the disease could be detected in his blood. Since he was doing so well, they wanted to see if he could manage without medication. When they told their oncologist about this decision, he pointed at consequences for the study, making his researcher role very apparent to them.

Emphasis on benefits

Both the pediatric oncologists and research coordinators expressed a strong belief in the benefits of combining treatment with research. These benefits included therapeutic benefits for participating patients, due to close monitoring, following strict protocol guidelines, and the use of innovative interventions. In addition, the health care professionals had high expectations from research to improve the field of pediatric oncology, increase survival chances and create benefits for future patients. (Quote 10 in Table 4)

Simultaneously, pediatric oncologists were convinced that patients are not harmed by research. Also, they thought that risks and burdens of additional studies are low, while for studies into cancer therapy these would generally be outweighed by the benefits. Approval of the study protocol by a Research Ethics Committee was considered a further safeguard.

Parents and adolescents said that participating in research increased their feeling of safety, due to the extra tests and check-ups. Also, they expressed a belief in the potential benefit of the intervention arm of an Randomised Controlled Trial (RCT). A father did not think research would be conducted if it was risky. For a mother it was unclear whether the procedures her daughter underwent were part of the standard treatment or were extra because she participated in an RCT. (Quote 11 in Table 4)

Discussion

Our study shows that in the Netherlands research is considered as a fundamental and indispensable characteristic of pediatric oncology practice. First, pediatric oncology professionals display a strong motivation to perform research and are generally involved in the conduct of studies in a variety of ways, such as obtaining informed consent or designing studies themselves. Since pediatric oncologists deem conducting research of pivotal importance, they convey this message to patients and their families. Moreover, pediatric oncology professionals emphasize the research contributions of past families affected by cancer and how these have shaped the current cancer treatment, thereby referring to an ‘ethic of reciprocity’.(19) In line with previous empirical studies,(20;21) our study shows that children with cancer and their parents realize that the current quality of treatments is contingent upon past research. Also, they recognize that their child receives benefits due to the families who have been willing to participate in pediatric oncology studies in the past. As a result, they are highly motivated to participate in research themselves, to contribute to further improvement of cancer therapy to the benefit of future children with cancer. As such, reciprocity leads to a continuous process in which families affected by cancer are ‘part of the chain of people’,(21) from past to present to future.

Second, according to our respondents, research is often combined with the provision of treatment. On the one hand, this finding confirms the standard view of pediatric oncology. On the other hand, our study adds a specification to the

general statement that in pediatric oncology research and care are intertwined. Commonly, it is meant to indicate that the majority of children with cancer participate in clinical trials (i.e. phase III RCTs) and sometimes can only receive treatment through research participation (phase I/II studies).(3) Our study adds that research and care are also intertwined in pediatric oncology because standard treatments have research elements. Examples are best available treatment protocols, which provide best current treatment, but also contain modifications to existing treatment regimens, of which the merits are systematically investigated. Although the study protocols used in clinical trials clearly qualify as research, best available treatment protocols can best be categorized as 'hybrid' protocols. So, all studies into cancer therapy combine research and treatment, but this is most apparent in best available treatment protocols, since the standard treatment is also research. As such, best available treatment protocols invoke the question of what type of ethical oversight is appropriate. This has implications for the protection of children with cancer who participate in pediatric oncology studies, since it should be prevented that protocols with relatively high risks are introduced as standard treatment without ethics review.

Third, whereas pediatric oncologists considered their care-giving role as primary, research considerations sometimes appeared overriding. This happened both in the informed consent context and in decisions about whether to treat a patient within a clinical study. So, although the pediatric oncologists indicated that their role as physician would always have priority over their researcher role, this was not fully reflected in the choices they made.

Finally, our respondents displayed a strong belief in the beneficial potential of research, both for individual children and for other children and the field of pediatric oncology in general. In contrast, risks and burdens of research were referred to as low or were considered being outweighed by the importance of the research question. Arguably, because both pediatric oncologists and parents and patients hope that participation in a trial will provide therapeutic benefit,(4;9) the various benefits of research receive relatively more attention than its risks and burdens for individual patients. As in research with adults, in pediatric research both the potential benefits to individual patients and the societal benefits are important to assess the acceptability of research with children, in addition to the risks and burdens.(22) However, due to the intertwinement of research and care and its accompanying emphasis on the various benefits of research, it could become unclear for parents which additional risks and burdens children are exposed to in comparison with care as usual.(4)

We see the advantages of combining the provision of treatment with research. Survival rates for most childhood cancers have rapidly improved in the past decades,(2;3;23;24) which has frequently been linked to the high rates of participation in medical research.(4;13;15;17;25-27) Especially in the field of pediatric medicine, where much is unknown or uncertain about which drugs are effective and how they work (28-33) this certainly is desirable. However, it seems that due to the self-evidence of combining treatments with research, the pediatric oncologists and research coordinators but also parents and adolescents may not reflect critically

enough on the possible conflicts that arise when research and care are intertwined. Since managing the conflicts between treatment and research is only possible if they are recognized by relevant actors,(4;34) it is essential that pediatric oncology stakeholders recognize potential tensions and discuss how to properly manage these in order to optimally combine research and care. This discussion could function as an important protection of the interests of children with cancer and their parents,(34) if within the inherent tensions that exist, explicit choices are made on how to safeguard patient and parent interests.

A strong feature of our study is that we invited different groups of respondents, to obtain an overall picture of the field from a variety of perspectives. A second strength is the combination of two different qualitative methods: focus groups and individual interviews. This enabled us to receive answers to our questions both in a setting in which respondents could discuss different topics and in a more personal setting, allowing each respondent to elaborate on their experiences.

A first limitation is the small number of interviewed adolescents. This is due to the complexity of approaching adolescents with cancer, who are already burdened by a severe disease and everything it entails. Yet, we do not consider this small number problematic, since qualitative research does not aim to provide generalizable results, but seeks to present relevant experiences of those involved in a certain practice. A second limitation is that we only discuss the Dutch pediatric oncology context. Ethical issues and their implications could vary, due to differences between the pediatric oncology contexts in different countries. Finally, there may be a bias in included patients and parents, since only those parents and adolescents could be contacted that were well enough to participate rather than those who had difficulty with coping with the disease.

Conclusions

Our study shows that in pediatric oncology, the conduct of research is considered a fundamental and indispensable characteristic of practice. This follows from the strong motivation of respondents to contribute to research, the research elements of standard treatments, choices made in favor of research interests and the emphasis on benefits of research. Pediatric oncology professionals, parents and patients have a very positive outlook on combining research and care, but may not reflect critically enough on potential conflicts that arise when research and care are intertwined. Yet, potential conflicts of combining research and care should also receive appropriate attention, since managing the conflicts between treatment and research is only possible if they are recognized as such by relevant actors. Increased discussion could function as an important protection of the interests of children with cancer and their parents if within the inherent tensions that exist, explicit choices are made on how to safeguard patient and parent interests.

Table 1. Characteristics of professionals (focus group and interviews)

Pediatric oncologists	(N= 16)[1]
Gender	
Male	8
Female	8
Experience (years)	
5-10	5
11-15	5
16-20	2
>20	4
Areas of interest: clinical oncology[2]	
No specific	2
Solid tumors	9
Lymphomas	4
Leukemia	8
Stem cell transplantation	4
Histiocytosis	2
Myelodysplastic syndrome	1
Areas of interest: research[2]	
Clinical drug trials	12
Laboratory research	6
Supportive care	6
Palliative care	3
Stem cell transplantation	4
Research coordinators	(N=3)
Gender	
Male	1
Female	2
Experience (years)	
0-5	2
5-10	1

[1] Six from the focus group, nine from the interviews and one additional from the expert meeting

[2] Pediatric oncologists could have various areas of interest

Table 2. Characteristics of parents and children (focus group and interviews)

Parents	Parents (N=14)[1]
Gender	
Male	8
Female	8
Age (years)	
34-39	4
40-44	3
45-50	7
Education	
Primary, lower secondary general, or lower vocational	2
Higher secondary general or intermediate vocational	5
Higher vocational or university	7
Children	(N=12)[2]
Gender	
Male	9
Female	3
Age (years)	
0-4	2
5-9	2
10-14	3
15-19	5
Diagnosis	
Acute lymphoblastic leukemia	3
Chronic myeloid leukemia	2
Rhabdomyosarcoma	1
Burkitt lymphoma	1
Hepatoblastoma	1
Osteosarcoma	1
Ewing sarcoma	1
Brain tumor (high grade glioma)	1
Hodgkin lymphoma	1

[1] Nine parents from the focus group and five from the interviews

[2] Six children from parents from the focus group and five children from the interviewed parents. One of these children, an adolescent female with a brain tumor, was also interviewed herself. The twelfth child was an adolescent male with Hodgkin Lymphoma who we interviewed. His parents were not interviewed.

Table 3. General topic list

- Advantages of the dual role of physician and investigator
- Disadvantages of the dual role of physician and investigator
- Role conflicts due to the combination of research and care
- Conflicts between conduct of research and provision of care
- Suggestions to resolve these conflicts
- Influence of the dual role on the child
- Implications of taking part in a study
- Categorization of pediatric oncology studies

Table 4. Quotes from focus groups and interviews

Number	Quotes
1	Pediactric oncologist: 'Almost all treatments that we give have a research component. You always have to obtain informed consent, so you are always engaged with research in some way. That is part of your job. Almost every time you discuss treatment with people, a study is part of that discussion.'
2	Pediactric oncologist: 'Sometimes I sense that parents do not want to say yes, but that they feel obliged in some way. To me as their doctor, to the hospital that is taking care of their child, to future patients. And also because they know that earlier research has made improvements in treatment from which their child benefits.'
3	Parent: 'Every child that gets cancer is unique and is one too many. So you want to do everything you can to help with research that can accomplish that.'
4	Adolescent: 'It is not a big effort to have some extra blood drawn and it was not a problem for me since they can help people with that.'
5	Pediactric oncologist: 'We know that children with a certain deletion of genetic material in the leukemia cells have a poorer prognosis. So a year of extra treatment has been added to the protocol, while we do not have evidence that that extra year will improve the prognosis. So we are testing a hypothesis, but it is presented as standard treatment.'
6	Parent: 'I think that it also depends on the type of research, because if it can help others and does not have that much impact, I think that every parent will say they participate. But if the research is more invasive so to say, then you listen more to your oncologist. Who is also the one to introduce such a study so... there is some difference in types of research.'
7	Pediactric oncologist: 'I think that we have not acted correctly with regard to this patient we had at our department, since I feel as though the study guided our decision rather than the patient himself.'
8	Pediactric oncologist: 'You want patients to enroll in a study, because you want to learn from what you do. Therefore, you should make a real effort to include your patients, but you should not push people over the edge. You could push them towards the edge to take a look, but the final push...'
9	Pediactric oncologist: 'I think people are overwhelmed by the diagnosis and do not have room for anything else. But that would mean that we could never do scientific research with this population, while research has brought us so much further. So, I definitely have the feeling that sometimes I ask too much, but I am convinced that this is the way to go to some extent, because it is the only way to learn from what we do.'
10	Pediactric oncologist: 'And I cooperate with a lot of studies and I think... conducting research is fun. I mean, because you learn from it and it helps you to make progress and otherwise you will not be able to change the field. And you want to change the field, because you want to be able to cure more children. So I think that it is really important, for everybody. If someone did not think [research] important I doubt whether one could work here.'
11	Parent: 'Those MRIs were a standard part of the study; these belonged to the study so to say. But I think that they would also have done these, if you just had the normal ... if you remove the word study, because that is the normal process for a patient with a brain tumor who needs a cure.'

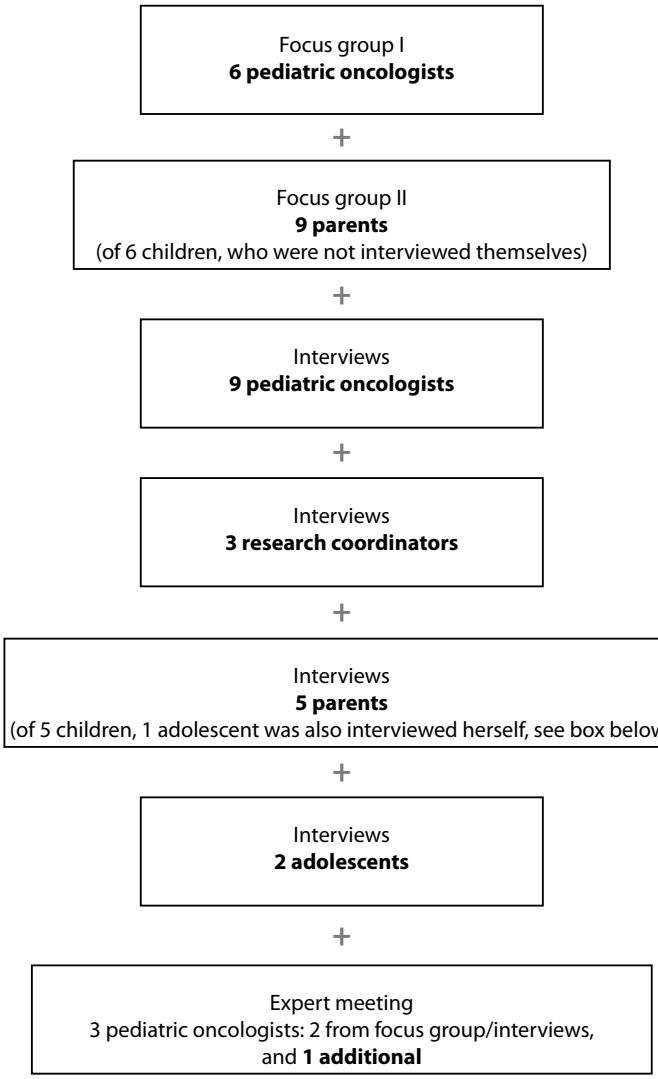
Table 5. Different types of studies in pediatric oncology and their relation to cancer therapy

	Cancer therapy studies	Description
TREATMENT	1. Best available treatment protocols	Single arm protocols that provide standard treatment, but also contain modifications to existing therapies that have not yet been fully studied. Therefore, these protocols are evaluated by clinical and epidemiological data collection and systematic analysis of disease characteristics, treatment results, side-effects, and serious adverse events. Furthermore, treatment results are compared to historical results and to results obtained by international research groups. As such, these treatment protocols simultaneously serve treatment and research goals. Additional studies can be added to this protocol.
↑	2. Phase III randomized controlled drug trials	Protocols that provide standard treatment, but also involve one or more research questions for which randomizations are designed and added to the protocol. These trials are called phase III trials because in the intervention arm a drug that was previously tested in phase I/II trials is now tested in phase III for effectiveness. Phase III trials also test combinations of two or more familiar drugs, or a different dosage of a standard drug. Despite the research goal, these studies are seen as part of the (frontline) treatment options that patients have.
↓	3. Phase I/II studies*	These are studies into experimental cancer therapy that have a prominent scientific objective, but also serve a therapeutic function for children with refractory disease.
RESEARCH	Non-cancer therapy studies	Description
	4. Additional studies	All studies that do not investigate cancer therapy itself: Laboratory research on blood, bone marrow and other tissue; or supportive care studies, which can take the form of a phase III study involving a randomization. These studies are considered as clearly separated from the cancer therapy patients receive. These studies are usually added to best available treatment protocols or phase III randomized controlled drug trials.

* In the Netherlands the risks and burdens of pediatric research without a prospect of direct benefit for the child should be minimal. Phase I oncology trials are not considered as potentially beneficial and generally involve more than minimal risk and/or burden. Therefore, it is only possible to conduct combined phase I/II studies, for which it is more likely that the individual patient may benefit or a clinical effect is to be expected based on adult studies with comparable tumors or in preclinical studies with pediatric tumor models.

Figure 1. Flow chart of respondents

Numbers in bold added up = the total number of respondents = 35



References

1. Krueger G. Hope and Suffering Children, Cancer and the Paradox of Experimental Medicine. Johns Hopkins University Press; 2008.
2. Jemal A, Thomas A, Murray T, Thun M. Cancer statistics, 2002. CA Cancer J Clin 2002 Jan;52(1):23-47.
3. Ablett S, Pinkerton CR. Recruiting children into cancer trials--role of the United Kingdom Children's Cancer Study Group (UKCCSG). Br J Cancer 2003 Jun 2;88(11):1661-5.
4. de Vries MC, Houtlosser M, Wit JM, Engberts DP, Bresters D, Kaspers GJ, et al. Ethical issues at the interface of clinical care and research practice in pediatric oncology: a narrative review of parents' and physicians' experiences. BMC Med Ethics 2011;12:18.
5. van Thiel GJMW, Van Delden JJM. Reflective Equilibrium as a Normative Empirical Model. Ethical Perspectives 2010;17(2):183-202.
6. Baker JN, Leek AC, Salas HS, Drotar D, Noll R, Rheingold SR, et al. Suggestions from adolescents, young adults, and parents for improving informed consent in phase 1 pediatric oncology trials. Cancer 2013 Dec 1;119(23):4154-61.
7. Yap TY, Yamokoski AD, Hizlan S, Zyzanski SJ, Angiolillo AL, Rheingold SR, et al. Informed consent for pediatric phase 1 cancer trials: physicians' perspectives. Cancer 2010 Jul 1;116(13):3244-50.
8. Miller VA, Baker JN, Leek AC, Hizlan S, Rheingold SR, Yamokoski AD, et al. Adolescent perspectives on phase I cancer research. Pediatr Blood Cancer 2012 Oct 3.
9. Kupst MJ, Patenaude AF, Walco GA, Sterling C. Clinical trials in pediatric cancer: parental perspectives on informed consent. J Pediatr Hematol Oncol 2003 Oct;25(10):787-90.
10. Oppenheim D, Geoerger B, Hartmann O. Ethical issues in pediatric oncology phase I-II trials based on a mother's point of view. Bull Cancer 2005 Nov;92(11):E57-E60.
11. de Vries MC, Wit JM, Engberts DP, Kaspers GJ, van Leeuwen E. Pediatric oncologists' attitudes towards involving adolescents in decision-making concerning research participation. Pediatr Blood Cancer 2010 Jul 15;55(1):123-8.
12. Deatrick JA, Angst DB, Moore C. Parents' views of their children's participation in phase I oncology clinical trials. J Pediatr Oncol Nurs 2002 Jul;19(4):114-21.
13. Eder ML, Yamokoski AD, Wittmann PW, Kodish ED. Improving informed consent: suggestions from parents of children with leukemia. Pediatrics 2007 Apr;119(4):e849-e859.
14. Chappuy H, Doz F, Blanche S, Gentet JC, Pons G, Treluyer JM. Parental consent in paediatric clinical research. Arch Dis Child 2006 Feb;91(2):112-6.
15. Eiser C, Davies H, Jenney M, Glaser A. Mothers' attitudes to the randomized controlled trial (RCT): the case of acute lymphoblastic leukaemia (ALL) in children. Child Care Health Dev 2005 Sep;31(5):517-23.
16. Stevens PE, Pletsch PK. Ethical issues of informed consent: mothers' experiences enrolling their children in bone marrow transplantation research. Cancer Nurs 2002 Apr;25(2):81-7.
17. Byrne-Davis LM, Salmon P, Gravenhorst K, Eden TO, Young B. Balancing high accrual and ethical recruitment in paediatric oncology: a qualitative study of the 'look and feel' of clinical trial discussions. BMC Med Res Methodol 2010;10:101.
18. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology 2006;(3):77-101.
19. Simon C, Eder M, Kodish E, Siminoff L. Altruistic discourse in the informed consent process for childhood cancer clinical trials. Am J Bioeth 2006 Sep;6(5):40-7.
20. Dixon-Woods M, Wilson D, Jackson C, Cavers D, Pritchard-Jones K. Human Tissue and 'the Public': The Case of Childhood Cancer Tumour Banking. BioSocieties 2008;3:57-80.
21. Woodgate RL, Yanofsky RA. Parents' experiences in decision making with childhood cancer clinical trials. Cancer Nurs 2010 Jan;33(1):11-8.
22. Shaddy RE, Denne SC. Clinical report--guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Pediatrics 2010 Apr;125(4):850-60.

23. SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011, based on November 2013 SEER data submission, posted to the SEER website, April 2014. 2014.
24. Gatta G, Zigon G, Capocaccia R, Coebergh JW, Desandes E, Kaatsch P, et al. Survival of European children and young adults with cancer diagnosed 1995-2002. Eur J Cancer 2009 Apr;45(6):992-1005.
25. Berg SL. Ethical challenges in cancer research in children. Oncologist 2007 Nov;12(11):1336-43.
26. Bond MC, Pritchard S. Understanding clinical trials in childhood cancer. Paediatr Child Health 2006 Mar;11(3):148-50.
27. Pritchard-Jones K, Dixon-Woods M, Naafs-Wilstra M, Valsecchi MG. Improving recruitment to clinical trials for cancer in childhood. Lancet Oncol 2008 Apr;9(4):392-9.
28. 't Jong GW, Vulto AG, de Hoog M, Schimmel KJ, Tibboel D, van den Anker JN. Unapproved and off-label use of drugs in a children's hospital. N Engl J Med 2000 Oct 12;343(15):1125.
29. Conroy S, Newman C, Gudka S. Unlicensed and off label drug use in acute lymphoblastic leukaemia and other malignancies in children. Ann Oncol 2003 Jan;14(1):42-7.
30. Kimland E, Nydert P, Odlind V, Bottiger Y, Lindemalm S. Paediatric drug use with focus on off-label prescriptions at Swedish hospitals - a nationwide study. Acta Paediatr 2012 Jul;101(7):772-8.
31. Lindell-Osuagwu L, Korhonen MJ, Saano S, Helin-Tanninen M, Naaranlahti T, Kokki H. Off-label and unlicensed drug prescribing in three paediatric wards in Finland and review of the international literature. J Clin Pharm Ther 2009 Jun;34(3):277-87.
32. Pandolfini C, Bonati M. A literature review on off-label drug use in children. Eur J Pediatr 2005 Sep;164(9):552-8.
33. van den Berg H, Tak N. Licensing and labelling of drugs in a paediatric oncology ward. Br J Clin Pharmacol 2011 Sep;72(3):474-81.
34. Miller FG, Rosenstein DL, DeRenzo EG. Professional integrity in clinical research. JAMA 1998 Oct 28;280(16):1449-54.

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Discriminating between research and care in pediatric oncology: ethical appraisal of the ALL-10 and 11 protocols of the Dutch Childhood Oncology Group (DCOG)

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Abstract

Pediatric oncology is a classic example of a field in which research and care are closely intertwined. Moreover, bioethicists have argued that in environments such as pediatric oncology we should no longer draw sharp distinctions between research and care. Recently, two Dutch protocols for the treatment of children with Acute Lymphoblastic Leukemia (ALL) have been categorized in two different ways, one as research (ALL-11) and the other as treatment (ALL-10). We analyzed these protocols in order to explore whether the distinction between research and care in pediatric oncology is morally relevant. We applied several characteristics of research to the ALL-10 and 11 protocols: the goal of producing generalizable knowledge; systematic collection of data; potentially high and uncertain risks; burdens and risks unrelated to treatment; and provision of treatment according to detailed protocols. Both ALL-protocols exhibit general characteristics of research. At the same time, both protocols also clearly satisfy the objective of delivering the best available treatment. Therefore, it remains to be discussed how to review these kinds of protocols that integrate a research goal with the objective of providing individual patients with best current treatment. A change in both research ethics regulation and oversight of conventional care is needed. More case studies are essential to expand the moral evaluation of the intertwinement between research and care in pediatric oncology.

Introduction

Currently, there is an intensive debate in bioethics about whether the practice of medical research should or should not be strictly distinguished from clinical care.(1-4) A classic example of a field in which research and care are highly integrated is pediatric oncology.(4;5) From the outset pediatric oncology has been constructed as a practice that closely combines research and care,(6) in order to overcome the lack of decisive knowledge currently present in pediatric medicine in general (7-10) and in pediatric oncology in particular.(11;12) The lack of evidence is due to the fact that research data from adult oncology are not generalizable to children for the most part, and that most childhood cancers are rare.(5) It is estimated that over 70% of patients take part in clinical trials.(13) Moreover, pediatric oncologists often regard clinical trials as providing state-of-the-art treatment.(14)

Not just oncologists, but bioethicists have also highlighted the integration of research and care in pediatric oncology. Recently, Kass and colleagues have presented pediatric oncology as an illustration of a practice where research and care are optimally combined for the benefit of both individual patients and groups of patients.(15) According to Kass et al., the context of pediatric oncology 'is constructed to bring the most pertinent forms of scientific understanding to bear on clinical care, and clinical care generates new scientific learning'.(15) They claim that in environments such as pediatric oncology the distinction between research and care is becoming increasingly blurred and ceases to be of moral importance for determining which activities need ethical oversight. This claim is in sharp contrast to the traditional bioethical paradigm that clearly distinguishes medical research from medical care.(16;17) The distinction is usually based on the premise that research is designed to develop generalizable knowledge for *groups* of patients, whereas the benefits of this knowledge for individual patients participating in the research are uncertain, and care is directly aimed at the promotion of health and wellbeing in *individual* patients.(16;18)

Unfortunately, Kass et al. do not provide concrete examples to substantiate their claim about pediatric oncology practice, nor do they pursue its moral implications. We believe that examples from practice can help in gaining insight into the validity and implications of their claims, because such examples provide an empirical assessment that could potentially result in a modification and reformulation of the normative outcome. As such, 'theory and practice ... mutually influence each other in the process of searching for reliable moral judgments and theories'.(19)

In this chapter we will explore pediatric oncology treatment protocols that are considered current best treatment, while they are simultaneously designed to answer study questions by collecting and evaluating treatment results. Examples of such studies are treatment protocols for children with Acute Lymphoblastic Leukemia (ALL). Evaluating best available treatments has greatly improved survival rates for children with ALL,(20) but simultaneously raises uncertainties as to how these kinds of protocols should be categorized.

This ambiguity is illustrated by the ALL-10 and ALL-11 protocols of the Dutch Childhood Oncology Group (DCOG). These two ALL-protocols are largely similar, but have been categorized differently. DCOG ALL-10 has been considered by a Research Ethics Committee (REC), which decided that it was exempt from ethical review. The DCOG ALL-11 protocol has been deemed a research protocol and was reviewed accordingly. We will compare both protocols in order to discover whether the distinction between research and treatment is morally relevant in pediatric oncology.

For our comparison, we will use the five "characteristics" of research that Kass et al. have recently listed as being generally used to distinguish research from care.(15) We apply these characteristics to the DCOG ALL-10 and ALL-11 protocols and consider the implications of our analysis for the moral obligations of physician-investigators in pediatric oncology, with regard to ethical review and informed consent in particular.

Comparison of DCOG ALL-10 and ALL-11

Based on ethical guidelines for medical research with human beings and scholarly literature, Kass and colleagues have assembled five characteristics of research. These are that research (1) is designed to develop generalizable knowledge and (2) requires systematic investigation. Furthermore, clinical research (3) potentially presents less net clinical benefit and greater overall risk than clinical practice, (4) introduces burdens or risks from activities that are not otherwise part of patients' clinical management, and (5) uses protocols to dictate which therapeutic or diagnostic interventions a patient receives.(15) We will apply these general research criteria to the two DCOG ALL-protocols in order to explore whether these protocols have research elements. See Figure 1 for an overview of the differences and similarities between the two protocols.

1. Research is designed to develop generalizable knowledge

The first characteristic of research is that research is designed to develop generalizable health knowledge. This characteristic is mainly based on research ethics guidelines such as the *Belmont Report* and the *International Ethical Guidelines for Biomedical Research involving Human Subjects* of the Council for International Organizations of Medical Sciences (CIOMS).(16;17)

At present, the primary aim of both ALL-10 and ALL-11 is to improve the overall treatment results for children with ALL in terms of Event Free Survival (EFS) compared to the previous DCOG ALL-protocols. The ALL-10 protocol contains several hypotheses about the treatment that is provided to different groups of patients. The protocol states that its aim is to investigate whether these hypotheses will be confirmed. For example, in patients with good prognoses the aim of the study is to investigate whether therapy reduction is feasible without increasing the risk of relapse. To assess whether these improvements have occurred, the outcome of the different patient groups is compared to the historical control groups and international groups

of patients from the German Berlin-Frankfurt-Munster (BFM) Study Group. Another part of the protocol is being performed in collaboration with the Australian and New Zealand Children's Cancer Study Group (ANZCCSG), which is said to be necessary in order to obtain sufficient patient numbers to produce statistically significant results. This international collaboration indicates the scientific objective of the ALL-10 protocol.

In addition to the treatment part of the protocols, ALL-10 and ALL-11 encompass several non-therapeutic research studies, to gather data on pharmacokinetics, pharmacodynamics, side effects, etc. As such, these research projects contribute to generalizable knowledge on ALL, drug characteristics and treatment effects. Furthermore, in the ALL-11-protocol a scientific goal is clearly present in the two randomizations, which are aimed at gaining knowledge on dosage of cancer drugs (Asparaginase) and the effects of prophylactic administration of immunoglobulins.

Nonetheless, Dutch pediatric oncologists consider the ALL-10 and ALL-11 protocols as best available treatment, because their treatment regimens are based on the knowledge and experience of the Dutch and international pediatric oncology community at that time. The protocols have implemented the latest insights of the field. Consequently, the objective of producing generalizable knowledge is integrated with the objective of delivering best available treatment for patients.

In sum, although ALL-10 and ALL-11 have been developed to provide state-of-the-art treatment for patients with ALL, they are also designed to produce generalizable knowledge on ALL treatment and the advancement of therapy for children with ALL as a group. Thus, the first defining feature of research applies to both leukemia protocols.

2. Research requires systematic investigation

The second characteristic of research involves 'the systematic collection of data according to a predefined method ... important [for] the production of generalizable knowledge'.(15) The ALL-10 and ALL-11 protocols are evaluated on a number of measures, such as Event Free Survival (EFS), Disease Free Survival (DFS), Overall Survival (OS), Cumulative Incidence of Relapse (CIR), side effects, and serious adverse events. To facilitate studying these factors, systematic collection of clinical and epidemiological data and storage of collected tissue is necessary. All data from patients are collected in a database, which contains data from all pediatric oncology centers in the Netherlands that treat patients with ALL. These data are systematically evaluated at the end of the running time of the protocols. For this registration and storage, informed consent is obtained from parents and adolescent patients.

In addition, for the ALL-11 protocol a drug monitoring program was developed. Serum levels of a regularly used cancer drug (Asparaginase) are measured in all patients at pre-established times, in order to determine whether the Asparaginase dosage is appropriate. Low levels decrease the chance of survival, while high levels increase

the risk of toxicity. These serum level data are used to effectively manage the care of individual patients while they are simultaneously employed to assess whether such a drug monitoring program improves outcomes for ALL patients as a group.

Thus, both protocols satisfy the second characteristic of research, since they involve systematic collection and investigation of treatment results, side effects, adverse events, serum levels and other patient data, which are used to contribute to knowledge about leukemia treatment. However, these data are also used for adapting and improving therapy for individual patients treated according to these protocols.

3. Research potentially presents less net clinical benefit and greater overall risk than clinical practice

In this section we analyze two aspects of ALL-10 and ALL-11 treatment that are of importance when considering the risks and expected benefits. First, therapy in both ALL-10 and ALL-11 is tailored to the risk of relapse. This means that patients who are at high risk of relapse and with a poor prognosis receive more intensive therapy than the ones with better prognoses. Second, irradiation of High Risk patients who receive a stem cell transplant is omitted from the ALL-11 protocol.

Tailoring of therapy

In ALL-10, patients are stratified into three risk groups: Standard Risk (SR), Medium Risk (MR) and High Risk (HR). This classification is primarily based on response to chemotherapy, most importantly the amount of residual leukemia cells that can be detected with molecular techniques at different times during treatment, the so-called Minimal Residual Disease (MRD). ALL-10 is the first Dutch ALL-protocol to make use of these new molecular techniques and MRD levels to stratify patients. Several studies have shown the clinical relevance of the detection of very low numbers of residual leukemic cells.(21) A landmark study by Van Dongen et al. has demonstrated that MRD levels can distinguish 'patients with good prognoses from those with poor prognoses, and this helps in decisions whether and how to modify treatment'.(22) Thus, risk group stratification is used to determine intensity of treatment.

For children in the Standard Risk group the treatment had been reduced compared to previous protocols in order to decrease the burden of the treatment while maintaining survival rates of more than 90%. Lowering the intensity of treatment could have enormous benefits for the patients, in terms of fewer or less severe side effects and a decrease in late effects of treatment when children mature. Improving quality of life for cancer survivors is an important aspect of current anti-cancer therapy.(23) The ALL-10 treatment strategy for Standard Risk patients turned out to be quite successful: survival rates for this group of patients were very high (>95%) without additional risk of relapse.

Patients in the Medium Risk group and the High Risk group received a much more intensive chemotherapy regimen than Standard Risk group patients and patients from previous ALL-protocols. This intensification of treatment could mean great advantages in survival.(24) However, since cancer drugs are toxic medications, more severe side effects were likely to occur in patients in the MR and HR groups, while it was uncertain whether the goal of increased survival rates would be achieved.

During the course of the ALL-10 protocol it was noticed that toxicity was severe, especially for patients with Down syndrome, leading to a relatively high number of deaths due to side effects. Therefore, a part of the treatment regimen was made less intensive to decrease treatment-related adverse events. These changes are maintained in ALL-11. Although the exact magnitude of the toxicity for patients was unexpected, severe toxicity in patients with Down syndrome had been previously reported. Increased sensitivity of patients with Down syndrome to some chemotherapeutic agents (especially methotrexate) had already been shown in 1987 (25) and is currently a well confirmed attribute of this group of patients.(26)

Summarizing, risk group stratification by Minimal Residual Disease levels and the subsequent intensification of treatment, although based on a variety of international studies, was a novel approach in the Netherlands when implemented at the start of ALL-10. Therefore, the level of the risks of this new approach was mostly unknown and could be expected to be considerable. Hence, the ALL-10 protocol satisfies the third characteristic of research. The treatment regimen of ALL-11 is closely based on ALL-10, which means that during the development of the ALL-11 protocol, interim results on the effectiveness of increasing therapy and appropriate dosage of medications were available. However, data from one study are not sufficient to provide conclusive evidence. Consequently, the risks and uncertainties of benefits of the treatment intensification seem to indicate that the third characteristic of research also applies to ALL-11. To further assess the validity of this conclusion, we describe another aspect of the ALL-11 protocol that involves uncertainty about risks and benefits.

Total Body Irradiation

In ALL-10, Total Body Irradiation (TBI) is used to prepare High Risk patients for Stem Cell Transplantation (the conditioning regimen). Due to the risks of several severe side effects, TBI is omitted from ALL-11 and a conditioning regimen of three different chemotherapeutic agents is introduced instead. In order to assess whether omission of TBI is a safe option, the non-inferiority of this conditioning regimen is monitored during the progress of ALL-11.

The ALL-11 protocol reviews several studies investigating the risks and benefits of different drugs compared to TBI. The protocol concludes that a regimen using a busulfan, fludarabin and clofarabin regimen can safely replace the TBI regimen, but data on its efficacy and the long-term side effects are lacking. Moreover, recent data suggest that regimens including TBI might even be preferred over regimens with chemotherapeutic drugs alone. A 2011 review comparing a regimen with TBI and one chemotherapeutic agent to a regimen with two chemotherapeutic agents

states that ‘there is conflicting data on the superiority of one regimen over the other’. (27) The review shows that the regimen that includes TBI is favored over the other regimen. Also, another study of TBI concludes that ‘conditioning for bone marrow transplantation without radiation is an attractive option, but is not sufficiently effective to completely replace TBI for the most common pediatric indications’.(28)

Thus, the studies discussed in the ALL-11 protocol give conflicting answers on the optimal conditioning regimen of HR patients prior to receiving Stem Cell Transplantation. At the moment of implementation of the ALL-11 protocol it was not clear whether TBI could be safely replaced by a chemotherapy conditioning regimen. Omission of TBI in ALL-11 is associated with several uncertainties regarding the risks and benefits, which satisfies the third characteristic of research.

4. Research introduces burdens or risks from activities that are not otherwise part of patient care

The ALL-10 and ALL-11 protocols include several research studies that are not part of the treatment of patients, which are reviewed by a Research Ethics Committee, and for which written informed consent is required from parents and, if applicable, patients themselves.

For the additional studies of the ALL-10 protocol, extra blood needs to be drawn, which is generally done during regular blood draws needed for diagnosis and treatment decisions. In addition, patients are requested to collect some buccal tissue using a cotton swab (five times). Furthermore, parents and adolescents are asked to keep a diary during the course of the treatment, to note fever and infection occurrences.

Also, for the ALL-11 research studies, extra blood needs to be drawn, generally during regular blood draw times. In addition, it may be necessary for patients to remain in the hospital 2-4 hours longer in order to administer blood compounds. Buccal tissue needs to be collected for one research question.

As we have already explained, the ALL-11 protocol includes two randomizations. The PEG-Asparaginase randomization does not involve any additional burdens or risks, since no extra interventions have to be performed. The immunoglobulin randomization involves the collection of extra blood during regular blood draws every six weeks. In addition, parents are asked to register on a website to record whether their child had a fever and whether the child had to be admitted to the hospital due to fever.

To summarize, both protocols involve extra research questions, which pose some additional risks and burdens upon patients and parents. The extra time investment or collection of tissue related to answering research questions would otherwise not have been necessary for the treatment of patients. Hence, both ALL-10 and ALL-11 exhibit this fourth characteristic of research.

5. Research uses protocols to dictate which therapeutic or diagnostic interventions a patient receives

The majority of pediatric oncology treatments are given according to detailed protocols regardless of their categorization as research or treatment.(29) The same holds for the ALL-protocols. Both ALL-10 and ALL-11 are protocols that describe in detail which medications should be given to patients at which phase of treatment. The treatment laid down in these protocols is based on up-to-date evidence provided by medical scientific research and clinical trials, both on adults and children. This evidence is collectively assessed and discussed extensively within the pediatric oncology community. Therefore, even when no decisive evidence is available at the moment of implementation of new protocols, a variety of sources are employed to determine next steps in treatment in order to provide optimal therapy to current patients and to further increase survival percentages.

Studies have shown that the use of strict and extensive treatment protocols improves the end result of that treatment. In the 1990's Bleyer already recognized the benefits of treatment according to protocols.(30) De Vries and colleagues note that this benefit 'would be due to the explicit description of treatment phases and follow-up and to strict guidelines indicating how to deal with side effects and relapses'.(5)

Providing treatment according to such detailed protocols does not mean that these protocols are followed blindly. Since all patients are closely monitored, the treating pediatric oncologist can, usually after consulting colleagues, decide to make individual adaptations on the basis of treatment results or side effects. So, although these pre-established protocols in principle determine treatment, patient care can be individualized.

In short, ALL-10 and ALL-11 provide treatment to patients according to well-defined and extensive protocols and thereby satisfy the fifth characteristic of research. However, protocol-controlled treatment is very common in pediatric oncology and has been shown to be beneficial to individual patients. Also, if medically indicated, patients can receive individualized care adapted to their needs. Hence, following strict protocol guidelines simultaneously serves a scientific purpose and the individual treatment needs of patients.

Summary

The two ALL-protocols meet all five characteristics that are generally used to distinguish research from care. Both protocols are designed to develop and to contribute to generalizable knowledge; employ systematic investigation of collected data; have uncertainties with regard to the level of risks and benefits; introduce burdens or risks from activities that are not otherwise part of patient care; and make use of strictly defined protocols to determine treatment. However, three of these characteristics seem compatible with a characteristic of standard treatment as well. First, in addition to the scientific objective, both protocols also involve the goal of

providing state-of-the-art treatment for current patients. The treatment regimens of the ALL-protocols are based on national and international scientific studies and consensus within the Dutch pediatric oncology community. Second, patients who receive treatment according to ALL-11 stand to benefit from the systematic data collection, most notably from the Asparaginase drug monitoring program. Third, treatment according to strict protocols has been shown to improve their results compared to treatment determined by individual physicians and is therefore also beneficial to patients. Thus, the two ALL-protocols do not seem to fall neatly into one of the two categories of research and treatment. Yet, from a traditional bioethical perspective, we have to conclude that both protocols deserved to be categorized as research, mainly due to the relative uncertainty with regard to the level of risks and benefits.

Discussion

Within the current ethical framework we can only conclude that the correct course of action should have been to regard the ALL-10 protocol as a research protocol with appropriate research ethics review. The reasons are the relatively uncertain level of risks associated with the innovative elements of the treatment regimen and the explicit scientific goal of evaluating this new treatment regimen.

However, if we regard ALL-10 as research, then the question arises, in what respect would research ethics review have improved the protection of patients being treated according to the ALL-10 regimen? Although more stringent regulatory requirements would have been applicable, such as national legislation (31) and European regulations,(18;32-34) these would not have added measures that had not already been taken. Monitoring of patients was quite extensive, a Data Safety Monitoring Board was installed, and a protocol for reporting serious adverse events (SAEs) and adverse events (AEs) was in place. Determining that the ALL-protocol was a research protocol would not have improved the monitoring. Also, because of the strict monitoring, the treatment regimen of the protocol could be adapted for subgroups of patients in case of multiple SAEs. Hence, even if the protocol had been considered research and had been submitted to the REC concerned as a research protocol, this would most likely not have improved the protection of patients from harm.

Another way in which categorization as a research protocol could provide an extra safeguard for patients, is the requirement of an elaborate informed consent process, finalized by signing the informed consent document. Generally, written informed consent is required only for medical research, while presumed or oral consent is acceptable for treatment.(35) In the case of ALL-10, parents and older patients had already been asked to provide written informed consent for receiving treatment according to the protocol. However, one could argue that the categorization of a certain activity, that is, as research or standard treatment, could alter the informed consent process, because it has an impact on the mind set of pediatric oncologists: categorizing a certain activity as research implies uncertainties, while a standard treatment label implies that the risks and benefits are relatively well known and

proportionate. Since a label is never neutral, this might influence the way physicians present the information with respect to a certain protocol. As such, the 'standard treatment' label of the ALL-10 protocol from our case could have influenced the way pediatric oncologists presented this protocol to parents and patients, possibly making pediatric oncologists less sensitive to conveying uncertainties. Parents and patients should have been informed of all the relevant aspects of the ALL-10 protocol, including the experimental nature of elements of the treatment regimen, to enable them to provide valid informed consent.(36) Consequently, if the ALL-10 protocol had been considered a research protocol this might have improved the informed consent process.

Furthermore, if the protocol had been regarded as research, patients and their parents should have been given the choice whether or not to participate. In theory, patients or their parents might have asked for the treatment regimen of a previous protocol. Some parents and adolescents might have favored more established therapy for which survival rates and side effects had already been evaluated. However, for pediatric oncologists it would be unthinkable to offer an older protocol as well, since they commonly believe it is unethical to withhold a certain treatment from patients if the entire pediatric oncology community regards it as best available treatment. As soon as a new protocol is implemented, the previous protocol is considered outdated. They will always prefer offering the treatment regimen of the new protocol to offering the treatment of a previous protocol. For pediatric oncologists offering something other than the ALL-10 protocol does not amount to a meaningful choice. Rather, it would mean delivering suboptimal care in order to give patients and parents freedom of choice.

With regard to the ALL-11 protocol, we believe that it was not solely its two randomizations that should have led to its categorization as research. There was also considerable uncertainty about the merits of omission of Total Body Irradiation as a conditioning regimen for patients who have to undergo Stem Cell Transplantation. Although good reasons support the omission of TBI, especially the severity of its side effects, data on the comparative risks and benefits of Total Body Irradiation and a chemotherapy regimen are uncertain. Normally, a reasonable option would have been to design a randomization to compare the different kinds of conditioning regimens. However, due to the relatively low number of HR patients who receive a Stem Cell Transplantation, conducting a randomization was impossible. Hence, the decision of Dutch pediatric oncologists to leave TBI out of the conditioning regimen is understandable. Still, we argue that decisions to alter a part of a treatment regimen for which the evidence is non-conclusive calls for categorization as research, since it will demonstrate the relative uncertainty accompanying the decision to leave out TBI.

In the current research ethics paradigm, with its strict distinction between research and care, both ALL-protocols should be regarded as research. However, in the future it remains to be discussed how to review hybrid protocols that integrate a research goal with the objective of simultaneously providing patients with best current

treatment. In line with Kass and colleagues we think that a change in both research ethics regulation and oversight of conventional care is needed. We should strive for a research oversight system that is able to do at least two things. First, it should accommodate hybrid protocols and other practices that integrate research with care. This system may call for a different manner of review and may have implications for the informed consent process when research and care turn out to be inseparable. Second, ethically, interventions that are considered standard of care should also be reviewed, due to the absence of available data on safety and effectiveness.

The initial scope of our findings is modest, since we have only discussed two protocols for the treatment of ALL in the Netherlands. However, ALL is the most common form of cancer in children.(20;37) Also, combining research and care is standard practice in international pediatric oncology,(5) which means that protocols such as those for the treatment of ALL are not unique and our findings are potentially generalizable. Additional case studies could help to determine whether the distinction between research and care in pediatric oncology should be upheld.

Conclusion

Even though research and treatment are being combined for the benefit of the individual and groups of patients, both ALL-protocols should now be regarded as research protocols since they satisfy five characteristics of research. Yet, in the future it remains to be discussed how to review hybrid protocols that integrate a research goal with the objective of providing individual patients with best current treatment. A change in both research ethics regulation and oversight of conventional care is needed. Further case studies are essential to deepen the moral evaluation of the intertwinement of research and care in pediatric oncology.

Figure 1: Comparison of the DCOG ALL-10 and ALL-11 protocols

Similarities between DOCG ALL-10 and ALL-11

- Protocols for the treatment of Acute Lymphoblastic Leukemia (ALL)
- Both conducted by the Dutch Childhood Oncology Group (DCOG)
- Children aged 1-19 years old
- With newly diagnosed ALL
- Treatment determined by detailed protocols
- Three risk groups based on initial response to therapy (Minimal Residual Disease (MRD) levels)
  - Standard Risk (SR)
  - Medium Risk (MR)
  - High Risk (HR)
- Intensity of treatment based on risk group (i.e., prognosis)
  - Decrease in therapy for SR patients
  - Increase in therapy for MR and HR patients
- Three phases of treatment
  - Induction (Protocols IA, IB and M)
  - Intensification (SR → protocol IV, MR → intensification 1 and 2, HR → 6 HR blocks or 3 HR blocks and Stem Cell Transplantation)
  - Maintenance
- Use of the same variety of chemotherapeutic agents

Differences between ALL-10 and ALL-11

ALL-10	ALL-11
◆ Single-arm treatment protocol	◆ National multicenter open-label randomized clinical trial (Phase III)
◆ No randomizations	◆ Two randomizations: ◆ Continuous vs. non-continuous dosage of PEG-Asparaginase ◆ Prophylactic administration of immunoglobulins
◆ Inclusion from 2004 to 2012, 780 patients included	◆ Inclusion from 2012 to 2018, 630 patients expected
◆ *E. coli* Asparaginase in induction	◆ PEG-Asparaginase in induction
◆ Same treatment for patients with Down syndrome	◆ Different treatment for patients with Down syndrome
◆ Standard dose of PEG-Asparaginase	◆ Lowered starting dose and individualized dosage of PEG-Asparaginase based on drug monitoring program
◆ Total Body Irradiation for HR patients who receive Stem Cell Transplantation	◆ No Total Body Irradiation for HR patients who receive Stem Cell Transplantation (chemotherapy instead)

References

1. Brody H, Miller FG. The clinician-investigator. Unavoidable but manageable tension. Kennedy Institute of Ethics Journal 2003;13(4):329-46.
2. Weijer C, Miller PB. Therapeutic obligation in clinical research. Hastings Cent Rep 2003;33(3):19-28.
3. Beauchamp TL. Viewpoint: why our conceptions of research and practice may not serve the best interest of patients and subjects. J Intern Med 2011 Apr;269(4):383-7.
4. Largent EA, Joffe S, Miller FG. Can research and care be ethically integrated? Hastings Cent Rep 2011 Jul;41(4):37-46.
5. de Vries MC, Houtlosser M, Wit JM, Engberts DP, Bresters D, Kaspers GJ, et al. Ethical issues at the interface of clinical care and research practice in pediatric oncology: a narrative review of parents' and physicians' experiences. BMC Med Ethics 2011;12:18.
6. Krueger G. Hope and suffering Children, cancer and the paradox of experimental medicine. Johns Hopkins University Press; 2008.
7. 't Jong GW, Vulto AG, de Hoog M, Schimmel KJ, Tibboel D, van den Anker JN. Unapproved and off-label use of drugs in a children's hospital. N Engl J Med 2000 Oct 12;343(15):1125.
8. Lindell-Osuagwu L, Korhonen MJ, Saano S, Helin-Tanninen M, Naaranlahti T, Kokki H. Off-label and unlicensed drug prescribing in three paediatric wards in Finland and review of the international literature. J Clin Pharm Ther 2009 Jun;34(3):277-87.
9. Kimland E, Nydert P, Odlind V, Bottiger Y, Lindemalm S. Paediatric drug use with focus on off-label prescriptions at Swedish hospitals - a nationwide study. Acta Paediatr 2012 Jul;101(7):772-8.
10. Pandolfini C, Bonati M. A literature review on off-label drug use in children. Eur J Pediatr 2005 Sep;164(9):552-8.
11. Conroy S, Newman C, Gudka S. Unlicensed and off label drug use in acute lymphoblastic leukaemia and other malignancies in children. Ann Oncol 2003 Jan;14(1):42-7.
12. van den Berg H, Tak N. Licensing and labelling of drugs in a paediatric oncology ward. Br J Clin Pharmacol 2011 Sep;72(3):474-81.
13. Ablett S, Pinkerton CR. Recruiting children into cancer trials--role of the United Kingdom Children's Cancer Study Group (UKCCSG). Br J Cancer 2003 Jun 2;88(11):1661-5.
14. Joffe S, Weeks JC. Views of American oncologists about the purposes of clinical trials. J Natl Cancer Inst 2002 Dec 18;94(24):1847-53.
15. Kass NE, Faden RR, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. The research-treatment distinction: a problematic approach for determining which activities should have ethical oversight. Hastings Cent Rep 2013 Jan;Spec No:S4-S15.
16. 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. 1978.
17. Council for International Organizations of Medical Sciences (CIOMS). International Ethical Guidelines for Biomedical Research involving Human Subjects. 2002.
18. Council of Europe. Convention on Human Rights and Biomedicine (Oviedo Convention), Additional Protocol concerning Biomedical Research. 2005 Jan 25.
19. Van Thiel GJMW, Van Delden JJM. Reflective Equilibrium as a Normative Empirical Model. Ethical Perspectives 2010;17(2):183-202.
20. Pieters R. [Acute lymphoblastic leukaemia in children and adolescents: chance of cure now higher than 80%]. Ned Tijdschr Geneeskd 2010;154:A1577.
21. Szczepanski T, Orfao A, van dV, V, San Miguel JF, van Dongen JJ. Minimal residual disease in leukaemia patients. Lancet Oncol 2001 Jul;2(7):409-17.
22. van Dongen JJ, Seriu T, Panzer-Grumayer ER, Biondi A, Pongers-Willemse MJ, Corral L, et al. Prognostic value of minimal residual disease in acute lymphoblastic leukaemia in childhood. Lancet 1998 Nov 28;352(9142):1731-8.
23. SKION Later richtlijn follow up na kinderkanker. ZonMw; 2010.

24. Nachman JB, Sather HN, Sensel MG, Trigg ME, Cherlow JM, Lukens JN, et al. Augmented post-induction therapy for children with high-risk acute lymphoblastic leukemia and a slow response to initial therapy. N Engl J Med 1998 Jun 4;338(23):1663-71.
25. Whitlock JA. Down syndrome and acute lymphoblastic leukaemia. Br J Haematol 2006 Dec;135(5):595-602.
26. Peeters M, Poon A. Down syndrome and leukemia: unusual clinical aspects and unexpected methotrexate sensitivity. Eur J Pediatr 1987 Jul;146(4):416-22.
27. Gupta T, Kannan S, Dantkale V, Laskar S. Cyclophosphamide plus total body irradiation compared with busulfan plus cyclophosphamide as a conditioning regimen prior to hematopoietic stem cell transplantation in patients with leukemia: a systematic review and meta-analysis. Hematol Oncol Stem Cell Ther 2011;4(1):17-29.
28. Linsenmeier C, Thoennessen D, Negretti L, Bourquin JP, Streller T, Lutolf UM, et al. Total body irradiation (TBI) in pediatric patients. A single-center experience after 30 years of low-dose rate irradiation. Strahlenther Onkol 2010 Nov;186(11):614-20.
29. Verschuur AC. De plaats van klinische trials in de kinderoncologie. Nederlands tijdschrift voor de oncologie 2004;(1):-30.
30. Bleyer WA. The U.S. pediatric cancer clinical trials programmes: international implications and the way forward. Eur J Cancer 1997 Aug;33(9):1439-47.
31. Dutch Medical Research involving Human Beings Act, 2006.
32. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001.
33. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006.
34. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014.
35. Grady C. Ethical issues in clinical trials. Semin Oncol Nurs 1991 Nov;7(4):288-96.
36. Informed consent, parental permission, and assent in pediatric practice. Committee on Bioethics, American Academy of Pediatrics. Pediatrics 1995 Feb;95(2):314-7.
37. Stiller C. Incidence of childhood leukaemia. 2009. World Health Organization Europe Region.

7

Pediatric oncology as a Learning Health care System: ethical implications of best available treatment protocols

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Abstract

Pediatric oncology is often considered as a textbook example of a so-called Learning Health care System (LHS), a system in which research is considered an important means to continuously improve the practice of care. Thus far, it has not been studied in what respect pediatric oncology can be seen as an LHS and if so, what the implications of this characterization are, in particular for review and consent procedures in this system.

We found that pediatric oncology can indeed be characterized as an LHS. In particular so-called 'best available treatment protocols' neatly integrate research and care activities. These hybrid protocols always contain research elements, even if the main goal of these protocols is to treat children diagnosed with cancer.

As long as oversight systems do not sufficiently embed hybrid protocols, it seems best to qualify these studies as research. This classification will prevent that research elements in treatment protocols will be overlooked and will ensure that patients understand the research components. In theory, however, risk-adapted approaches may be adopted in order to determine the level of review needed. And scientific citizenship may be stimulated in order to engage patients in a process in which research and care are inextricably intertwined.

Introduction

Pediatric oncology is often considered as a textbook example of a so-called Learning Health care System (LHS),(1;2) a system in which research is embedded in the practice of care to ensure 'the best evidence for the collaborative health care choices of each patient and provider' and 'innovation, quality, safety, and value in health care'.(3) The LHS starts from the presumption that the practices of research and care are no longer sharply distinct.(1;3;4) In an LHS, both research and care activities aim to yield generalizable knowledge, are systematically performed, subject patients to procedures and interventions that are not (only) in their own interests which also may entail high risks, and assign treatments according to protocols.(4) Giving up the distinction has implications for review and for informed consent procedures, since traditionally research practices have been subject to more stringent (inter)national laws and regulations than other medical learning activities involving human beings, such as quality improvement studies.(1;4;5) Although the implications of the LHS have been widely discussed in the field of pragmatic trials, it has received little attention what actually constitutes the integration of care and research in other learning activities, like in pediatric oncology.(6) In this chapter, we argue that in particular so-called best available treatment protocols seem to contribute to the idea of pediatric oncology as an LHS,(7) and we consider the implications for review and consent of these protocols.

Pediatric oncology as an LHS

There are at least two reasons why pediatric oncology can be characterized as an LHS. First, research is considered as a fundamental aspect of pediatric oncology. Pediatric oncologists have a strong drive to advance their field and improve the survival chances of children with cancer, leading to a mindset of continuous learning from current practice.(8;9) In addition, parents and (older) children are highly motivated to help to improve the diagnosis and treatment of childhood cancer in general.(6)

A second reason is that research and care in pediatric oncology appear to be closely intertwined. First, in many countries children with cancer are registered in cooperative group databases and/or in national cancer registries. These databases may be used for epidemiological studies and for selecting disease groups where improvements are needed, followed by guideline development and evaluation.(10) Second, for many cancers children will be treated according to a so-called best available treatment protocol.(6) Best available treatment protocols provide children with the best currently available treatment, which is usually an optimized version of the previous treatment regimen.(11) The protocols are developed based on data collection, experience and (inter)national consensus among pediatric oncologists.(11) Apart from best available treatment protocols for many diseases there are collaborative group or international (e.g. European or even TransAtlantic) phase III studies, and sometimes also open phase I/II studies. Children with cancer often participate in more than one of these studies, for instance because they experience

a relapse or because they also participate in intervention studies in supportive care, on psycho-social interventions and the like. Finally, children often participate in studies that are “added” to best available treatment protocols or phase I-III studies. These “add-on” studies run from laboratory studies with left over tumor material to biomarker development or implementation of new radiological techniques.(6;8)

Thus, the enormous drive to improve the field and the high rate of research participation may turn pediatric oncology into an LHS. Yet, despite their close intertwinement, in many of these cases research and care practices can be distinguished. For instance, data-collection and supportive care studies are usually experienced as research.(6) But the lines between research and care are blurred in best available treatment protocols.(7) We think that in particular the integration of care and research in best available treatment protocols turns pediatric oncology into an LHS.

Best available treatment protocols and the LHS

In general, best available treatment protocols not only prescribe how childhood cancers ought to be treated, but also include data-collection regarding diagnosis, risk-group stratification, treatment and outcome in order to improve the survival of present and future children with cancer.(7) The protocol may also involve centralized pathology or radiology review. Since the new treatment protocol is established on the basis of prior experience and (inter)national consensus, but not (always) on conclusive evidence (for example from randomized controlled trials), pediatric oncologists typically use data-collection methods and for instance early stopping rules to secure the safety and efficacy of the patients enrolled in the new treatment protocol. Data-collection in subsequent single-arm studies rather than conclusive evidence in the form of randomized trials is also inevitable in some childhood cancers given their rarity. But it is not merely the data collection related to these treatment protocols that makes them subject to research. It is also, or perhaps in particular, the uncertainty over the relative merits of the current intervention that is considered the standard of care. To a certain extent, this uncertainty is underemphasized since pediatric oncologists consider the previous protocol as outdated and no longer as the best current treatment once a new protocol has been developed.(7) There is often a strong belief that the treatment recommended in the latest version of the ‘best available treatment’ protocol should not be withheld from children, since it is considered the best available medical alternative. There are however examples where this in hindsight did not appear to be the case. For instance the Dutch Childhood Oncology Group (DCOG) Acute Lymphoblastic Leukemia (ALL)- 7 protocol resulted in worse outcome compared to the BFM-study it was based upon and was stopped prematurely.(12)

Review

Ethical review of best available treatment protocols currently depends on its categorization. If the protocol is labeled as care the protocol is exempted from review, if it is labeled as research it is subjected to review. Some protocols will clearly be classified as research, when considerable uncertainty about the relative merits of a new intervention exists.(13) However, in other situations a protocol may be classified as care, while certain elements of the protocol would arguably demand ethical review. An example is the DCOG ALL-10 protocol. This protocol for the treatment of children with acute lymphoblastic leukemia was discussed in the previous chapter. (7)

The ALL-10 protocol contained a significant modification compared with previous ALL protocols. The therapy for patients in ALL-10 was tailored to a risk stratification that had not been part of previous protocols. This tailored therapy meant that Standard Risk patients received less intensive therapy than in the previous protocol, whereas for Medium and High Risk patients the intensity of chemotherapy was significantly increased. Although it was expected, based on a variety of smaller studies, that these changes would improve outcomes for patients, there was still a considerable level of uncertainty.(7) The researchers submitted their protocol to a Research Ethics Committee which decided that the protocol was not research since children were not subjected to experimental procedures. We argued that the introduction of risk stratification and accordingly tailored treatment regimen might have been a reason to consider the protocol as subjected to ethical review that is common for research. (7)

Classification of best available treatment protocols thus apparently varies. But even if we were able to label these protocols in a more uniform way, applying one label is a sheer impossibility, since protocols are not merely research or care. We argue that to determine the level of review needed, an analysis of the protocol in research and care elements is important. Then, the risks associated with the research elements could be identified in order to be able to determine whether and which level of review is essential.(14) Although this risk-adaptive review approach also requires that research elements - meaning those elements that are designed to develop generalizable health knowledge by means of a systematic investigation - are more carefully scrutinized it is no longer a single label (for the whole protocol) that determines whether review is needed. This approach to hybrid protocols may prevent both that research elements with more than minimal risks are overlooked and that the interests of patients are overprotected when the risks are minimal and the protocol is predominantly care orientated.

But since current ethical guidelines and oversight systems for human subjects research do not accommodate for hybrid protocols, it may be best to classify them as research protocols and to submit them to RECs, provided that RECs are in the position to evaluate the status of these protocols. RECs could then still decide to adopt a risk-adapted approach, for example by applying less stringent rules for

ethical review of these protocols if risks are minimal. For example, we may think of some best available treatment protocols as so-called low-intervention trials as defined in the new EU regulation.(15) Low-intervention trials may be subjected to 'less stringent rules, as regards monitoring, requirements for the contents of the master file and traceability of investigational medicinal products'.(15) In order to assist RECs, a revised version of the EU regulation may introduce the label 'best available treatment protocols' and compare it to the exceptions in this regulation for low-intervention trials, which would be a first step in the recognition of these hybrid protocols.

Informed consent

Another ethical challenge is the informed consent process for hybrid protocols. First, children and their parents cannot meaningfully opt out of best available treatment protocols. Physicians are usually reluctant to provide patients with the treatment of the previous protocol as it is considered outdated.(7) Although many jurisdictions in general will allow children and their parents to refuse treatment, patients cannot refuse the research component since this is an inherent aspect of the protocol. In other words, voluntary informed consent for these protocols is compromised.(16)

Second, when a best available treatment protocol is classified as care, it may not be immediately clear to parents and their children that the protocol contains research elements. If it is classified as research, it is problematic that consent for the standard treatment is formulated through the lens of a research perspective. Then elements of care may be underemphasized. Thus, the hybrid status of these protocols may influence the way in which these protocols are understood.

Compromises to voluntary informed consent cannot be easily mitigated. But they may be considered as acceptable, when the social value of the research is compelling, and the study is the best available medical alternative for the child.

But the level of understanding of best available treatment protocols can be improved. If there were regulatory oversight for hybrid protocols, physicians might use an integrated form of consent.(17) They might explain that on the one hand the treatment is considered the best available alternative according to the medical professional standard, but on the other hand may be relatively uncertain. In the same vein, a form of "scientific citizenship"(18) might be warranted: in order to foster the autonomy of parents and their children they should be informed about the pervasiveness of research and its sometimes inextricable link with care. It has been argued that patients in an LHS should sometimes accept that they participate in widely accepted research activities without their explicit informed consent.(4) Instead, we think that scientific citizenship would require that patients are meaningfully engaged, so that researchers and patients recognize that they collectively generate knowledge to improve the field.

However, since in the current oversight paradigm the safest option is to regard these protocols as research, and hence to ask individual informed consent from a research perspective. Not an ideal solution, since it denies the hybrid nature of these protocols.

Conclusion

Best available treatment protocols are at the core of pediatric oncology as a Learning Health care System. We will have to find new ways to accommodate for the oversight of best available treatment protocols that neatly integrate research and care. As long as existing ethical and legal oversight systems do not sufficiently embed hybrid protocols, it seems best to qualify these studies as research in order to prevent that research elements in treatment protocols will be overlooked. In theory, however, whether these protocols need ethical review will depend on the risks associated with their research elements. When the risks of best available treatment protocols are low and the protocols predominantly focus on the treatment of patients, one may argue that these protocols can be exempted from review or at least be subject to less stringent regulation as is the case for low-intervention trials.

In most jurisdictions informed consent for hybrid protocols will also hinge on the classification of research and care. If protocols are seen as care protocols, parents and children may give informed consent for treatment rather than for a study. But since research elements are embedded in the treatment of patients, even in protocols that are predominantly care-orientated, oversight systems may want to accommodate for protocols that meaningfully engage patients and to require transparency about the sometimes inextricable intertwinement of research and care in pediatric oncology.

References

1. Kass NE, Faden RR, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. The research-treatment distinction: a problematic approach for determining which activities should have ethical oversight. Hastings Cent Rep 2013 Jan;Spec No:S4-S15.
2. Largent EA, Joffe S, Miller FG. Can research and care be ethically integrated? Hastings Cent Rep 2011 Jul;41(4):37-46.
3. Institute of Medicine, IOM Roundtable on Evidence-Based Medicine, the Learning Health care System. Washington DC: National Academies Press (US); 2007.
4. Faden RR, Kass NE, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. An ethics framework for a learning health care system: a departure from traditional research ethics and clinical ethics. Hastings Cent Rep 2013 Jan;Spec No:S16-S27.
5. World Medical Association. World Medical Association's Declaration of Helsinki. 2013 Oct.
6. Dekking SA, van der Graaf R, Kars MC, Beishuizen A, de Vries MC, van Delden JJ. Balancing research interests and patient interests: a qualitative study into the intertwinement of care and research in paediatric oncology. Pediatr Blood Cancer 2015 May;62(5):816-22.
7. Dekking SA, van der Graaf R, de Vries MC, Bierings MB, van Delden JJ, Kodish E, et al. Is a New Protocol for Acute Lymphoblastic Leukemia Research or Standard Therapy? Pediatrics 2015 Aug 17.
8. de Vries MC, Houtlosser M, Wit JM, Engberts DP, Bresters D, Kaspers GJ, et al. Ethical issues at the interface of clinical care and research practice in pediatric oncology: a narrative review of parents' and physicians' experiences. BMC Med Ethics 2011;12:18.
9. Unguru Y. The successful integration of research and care: how pediatric oncology became the subspecialty in which research defines the standard of care. Pediatr Blood Cancer 2011 Jul 1;56(7):1019-25.
10. Gatta G, Botta L, Rossi S, Aareleid T, Bielska-Lasota M, Clavel J, et al. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5--a population-based study. Lancet Oncol 2014 Jan;15(1):35-47.
11. Pritchard-Jones K. Clinical trials for children with cancer in Europe - still a long way from harmonisation: a report from SIOP Europe. Eur J Cancer 2008 Oct;44(15):2106-11.
12. Kamps WA, Bokkerink JP, Hahlen K, Hermans J, Riehm H, Gadner H, et al. Intensive treatment of children with acute lymphoblastic leukemia according to ALL-BFM-86 without cranial radiotherapy: results of Dutch Childhood Leukemia Study Group Protocol ALL-7 (1988-1991). Blood 1999 Aug 15;94(4):1226-36.
13. Buehrlen M, Zwaan CM, Granzen B, Lassay L, Deutz P, Vorwerk P, et al. Multimodal treatment, including interferon beta, of nasopharyngeal carcinoma in children and young adults: preliminary results from the prospective, multicenter study NPC-2003-GPOH/DCOG. Cancer 2012 Oct 1;118(19):4892-900.
14. Rid A. How should we regulate risk in biomedical research? An ethical analysis of recent policy proposals and initiatives. Health Policy 2014 Sep;117(3):409-20.
15. European Parliament CotEU. Regulation (EU) 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Official Journal of the European Union 2014 May 27;1-76.
16. Dekking SA, van der Graaf R, van Delden JJ. Voluntary Informed Consent in Paediatric Oncology Research. Bioethics 2015 Dec 21.
17. Kim SY, Miller FG. Informed consent for pragmatic trials--the integrated consent model. N Engl J Med 2014 Feb 20;370(8):769-72.
18. Giesbertz NA, Bredenoord AL, van Delden JJ. Inclusion of residual tissue in biobanks: opt-in or opt-out? PLoS Biol 2012;10(8):e1001373.

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Best available treatment protocols in pediatric oncology: recommendations for practice

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Abstract

Pediatric oncology is regarded as a practice where research and treatment are strongly intertwined. This integration of research and care holds in particular for treatments that are combined with research in best available treatment protocols. These 'hybrid' protocols provide the best currently available treatment, but also contain modifications to existing treatment regimens, of which the merits are systematically investigated. Since best available treatment protocols operate on the border between research and standard treatments, their moral status is complex. Their hybrid nature calls for ethical guidance based on the available literature, to be used by pediatric oncology physicians, investigators en Research Ethics Committees. We suggest three recommendations. First, pediatric oncologists should clarify that the research component of the protocol is an inherent part of receiving treatment. They should explain that best available treatment protocols combine treatment and scientific goals, and clarify what is novel or changed compared to the prior best available treatment. Second, despite the research component, it may be acceptable for the child's treating pediatric oncologist to obtain informed consent instead of an independent physician, because of the treatment context in which the protocols are offered. Third, pediatric oncology professionals should recognize that best available treatment protocols with research elements need ethical review. Research Ethics Committees should learn to discern this type of protocols as special cases, should be aware that treatment protocols may contain research elements, and should be prepared to review these protocols.

Research culture of pediatric oncology

From the beginning pediatric oncology has been characterized by a strong research culture.(1;2) The majority of children with cancer participate in clinical trials (estimations vary between 50% and 70%).(3;4) This systematic research culture has greatly improved the treatment for and survival chances of children with cancer.(5;6) A general sentiment exists that research is a joined enterprise and that all who are involved in pediatric oncology should strive to increase survival of children affected by cancer.(7) Most noticeable is that not only the pediatric oncology professionals, but also children with cancer themselves and their parents have an optimistic outlook on combining research with care. Although there exists some variability on families' attitudes towards research, both parents and patients are committed to the overall goal of improvements in the diagnosis and treatment of childhood cancer.(7-16)

Best available treatment protocols

Based on high inclusion rates of children with cancer in clinical trials, and the number of other types of (preclinical) studies that are conducted, pediatric oncology is considered as an example of a medical field where research and treatment are integrated.(17;18) In addition, research and care are also integrated in so-called best available treatment protocols. Although based on (inter)national expert opinion and on results from (pre)clinical studies, genuine uncertainty usually exists with respect to the specific merits due to changes that are made compared to the previous protocol. As such, these protocols are designed to simultaneously develop generalizable health knowledge for a group of pediatric cancer patients and to optimally treat individual patients.(8;19;20) These protocols can be regarded as 'hybrid protocols'. (20) They are often used in situations where numbers prohibit a more rigorous scientific approach such as a randomized controlled trial (RCT).

After the implementation of a new best available treatment protocol, the previous one is considered outdated and no longer offered to patients and their parents.(20) This situation implies that they do not have alternative treatment options to choose from besides the currently endorsed best available treatment protocol, which is inextricably linked to the conduct of research.

Since best available treatment protocols operate on the border between research and standard of care treatment, their moral status is complex due to the different objectives of research and care. Traditionally, care has been defined in light of its aim to benefit the individual patient, whereas research is designed to develop generalizable knowledge to benefit future groups of patients.(18;21) In order to provide ethical guidance for pediatric oncology professionals and Research Ethics Committees with respect to best available treatment protocols, we provide three recommendations.

1. Informed consent for best available treatment protocols

Recommendation 1: Pediatric oncologists should clarify to patients and their parents that in a best available treatment protocol the research component is an inherent part of receiving treatment. They should explain that although best available treatment protocols aim to provide the child with the best current treatment, they also aim to investigate whether modifications to previous treatment regimens improve survival of future patients.

Leading ethical guidelines and regulations for human subjects research demand that researchers explain to potential participants that participation in research is voluntary and that they always have the right to withdraw.(21-24) However, this requirement cannot pertain to best available treatment protocols to the same extent, as the research component and the treatment are inextricably linked. As we argued earlier, it is not possible to receive the treatment and decline the research component, which implies a compromise to the voluntariness of parental consent.(25)

Voluntariness of consent is compromised or undermined if there are controlling influences on a person's decision.(26) One type of potentially controlling influence is manipulation of available options, for example through controlling access to treatments.(26) In the case of best available treatment protocols, the pediatric oncology community alters the choice situation, as they develop a new protocol with an inherent research component which cannot be refused. In addition, it is decided that the previous treatment protocol is outdated and no longer offered as a treatment option. Therefore, best available treatment protocols constitute manipulation of options, and therefore qualify as a controlling influence on parental decision making. Consequently, voluntariness of consent for the research component is compromised. (25)

Although it does not seem possible to overcome this compromise to voluntariness of informed consent, there may be instances where it could be considered acceptable. That is, when the social value of the best available treatment protocol is compelling, and research is the best available medical alternative.(25;27) In this context, it is essential that parents understand the nature of a best available treatment protocol and the reason why the treatment their child will receive is connected with research. They should also understand that it is not possible for the child to receive treatment according to the previous best available treatment protocol, but that this is considered acceptable because the old protocol is regarded as outdated. To that end, pediatric oncologists should explain that patients will receive a treatment that on the one hand is considered the best available alternative according to the medical professional standard, but on the other hand may be relatively uncertain, because new elements are added that are thought to improve patient survival chances but haven't yet been proven to do so.(20;27)

2. Dependent relationships and best available treatment protocols

Recommendation 2: As a general rule, treating physicians should not obtain informed consent for research from their own patients, due to the potential influence of the dependent relationship on voluntariness. Since best available treatment protocols aim to provide patients with best current treatment, it may be acceptable that the child's treating physician obtains informed consent for the child's participation in these protocols.

In the treating relationship between patients and physicians there often exists a certain level of dependence on the side of the patient.(28) Therefore, both research ethics literature and ethical guidelines for research with human subjects demand that treating physicians should not obtain informed consent for research from their own patients, because this may negatively influence the voluntary nature of the patients' consent.(29-32) Instead, it is recommended that the informed consent procedure should be performed by someone who is independent of the treating relationship.(17) Most common is to have research nurses perform informed consent procedures.

In the case of best available treatment protocols the context is different than for more 'traditional' types of research, because despite the research component, this type of protocols aims to provide patients with a treatment that is considered the best available medical alternative.(27) In that respect, best available treatment protocols resemble the context of informed consent for care. Consequently, because the treating pediatric oncologist has optimal knowledge of the necessary cancer treatments, and will be the one to provide guidance and assistance throughout the treatment trajectory, it may acceptable that he or she provides information and includes own patients in the protocol. However, as a safeguard, it may be advisable that a research nurse, or equally qualified colleague, is present during the official moment of signing the informed consent form.(24)

3. Review of best available treatment protocols

Recommendation 3: Pediatric oncology professionals should recognize that best available treatment protocols with research elements need ethical review. Research Ethics Committee (REC) members should learn to discern this type of protocols as special cases, should be aware that treatment protocols may contain research elements, and should be prepared to review these protocols.

Since best available treatment protocols integrate research and treatment goals, it is difficult to categorize these protocols as either treatment or research.(20) Currently, most ethical oversight systems do not accommodate for best available treatment protocols, as these systems uphold a strict distinction between research and care. If the research elements of hybrid protocols, such as best available treatment protocols, are not recognized (either by the investigators themselves or by RECs), these protocols are easily classified as standard treatment.(20) In that case, best available treatment protocols do not receive (sufficient) ethical review, as different standards of review apply to treatment than to research protocols.(20) Usually, standard care does not receive any form of review at all.(18)

Since best available treatment protocols may involve elements that warrant ethical review, in the current oversight system it seems best to submit these protocols to RECs, due to the uncertainty about the merits of modifications made to previous protocols.(27) When current guidelines for human subjects research do not accommodate for these protocols, it is important that RECs recognize hybrid protocols as special cases and become aware that what they have traditionally considered as treatment protocols may contain research elements that demand ethical review. At the same time, best available treatment protocols that are predominantly care oriented and face minimal risks may resemble “low intervention trials” as defined by the new EU regulation on clinical trials on medicinal products for human use.(33) In a low intervention trial, two or more evidence-based drugs are being compared, with minimal risks and burdens for patients. Low-intervention trials may be subjected to less stringent rules, such as those on monitoring.

It should be noted that it will vary between countries what kind of authorizations and qualifications ethical committees have, and whether they are in the position to evaluate protocols that appear to mainly provide care.(27)

Discussion

We provided three recommendations that offer moral guidance concerning best available treatment protocols, both to pediatric oncology professionals and Research Ethics Committee members.

The first recommendation differs from common ideas on informed consent and the right to withdraw, as in our view the research component is not an optional part of the best available treatment protocol. Therefore, this type of protocols seems to compromise the voluntariness of parents' consent to the research component from the start. As we argued earlier,(25) the choice environment in which research is an inherent part of receiving treatment is created by the pediatric oncology community. Therefore, it constitutes a controlling influence on parental decision-making, undermining voluntary informed consent for research.

We argued however, that the compromise to voluntariness may be considered as acceptable if the social value of the research is compelling, and pediatric oncologists can justify that the treatment regimen of a protocol is the best available medical alternative. In addition, it is important to bear in mind that, although of considerable importance, voluntariness is not an absolute requirement for participation in research, for example for cluster randomized trials in which individuals within a cluster cannot meaningfully escape the intervention, such as fluoridation of drinking-water.(27;34)

At the same time, transparency about the nature of a best available treatment protocol provides clarity about goals and interests and may thereby enhance the 'understanding component of informed consent. With regard to pediatric oncologists, openly recognizing the dual objective of best available treatment protocols may positively affect their ability to explain and describe the treatment to patients and their parents.(35) Consequently, this enhanced explanation could support families in weighing and appreciating the risks and benefits of the protocol, and understand the background of the research component and why it is an inherent part of the child's treatment.

Our second recommendation is in contrast with existing ethical guidelines for research with human beings, as these generally demand that treating physicians do not obtain informed consent from their own patients to participate in medical research. As was mentioned before, it is assumed that if informed consent is obtained by the own physician, this could put undue pressure on patients to consent to research participation.(21-23) Contrary to these requirements, we suggest that it can be accepted that the treating pediatric oncologist explains a best available treatment protocol and obtains informed consent from parents. Since best available treatment protocols involve the main treatment for the child, the treating physician may be an appropriate partner for children and parents in the process of enrolment in a best available treatment protocol,(24) equal to other situations that involve treatment decisions.

The third and final recommendation is new, since current guidelines do not provide guidance for activities with a hybrid nature. As argued by Kass and colleagues,(18) the current research oversight system results both in overprotection and in under protection of patients. On the one hand, quality improvement initiatives with no additional risk are subjected to an elaborated review process because they are generally classified as research. On the other hand, risky procedures in the context of care are not subjected to ethical review, because they are considered standard treatments. In our (currently still theoretical) proposal, we tried to find a balance between these two undesirable side effects of the current processes of regulation. In a system that differentiates between different risk levels of best available treatment protocols, it is prevented that high risks of protocols are overlooked. Simultaneously, for low risk protocols that are predominantly care orientated, less stringent rules for ethical review can be applied. In such a system, pediatric oncology, and best available treatment protocols in particular, can be considered as a clear example of a Learning Health care System, in which research and care are integrated in order to optimally serve the interests of both current and future patients.(27;36)

Conclusion

Best available treatment protocols pose ethical challenges, as they comprise an integration of treatment and research goals. The three recommendations of our moral framework provide ethical guidance to pediatric oncology professionals and Research Ethics Committee members, concerning review and informed consent.

References

1. Krueger G. Hope and Suffering Children, Cancer and the Paradox of Experimental Medicine. Johns Hopkins University Press; 2008.
2. Unguru Y. The successful integration of research and care: how pediatric oncology became the subspecialty in which research defines the standard of care. Pediatr Blood Cancer 2011 Jul 1;56(7):1019-25.
3. Ablett S, Pinkerton CR. Recruiting children into cancer trials--role of the United Kingdom Children's Cancer Study Group (UKCCSG). Br J Cancer 2003 Jun 2;88(11):1661-5.
4. Bleyer WA. The U.S. pediatric cancer clinical trials programmes: international implications and the way forward. Eur J Cancer 1997 Aug;33(9):1439-47.
5. SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011, based on November 2013 SEER data submission, posted to the SEER website, April 2014. 2014.
6. Gatta G, Zigon G, Capocaccia R, Coebergh JW, Desandes E, Kaatsch P, et al. Survival of European children and young adults with cancer diagnosed 1995-2002. Eur J Cancer 2009 Apr;45(6):992-1005.
7. Dixon-Woods M, Wilson D, Jackson C, Cavers D, Pritchard-Jones K. Human Tissue and 'the Public': The Case of Childhood Cancer Tumour Banking. BioSocieties 2008;3:57-80.
8. Dekking SA, van der Graaf R, Kars MC, Beishuizen A, de Vries MC, van Delden JJ. Balancing research interests and patient interests: A qualitative study into the intertwinement of care and research in paediatric oncology. Pediatr Blood Cancer 2015 Mar 1.
9. Soto C, Tarrant C, Pritchard-Jones K, xon-Woods M. Consent to tissue banking for research: qualitative study and recommendations. Arch Dis Child 2012 Jul;97(7):632-6.
10. Berg SL, Winick N, Ingle AM, Adamson PC, Blaney SM. Reasons for participation in optional pharmacokinetic studies in children with cancer: a Children's Oncology Group phase 1 consortium study. Pediatr Blood Cancer 2010 Jul 15;55(1):119-22.
11. Eiser C, Davies H, Jenney M, Glaser A. Mothers' attitudes to the randomized controlled trial (RCT): the case of acute lymphoblastic leukaemia (ALL) in children. Child Care Health Dev 2005 Sep;31(5):517-23.
12. Levi RB, Marsick R, Drotar D, Kodish ED. Diagnosis, disclosure, and informed consent: learning from parents of children with cancer. J Pediatr Hematol Oncol 2000 Jan;22(1):3-12.
13. McMurter B, Parker L, Fraser RB, Magee JF, Kozancyzn C, Fernandez CV. Parental views on tissue banking in pediatric oncology patients. Pediatr Blood Cancer 2011 Dec 15;57(7):1217-21.
14. Read K, Fernandez CV, Gao J, Strahlendorf C, Moghrabi A, Pentz RD, et al. Decision-making by adolescents and parents of children with cancer regarding health research participation. Pediatrics 2009 Sep;124(3):959-65.
15. Stevens PE, Pletsch PK. Ethical issues of informed consent: mothers' experiences enrolling their children in bone marrow transplantation research. Cancer Nurs 2002 Apr;25(2):81-7.
16. Woodgate RL, Yanofsky RA. Parents' experiences in decision making with childhood cancer clinical trials. Cancer Nurs 2010 Jan;33(1):11-8.
17. de Vries MC, Houtlosser M, Wit JM, Engberts DP, Bresters D, Kaspers GJ, et al. Ethical issues at the interface of clinical care and research practice in pediatric oncology: a narrative review of parents' and physicians' experiences. BMC Med Ethics 2011;12:18.
18. Kass NE, Faden RR, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. The research-treatment distinction: a problematic approach for determining which activities should have ethical oversight. Hastings Cent Rep 2013 Jan;Spec No:S4-S15.
19. Pritchard-Jones K. Clinical trials for children with cancer in Europe - still a long way from harmonisation: a report from SIOP Europe. Eur J Cancer 2008 Oct;44(15):2106-11.
20. Dekking SA, van der Graaf R, de Vries MC, Bierings MB, van Delden JJ, Kodish E, et al. Is a New Protocol for Acute Lymphoblastic Leukemia Research or Standard Therapy? Pediatrics 2015 Aug 17.

21. 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. 1978.
22. Council for International Organizations of Medical Sciences (CIOMS). International Ethical Guidelines for Biomedical Research involving Human Subjects. 2002.
23. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013 Nov 27;310(20):2191-4.
24. Dekking SA, van der Graaf R, van Delden JJ. Strengths and weaknesses of guideline approaches to safeguard voluntary informed consent of patients within a dependent relationship. BMC Med 2014;12:52.
25. Dekking SA, van der Graaf R, van Delden JJ. Voluntary Informed Consent in Paediatric Oncology Research. Bioethics 2015 Dec 21.
26. Nelson RM, Beauchamp T, Miller VA, Reynolds W, Ittenbach RF, Luce MF. The concept of voluntary consent. Am J Bioeth 2011 Aug;11(8):6-16.
27. van der Graaf R, Dekking SA, de Vries MC, Zwaan CM, van Delden JJ. Pediatric oncology as a Learning Health care System: ethical implications of best available treatment protocols. submitted 2016.
28. Pellegrino ED. Toward a reconstruction of medical morality: the primacy of the act of profession and the fact of illness. J Med Philos 1979 Mar;4(1):32-56.
29. World Medical Association. World Medical Association's Declaration of Helsinki. 2013 Oct.
30. Appelbaum PS, Lidz CW, Klitzman R. Voluntariness of consent to research: a preliminary empirical investigation. IRB 2009 Nov;31(6):10-4.
31. Black L, Batist G, Avard D, Rousseau C, Diaz Z, Knoppers BM. Physician recruitment of patients to non-therapeutic oncology clinical trials: ethics revisited. Front Pharmacol 2013;4:25.
32. Miller FG. Recruiting Research Participants. In: Emanuel et al e, editor. The Oxford Textbook of Clinical Research Ethics.Oxford [etc.]: OUP; 2008. p. 397-403.
33. European Parliament CotEU. Regulation (EU) 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Official Journal of the European Union 2014 May 27;1-76.
34. van der Graaf R, Koffijberg H, Grobbee DE, de HE, Moons KG, van Thiel GJ, et al. The ethics of cluster-randomized trials requires further evaluation: a refinement of the Ottawa Statement. J Clin Epidemiol 2015 Sep;68(9):1108-14.
35. King NM. Experimental treatment. Oxymoron or aspiration? Hastings Cent Rep 1995 Jul;25(4):6-15.
36. Faden RR, Kass NE, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. An ethics framework for a learning health care system: a departure from traditional research ethics and clinical ethics. Hastings Cent Rep 2013 Jan;Spec No:S16-S27.

9

General discussion

This thesis evaluated the challenges and advantages that come with the integration of research and care in pediatric oncology. We focused on two main themes, 'Dependent relationships and voluntary informed consent' and 'The distinction between research and care'. In this final chapter, I will reflect on the main findings from this thesis, and argue under which conditions the integration of research and care is morally acceptable.

I will first summarize and reflect on both main themes and their main findings subsequently. Then, based on the four paradigms of clinical research and oversight as described by Emanuel and Grady,(1) I will discuss which perspectives on the integration of research and care present themselves in this thesis.

Part I: Dependent relationships and voluntary informed consent

Chapters 2 and 3 analyze two strategies or approaches to protect voluntary informed consent in a dependent relationship, based on a review of ethical guidelines and on our qualitative study. A first approach focuses on the process of obtaining informed consent (which we have called 'the process approach'). This approach recommends that an independent individual, such as a research nurse, obtains informed consent. An advantage of this approach is that the direct influence of the physician on the patient and on the decision-making process is diminished, or even removed, thereby increasing the room for voluntary informed consent from the research participant. However, indirect influence by the treating physician is difficult to remove or prevent. As we argue in **Chapter 2**, in many cases the treating physician will ultimately be informed of a patient's decision, either because the physician is also the investigator or because the research participation will have an influence on the clinical management of the patient. Especially in pediatric oncology, where virtually all physicians are also researchers, and research is connected with treatments, influence of the physician is difficult to diminish. Moreover, designating an independent individual to obtain the patient's consent does not prevent that prior to the actual, official informed consent conversation (where the final decision is made and registered) influence or even pressure is exerted on patients.(2)

The second approach focuses on information that patients should receive ('the content approach'). It requires that the voluntary nature of research participation and the right to withdraw should be clearly communicated to patients. This requirement is not unique for situations of dependency, as it is a general requirement of ethical guidelines for research with human beings. However, it makes sense to emphasize the voluntary nature of participation in the context of dependent relationships. When research and care are combined it may be less clear to patients that an invitation to a clinical study is to be understood as an invitation as opposed to a recommendation or even an inherent part of treatment. Accordingly, as was argued in **Chapter 2**, in the context of a dependent relationship a gap may exist between knowing something and acting upon it.

This gap implies that even if patients know and understand their rights, they could be hesitant to withdraw from the study, since they do not want to disappoint their treating physician.(3)

Thus, as we concluded in **Chapter 2**, both approaches do not appropriately safeguard voluntary informed consent of patients when their treating physician obtains informed consent. Appointing independent counselors is suggested as an additional safeguard in **Chapters 2 and 3,** to create a possibility for families to discuss the offered best available treatment protocol outside the relationship with the treating oncologist or a research nurse. Here, we advise that these counselors should receive specific training to be able to appropriately guide children with cancer and their families in the research decision-making process, in order to promote voluntariness. However, we realize that this is not an ideal solution and that there exist several challenges for these counselors. First, it may turn out unfeasible for many pediatric oncology centers to appoint such independent counselors, both from a practical and a financial perspective. Second, as is the case with research nurses, it may be difficult for counselors to remain their independent status, especially when they are appointed at the pediatric oncology department itself. Third, counselors may interfere with the social dynamics between physicians and families and add up to the already large number of professionals that children with cancer and their parents encounter. Consequently, it is not self-evident that they are in a better position to provide guidance to parents than are the pediatric oncologists themselves, which may also be something pediatric oncologists themselves feel.

Simultaneously, it was suggested that inclusion within a dependent relationship does not necessarily negatively influence voluntary informed consent for research. In **Chapter 3**, we explored the experiences of those involved in pediatric oncology with voluntary informed consent within a dependent relationship. Although some respondents (mainly pediatric oncology professionals) indicated that inclusion for research within the dependent relationship might pose a threat to voluntariness, this was not experienced as such by adolescents with cancer or their parents. They generally do not feel pressure to consent to research if the child's treating oncologist obtains consent. However, in **Chapters 3 and 5**, pediatric oncologists indicated that they can have considerable influence on the research decision-making process. For example, in **Chapter 3**, pediatric oncologists said that if they emphasize the importance of a certain study, most parents are inclined to consent to participation of their child.

By way of theoretical analysis, **Chapter 4** demonstrates that the integration of research and care in pediatric oncology may have impact on voluntary informed consent, but that this does not necessarily compromise voluntariness. We performed a conceptual analysis of voluntariness of consent in order to evaluate two scenarios that potentially threaten voluntary informed consent of parents of children with cancer, due to the intertwinement of research and care. We focused on parental consent, because parents are the main decision makers concerning research participation for their children, both practically and legally.(4;5) The first scenario concerns three

ways in which the treating physician may influence decision making of parents and the voluntariness of their consent to research. That is, the dependent relationship, physician appeal to reciprocity, and framing of information. The second scenario discusses cancer treatments that are made contingent on research participation, either new treatments that are part of an RCT or treatment protocols with an inherent research component. In this **Chapter 4**, we conclude that none of the influences is morally problematic, but argue that the combination of different factors could create situations in which parental informed consent is no longer sufficiently voluntary. A suggestion we provide in this chapter to mitigate any initial compromises to voluntariness is that pediatric oncology researchers could introduce 'a moment of reconsideration'. This moment of reconsideration entails that during a study, patients and their parents should be asked whether they wish to continue in the study, to ensure that continued participation is voluntary.

Furthermore, **Chapter 4** shows that it is important to distinguish between objective and subjective voluntariness. Objective voluntariness refers to decisions that are made free from actual influences, whereas subjective voluntariness refers to the way people perceive influences, regardless of whether these are actually exerted. (6) Consequently, informed consent could be objectively voluntary, but subjectively involuntary and vice versa. Ideally, both types of voluntariness are satisfied when parents provide informed consent for pediatric oncology studies. As discussed in **Chapter 4**, to assess whether voluntariness of informed consent is impaired from an objective perspective, it is possible to determine which influences there are on parents' decision-making process, and whether these influences are substantially controlling. That is, all influences can be positioned on a continuum, from completely controlling to completely non-controlling. On this continuum, only influences that are substantially controlling deprive persons of their voluntariness. As regards subjective voluntariness, empirical studies should be conducted to ask parents about their experiences with informed consent in specific circumstances. It should be studied whether parents felt that their consent was voluntary or whether they experienced certain influences as controlling. A difficult aspect of subjective voluntariness is that this may differ considerably between families, rendering it impossible to provide definite answers on subjective voluntary informed consent.

Interestingly, our qualitative study (**Chapters 3 and 5**) suggests that one route to promote (subjective) voluntary informed consent would be through support of the pediatric oncologists. For some types of research (those closely linked to treatment such as phase III randomized controlled trials), pediatric oncologists see themselves as the optimal person to perform the informed consent procedure. They indicate that they are in the position to ensure that parents feel free to make their own decisions and also to refuse if they do not feel comfortable with their child's enrolment. Similarly, in **Chapter 3** parents expressed that they valued involvement of their child's treating physician, for example if a study was expected to have severe side effects. In a similar vein, a qualitative study shows that although patients and parents of an ill child regard research on accepted medical practices as distinct from usual care, they frame the research in the patient-physician relationship. They strongly rely on their

physician to make decisions and prefer to receive information about the study from this physician.(7) However, others maintain that even in an integrated research-care environment, in general, research can and should be distinguished from standard care, and that involvement of physicians in the informed consent process is not self-evident due to conflicting obligations.(8-11)

Thus, tension exists between different evaluations of the influence of the dependent relationship on voluntary informed consent, and accordingly on the appropriate role of the treating pediatric oncologist. On the one hand, dependent relationships, and physicians that are part of them, are considered as a potential undue influence on voluntary informed consent of research. On the other hand, there is no clear evidence that patients and parents indeed experience pressure due to their dependent status when the treating pediatric oncologist obtains informed consent. However, an absence of evidence does not prove that dependent relationships should be generally permitted, since more subtle or indirect influence of the physician on families may still undermine their voluntariness, as we suggest in **Chapter 3**. Also, there will exist differences between families and their experiences, rendering it plausible that some families may experiences the dependent relationship as a threat to their voluntariness. Hence, despite some situations in which it may be acceptable that the treating physician obtains informed consent, it is advisable to also appoint independent persons, to reduce the risk of compromised voluntariness.

Part II: The distinction between research and care

The second part of this thesis explores the distinction between research and care in pediatric oncology, and implications for the categorization of pediatric oncology studies, ethical review and informed consent. **Chapter 5** demonstrates that pediatric oncologists categorize pediatric oncology protocols based on the relation a protocol has with cancer therapy. Studies into cancer therapy (mainly chemotherapeutics) are considered as studies that are part of the treatment options that patients have. Accordingly, pediatric oncologists feel that they themselves should be involved in discussions about enrolment in these studies, as they are in the best position to explain its (medical) details and guide parents in the decision making process. In contrast, they suggest that studies that are not connected to cancer treatment (such as lab research or supportive care studies) could more easily be discussed outside the physician-patient relationship.

In addition, in **Chapter 5**, the pediatric oncologists describe pediatric oncology protocols where research and care are indistinguishable. These protocols provide best current treatment to individual patients and simultaneously investigate whether modifications compared to the previous protocol improve survival rates. In the following three chapters, we focused on these ‘best available treatment protocols’. Since physicians call these protocols ‘best available treatment protocols’, we have adopted their terminology. But it is important to realize that these protocols are not restricted to the realm of patient care, but also involve research elements. In **Chapter 6**, it is determined that these protocols have a hybrid nature and cannot be

categorized as either research or care. However, we also argue that hybrid protocols should receive ethical review, due to the significant uncertainties that are associated with the introduction of new or different treatment elements.

At the same time, the current system of ethical oversight starts from the distinction between research and care and does not accommodate for hybrid protocols. Therefore, we considered how, taking into account the existing systems of ethical oversight, hybrid protocols should be reviewed and what form of informed consent is appropriate. **Chapter 7** describes a suggestion to provide the appropriate level of review for different best available treatment protocols in pediatric oncology. The main research element of these type of protocols concerns changes that are made of which it is uncertain whether these improve survival of children with cancer when compared to previous protocols. We suggest that in the current oversight system all best available treatment protocols should be ethically reviewed, to ensure that research elements of these protocols are not overlooked. An option in the current system would be to apply less stringent rules to minimal risk protocols that resemble "low intervention trials" as defined by the EU regulation on clinical trials on medicinal products for human use,(12) for example with respect to monitoring, in particular if these protocols predominantly focus on the treatment of patients. However, as we wrote in **Chapters 7 and 8**, the jurisdiction of different countries will determine whether our proposal is feasible there.

In **Chapter 7**, we explain that when parents provide informed consent for their child's treatment according to a best available treatment protocol, they also consent to its research component. Although this seems to compromise voluntariness from the start, we suggest that this compromise may be considered acceptable if certain conditions are fulfilled. In **Chapter 8**, it is suggested that the treating pediatric oncologist may be the one to obtain informed consent for participation of the child in the protocol, despite its inherent research component, since a protocol also concerns the main treatment of the child. In that case, the roles of researcher and physician collide, and physicians should be cautious not to let research interests override their patient's interests, and be open about the research component of best available treatment protocols. In other situations, the two roles of physician and researcher may come into conflict, due to the inherently diverging goals of research and treatment. For example, if a pediatric oncologist is involved in a phase III randomized controlled trial, and includes his or her own patients in this trial, then the oncologist's obligations towards patients may come into conflict with scientific obligations and goals.

Interestingly, **Chapter 5** shows that pediatric oncologists do not experience many conflicts between their roles as physician and as researcher, mainly because they regarded themselves foremost as physicians. On the one hand, the conviction that research and care obligations cannot come into conflict clearly demonstrates the general idea of pediatric oncology. The starting point in pediatric oncology is that every activity performed is both an investigation and a valuable treatment option. On the other hand, this conviction is counterintuitive, since in a context

where many physicians have a dual role, like in pediatric oncology, conflicts between research and care will always be present.(3) Therefore, as we suggest in **Chapter 5**, pediatric oncologists should be attentive to possible role conflicts in order to be able to recognize these conflicts and find a suitable solution. Pediatric oncologists should stay committed to the individual child's wellbeing, and ensure that the child's interests are not overridden by research interests.(11)

Interestingly, **Chapter 5** illustrates that the notion of diverging interests is not necessarily applicable to pediatric oncology. Although parents do differentiate between their child's interests and that of the larger group of children, they regard the improvement of therapy through the conduct of research as a mutual interest. Parents and older patients seem to recognize 'that "the program" or social organization of the medical care of cancer is organized to include research'.(13) Furthermore, as discussed in **Chapter 5**, reciprocity is an important notion in the interactions between families and the pediatric oncology professionals. Both children with cancer and their parents display the desire to do something back to families who have participated in pediatric oncology studies in the past. The value of reciprocity results in a shared view of research as a joined interest, to which all contribute and from which all can benefit. Accordingly, families affected by cancer feel part of the 'childhood cancer community'.(14) This strong sense of belonging to the paediatric oncology community maintains the prevailing research minded norms in this practice, thereby strengthening the desire to reciprocate.(15)

The view of paediatric oncology as a research community is in line with the changing research ethics paradigm we discussed in **Chapters 6 and 7** and its emphasis on the active involvement of all stakeholders in medical research.(16) Recently, a group of influential American bioethicists developed a moral framework for Learning Health care Systems (LHS), in which 'practice is a continuous source of data for the production of generalizable knowledge, and the knowledge that is produced is used to continuously change and improve practice'.(17) One of the foundations of their framework is the moral priority on learning, which implies that not only health care professionals but also patients 'have an obligation to contribute to, participate in, and otherwise facilitate learning'.(16)

They derive this obligation from the principle of the common good, as it was defined by the political philosopher John Rawls.(18) The common good can be defined as a shared good that is beneficial for all or the majority of members from a society. In the context of the LHS, this common good is high-quality and accessible health- care. Faden and colleagues suggest that as we all have an interest in an adequate health care system, we should all be committed to the goal, or common purpose, of maintaining and even improving this system.(16) In short, since we all reap the benefits of the common good of health care, we should all be committed to the common purpose of maintaining or even improving this common good through medical research. Notably, the way Faden and colleagues give further content to the norm of common purpose echoes our earlier description of pediatric oncology and its emphasis on the value of reciprocity in **Chapter 5**. They assert that the goals of the LHS 'cannot

be reached efficiently without near-universal participation in learning activities, *through which patients benefit from the past contributions of other patients whose information has helped advance knowledge and improve care'* (emphasis added). The justification for this norm of common purpose is the 'reciprocal obligation that arises among strangers who occupy the role of patient over time'.(16) That is, patients have an obligation to take part in research, in order to reciprocate the benefits that they receive through research participation of past patients (as also John Harris has argued (19)). This obligation does not have to be directed towards specific others, but could be towards a group of others, for example the community of patients, based on a general sentiment to help others if you have been helped yourself.(15)

As both our qualitative study (**Chapter 5**), and other empirical research has shown,(14) parents and older patients realize that they are part of a chain of patients whose research participation has increased knowledge and has improved treatments to their benefit. Accordingly, pediatric oncology has successfully established a (moral) norm of common purpose, which arguably may be one of the contributing factors to the high participation rates this field.

Perspectives on the integration of research and care

In the previous sections, three perspectives on the integration of research and care in pediatric oncology can be identified. These three perspectives resemble three of the four paradigms of clinical research and research oversight as described by Emanuel and Grady,(1) that is 'Researcher Paternalism', 'Regulatory Protectionism', and 'Participant Access'. As the way research (and care) are conceptualized influences what we regard as proper conduct in the research context, insights from these paradigms could enhance the current evaluation of the integration of research and care in pediatric oncology, and the accompanying themes of dependent relationships, voluntary informed consent and ethical oversight. In the same paper, Emanuel and Grady define a fourth paradigm or perspective, that of collaborative partnership. Although this perspective is only slightly touched upon in **Chapter 7**, I will also discuss this perspective as it can provide additional insights into the integration of research and care in pediatric oncology.

In what follows, I will describe each perspective as it is reflected in this thesis, and discuss its implications for the moral elevation of the integration of research and care in pediatric oncology.

1. Researcher Paternalism

The first perspective on clinical research and research oversight focuses on the profession itself and the ability of researchers to decide what is acceptable. It rests on the assumption that health care professionals uphold standards of integrity, and possess character qualities that make them trustworthy.(1) In pediatric oncology, this perspective is exemplified by best available treatment protocols (such as the ALL-10

protocol of the Dutch Childhood Oncology Group), which are not always regarded as research, and are therefore not always fully reviewed. Also, considering the involvement of the treating oncologist in informed consent discussions as acceptable under conditions, illustrates this perspective in which the profession is deemed able to provide appropriate protection of patients. From this first perspective, the integration of research and care and inclusion for research by the treating pediatric oncologists do not appear morally problematic, as it is deemed appropriate for physicians themselves to be the ones who guide patients and parents in the research decision-making process.

2. Regulatory protectionism

The second perspective on clinical research and research oversight regards research as a potentially dangerous activity, which implies that participants are in need of protection. Moreover, since researchers generally have conflicting obligations, they are not regarded as the appropriate individuals to oversee the interests of patients in the context of research.(1) Therefore, external regulation and oversight, with a focus on informed consent and independent review, are deemed necessary. As regards pediatric oncology, our suggestion that in the current system of ethical oversight all best available treatment protocols should be reviewed is part of this second perspective. In addition, the recommendation that in general a research nurse or independent person should obtain informed consent for pediatric oncology protocols, as well as availability of an independent counselor, fits well within the idea that external control is important. Seen from this second perspective, research and care are and should remain distinct practices. Furthermore, the integration of research and care is seen as inherently problematic, due to the different objectives of these two activities and the inherent tension between the roles of physician and researcher. Moreover, the perspective of regulatory protectionism assumes that due to this tension, there will always be a risk of making choices in which children's interests are not prioritized. This entails that, if possible, inclusion within a dependent relationship should be prevented. And, if this turns out unworkable, that appropriate safeguards should be implemented.

3. Participant Access

The third perspective on clinical research and research oversight takes the starting point that research is a potentially beneficial activity rather than a dangerous one. Patients themselves are able to determine which risks they consider acceptable to obtain a certain chance of benefit as opposed to regulations deciding what is in patients' best interests. As such, this perspective is mostly applicable to therapeutic intervention studies.(1) The third perspective is a reaction to the paucity of available evidence for many diseases, concurrent high use of off label drugs and limited access to safe and effective medication due to regulatory hurdles. In pediatric oncology, this perspective is illustrated by the emphasis that is placed on the benefits that research can bring, both for current individual patients and for children with cancer in the future. Research is regarded as a proper opportunity for treatment, and combining

the provision of treatments with research is not only considered acceptable, but even preferable as a means to simultaneously provide patients with state-of-the art treatment and continuously improve treatments for patients in the future. In addition, since the third perspective focuses on what patients, and in our case, also their parents, consider important for their health and treatment, the potential influence of the treating pediatric oncologist on the decision-making process is not on the forefront. If patients or their parents regard a certain study as a potentially valuable treatment option, it is less likely that consent was provided due to pressure of the dependent relationship. As such, the dependent relationship appears less ethically problematic in the context of patient decision-making and voluntary informed consent.

4. Collaborative partnership

In the fourth perspective on clinical research and research oversight, it is increasingly recognized that medical research does not occur in isolation, but that it is a collaborative, social enterprise that requires the involvement of communities in the research process. Also, involvement or active participation of patients is put forward as the best means of protection.(1) In patient engagement initiatives patients are considered as active partners in the research process.(20) As patient involvement in research 'aims to enhance the quality, appropriateness, acceptability and relevance of research',(21) it can be considered as a way to promote and protect patients' interests. Patient engagement (which has been given a variety of different names, such as participatory research, PPI, partnership, collaboration) requires that patients closely collaborate with researchers, ideally throughout the full cycle of research. This means that patients may be involved with agenda setting, formulating research questions, developing study designs, participant recruitment, data analysis, and publication, dissemination and implementation of study results.(22) I will first elaborate on this perspective, both for children in general and for children with cancer. Then, I will discuss what this perspective means for the evaluation of the integration of research and care in pediatric oncology.

Engagement of children in research

The call for active involvement of patients has not just focused on adults, but also increasingly on children. It is argued that children's own accounts of and experiences with pediatric health care should be included in research, based on the right of the child to be listened to. (23) The starting point is that children have unique knowledge about themselves and the way they perceive the world, which can provide valuable insights for researchers.(24) Key notions are those of partnership and shared decision-making, to ensure that children are actually listened to rather than merely participating in research.(25) Good examples are the Young Person's Advisory Board from the UK Medicines for Children Research Network and the Nuffield Council, which has published a report on children and clinical research based on frequent consultations with children themselves.(26;27) Several benefits of children's engagement in health research have been proposed, such as improving the relevance of research, strengthening its claims to reliability and validity, increasing children's confidence,

and revealing unexpected views and ideas.(24;25) However, the evidence base for the actual occurrence of these benefits is poor, in particular for medical research.(25) Moreover, engaging children in research may also be accompanied with a variety of risks and challenges. A research project may raise unrealistic expectations of children, and place unreasonable burdens on them.(28) In addition, it takes a lot of time to properly conduct a research project that engages with children, and it is difficult to make sure everyone involved is heard.(25) Also, participatory research with children runs the risk of pushing adult rules on children, by imposing on them pre-defined techniques. Moreover, knowledge gained from children may be used to regulate them.(29)

Engagement of children in pediatric oncology research

Especially in a field like pediatric oncology, with children who have a life-threatening disease, the way in which patient engagement in research could be materialized is not self-evident. The risk of placing unreasonable burdens on children with cancer is imminent, as they have they undergo many burdensome treatments, with often severe side effects. To protect children with cancer, a valuable option would be to actively engage their parents in the research process, and infer from them what their children dislike or prefer. However, if children are exclusively considered as vulnerable and in need of protection, this may reduce opportunities for active involvement, and even reinforce their vulnerable position.(24;30) A suitable approach would be to 'ask what children can bring to the research process'.(24)

Despite existing challenges, incorporating the views of children with cancer in research seems a promising way to contribute to the protection of their rights and interests.(28) More specifically, based on the fact that children with cancer have to undergo intensive and burdensome treatments, often combined with research, the question to ask is what children experience as major discomforts and how these could be minimized. As adult views and ideas frequently differ from those of children,(24) it is important to inquire what children themselves experience as burdensome or uncomfortable. Moreover, healthy children have different preferences and experiences than severely or chronically ill children. This has been illustrated in an interview study with a variety of children, in which only the ill children worried about missing out on school, as they already have to miss school on many occasions.(31) Therefore, generalizations from studies with other groups of children are difficult to make,(32) rendering it essential that children with cancer themselves are involved in study design, development of information letters, and possibly also dissemination of results. Although from the perspective of vulnerability it appears plausible to involve children who have finished their treatment (so-called survivors), those still undergoing treatments should not be automatically excluded. Their experiences and ideas can be valuable as well, and will differ from children who are further in the treatment process. Undertaking participatory research with children with cancer demands pediatric oncology researchers to employ and develop skills in order to (learn to) properly engage with children.(32)

Implications for the moral evaluation of the integration of research and care

The fourth perspective on clinical research provides an interesting approach for our main topic of the integration of research and care in pediatric oncology. In line with the previous perspective of 'patient access', a shift of focus occurs: from the power and authority of physicians to the choices and (developing) autonomy of children and their parents. Although it is recognized that children are dependent and vulnerable, these characteristics are not what completely defines them. In this thesis, this perspective is illustrated by our qualitative study, which shows that children with cancer and their parents may be less vulnerable than generally depicted. Furthermore, they recognize the importance of research, and are highly motivated to contribute to the development of new cancer treatments. They feel part of a childhood cancer community of which participation in research is considered an essential element.

If research increasingly takes the preferences, experiences and opinions of both patients and their parents into account, and research is designed based on what is most convenient and less burdensome for families, research will be more aligned with their interests. Consequently, it will not necessarily be relevant how a certain activity is labeled. Instead, the main demand is that patients and their parents have an active role in shaping the different research or care activities, to render these optimally beneficial for both current and future patients.

In addition, due to a decrease in conflicting interests, the dependent relationship will become less problematic, even though the pressure on decision making that may occur when the treating pediatric oncologists obtains informed consent will not necessarily disappear. Moreover, if families have a larger say in the way research is conducted, they become more equal to the professionals, which also mitigates their dependency. However, as the children and parents who were involved in the research process will generally not be the same as those participating in the actual study, the patient engagement is not the final solution. Still, it provides a different perspective on the integration of research and care, the dependent relationship, and the way we regard the status and position of the different persons involved.

Concluding remarks on the different perspectives

Especially the first two perspectives seem inherently conflicting, as the first states that oversight and regulation can be left to the pediatric oncology profession itself, whereas the second perspective emphasizes external and independent forms of regulation. The third and fourth perspectives take an entirely different approach, by focusing on patients (and parents) themselves, and what they regard as desirable and worthwhile. Because from these perspectives research and care are increasingly seen as intimately linked, regulations to protect research participants are regarded as obstacles rather than as safety measures.(1)

However, as Emanuel and Grady emphasize, although the different paradigms are illustrative of a certain period in history, they should not be conceived of as four distinct periods.(1) This implies that elements of all paradigms can be simultaneously present in a certain practice and can coexist, as they do in pediatric oncology. However, based on the inherently problematic nature of the integration of research and care and accompanying role conflicts, the Researcher Paternalism perspective is not ideal. Therefore, involvement of the treating pediatric oncologist in the informed consent process is only acceptable under certain conditions. Moreover, in general, it is advisable to have an independent person perform the informed consent procedure. In addition, external regulation and protection by Research Ethics Committees is essential, but the perspective of Regulatory Protectionism will not fully resolve the ethical issues associated with the integration of research and care. Patient engagement, with its strong focus on what patients and parents themselves consider important, could mitigate dilemmas around the integration of research and care in pediatric oncology. Thus, the perspective of patient engagement combined with the valuable elements of the other perspectives seems preferable to optimally safeguard the interests of children with cancer and their families, without compromising the conduct of research and advancement of pediatric oncology.

Moreover, patient engagement can be viewed as an essential aspect of the current movement towards letting go of the distinction between research and care in Learning Health care Systems, which was discussed previously. These systems no longer focus on research as separate projects, but aim to establish facilities where research is continuously conducted during the provision of care. Participation in research is an inherent part of receiving treatment in these systems, and safeguards are implemented on a systemic rather than on an individual level. Importantly, Learning Health care Systems will only prove acceptable and feasible if patients are allocated a considerable and genuine role in deciding what kind of research is conducted, how it is conducted and in what way the results are used.

Conclusions

This thesis evaluated the challenges and advantages that come with the integration of research and care in pediatric oncology. A challenge is that in pediatric oncology almost every treatment is connected to one or more research aspects, rendering it difficult to disentangle the different activities. Consequently, treating physicians are often involved in informed consent procedures and the ones to obtain written informed consent, sometimes for studies they have developed themselves. As such, many pediatric oncologists have an inherent role conflict of being a clinician and a researcher. Moreover, treating pediatric oncologists may have considerable influence on the decisions families make regarding research participation. The extent of this influence may differ significantly between families, and will probably mainly affect voluntary informed consent of parents who are more vulnerable to the influence of others, such as physicians. Furthermore, the integration of research and care raises challenges for the kind of review and consent that is required, in particular for best available treatment protocols.

A significant advantage of combining research with treatments is that cancer therapy has rapidly improved in the past decades, increasing survival rates for children with cancer. Advantages of the dependent relationship are that pediatric oncologists may have a positive influence on the decision making process, enhancing voluntary informed consent. Especially when they are involved with the study in question, they possess detailed knowledge, which they can communicate in light of the child's medical situation, and the needs and preferences of the concerning family. Also, parents may prefer to receive explanation about a study from a physician they are familiar with. In addition, involvement of the treating physician limits the number of people that families encounter during the time in the hospital.

We conclude that although the integration of research and care is in theory problematic for voluntary informed consent and ethical review in pediatric oncology, in practice it may be acceptable under certain conditions. First, during informed consent conversations the voluntary nature of research participation and the right to withdraw should be emphasized. Second, in principle an independent person such as a research nurse should obtain informed consent for pediatric oncology studies. However, in cases where research is part of the treatment or where a physician will be better able to explain the research protocol than the research nurse, deviations from this rule are conceivable. In that case, he or she should be aware of the potential role conflicts and ensure that the child's interests are safeguarded. Third, independent counselors should be appointed to offer guidance in the research decision-making process. Fourth, introduction of reconsideration as part of the informed consent process may also be helpful to increase voluntary participation. Fifth, the dual nature of best available treatment protocols should clearly be communicated to patients and their families, including the investigational objective of these protocols.

Sixth, despite the research component, it can be considered acceptable that the treating pediatric oncologist obtains informed consent for the child's enrollment, because a best available treatment protocol aims to provide patients with best current treatment. Seventh, in the current oversight system, best available treatment protocols should receive ethical review, to prevent that research elements are overlooked. As such, our research project has strived to contribute to the ethically sound integration of research and care in pediatric oncology.

References

1. Emanuel EJ, Grady C. Four paradigms of clinical research and research oversight. Camb Q Healthc Ethics 2007;16(1):82-96.
2. Shah A, Porter K, Juul S, Wilfond BS. Precluding consent by clinicians who are both the attending and the investigator: an outdated shibboleth? Am J Bioeth 2015;15(4):80-2.
3. Brody H, Miller FG. The clinician-investigator: unavoidable but manageable tension. Kennedy Inst Ethics J 2003 Dec;13(4):329-46.
4. Martenson EK, Fagerskiold AM. A review of children's decision-making competence in health care. J Clin Nurs 2008 Dec;17(23):3131-41.
5. Joffe S, Fernandez CV, Pentz RD, Ungar DR, Mathew NA, Turner CW, et al. Involving children with cancer in decision-making about research participation. J Pediatr 2006 Dec;149(6):862-8.
6. Nelson RM, Beauchamp T, Miller VA, Reynolds W, Ittenbach RF, Luce MF. The concept of voluntary consent. Am J Bioeth 2011 Aug;11(8):6-16.
7. Kelley M, James C, Alessi KS, Korngiebel D, Wijangco I, Rosenthal E, et al. Patient Perspectives on the Learning Health System: The Importance of Trust and Shared Decision Making. Am J Bioeth 2015;15(9):4-17.
8. Sugarman J. Is Shared Decision Making an Appropriate Analytic Frame for Research on Medical Practices? Am J Bioeth 2015;15(9):18-20.
9. D'Angio CT. "I'm Really Torn, I Guess": Reconciling Conflicting Roles Among Physicians Seeking Research Consent. Am J Bioeth 2015;15(9):20-2.
10. Largent EA. What's Trust Got to Do With It? Trust and the Importance of the Research-Care Distinction. Am J Bioeth 2015;15(9):22-4.
11. Brody H, Miller FG. The research-clinical practice distinction, learning health systems, and relationships. Hastings Cent Rep 2013 Sep;43(5):41-7.
12. European Parliament CotEU. Regulation (EU) 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Official Journal of the European Union 2014 May 27;1-76.
13. Liaschenko J, Underwood SM. Children in Research: Father in Cancer Research - Meanings and Reasons for Participation. Journal of Family Nursing 2001;7(1):71-91.
14. Dixon-Woods M, Wilson D, Jackson C, Cavers D, Pritchard-Jones K. Human Tissue and 'the Public': The Case of Childhood Cancer Tumour Banking. BioSocieties 2008;3:57-80.
15. Kolm S-C. Reciprocity: Its Scope, Rationale, and Consequences. In: Kolm S-C, Ythier JM, editors. Handbook of the economics of giving, altruism and reciprocity: Applications.Oxford: North Holland; 2006.
16. Faden RR, Kass NE, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. An ethics framework for a learning health care system: a departure from traditional research ethics and clinical ethics. Hastings Cent Rep 2013 Jan;Spec No:S16-S27.
17. Kass NE, Faden RR, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. The research-treatment distinction: a problematic approach for determining which activities should have ethical oversight. Hastings Cent Rep 2013 Jan;Spec No:S4-S15.
18. Rawls J. A theory of justice. Revised edition. Cambridge, MA: Harvard University Press; 1999.
19. Harris J. Scientific research is a moral duty. J Med Ethics 2005 Apr;31(4):242-8.
20. Petit-Zeman S, Locock L. Health care: Bring on the evidence. Nature 2013 Sep 12;501(7466):160-1.
21. Staniszewska S, Denegri S. Patient and public involvement in research: future challenges. Evid Based Nurs 2013 Jul;16(3):69.
22. van Thiel GJMW, Stolk P. Priority Medicines for Europe and the World "A Public Health Approach to Innovation" Update on 2004 Background Paper. 2013.
23. Summary of the United Nations convention on the rights of the child. UNICEF; 2009.

24. Clavering EK, McLaughlin J. Children's participation in health research: from objects to agents? Child Care Health Dev 2010 Sep;36(5):603-11.
25. Bird D, Culley L, Lakhanpaul M. Why collaborate with children in health research: an analysis of the risks and benefits of collaboration with children. Arch Dis Child Educ Pract Ed 2013 Apr;98(2):42-8.
26. Involving children and young people in health research - ethical issues. Nuffield Council on Bioethics; 2015.
27. GenerationR: Young people improving research. National Institues of Health Research, Medicines for Children Research Network; 2013.
28. Schenk K, Murove T, Williamson J. Protecting children's rights in the collection of health and welfare data. Health Hum Rights 2006;9(1):80-100.
29. Gallacher L-A, Gallagher M. Methodological immaturity in childhood research? Thinking through 'participatory methods'. Childhood 2009;15(4):499-516.
30. Coyne I. Accessing children as research participants: examining the role of gatekeepers. Child Care Health Dev 2010 Jul;36(4):452-4.
31. Staphorst MS, Hunfeld JA, van d, V, Passchier J, van Goudoever JB. Children's self reported discomforts as participants in clinical research. Soc Sci Med 2015 Oct;142:154-62.
32. Carter B. Tick box for child? The ethical positioning of children as vulnerable, researchers as Barbarians and reviewers as overly cautious. Int J Nurs Stud 2009 Jun;46(6):858-64.

SUMMARY

The large majority of children with cancer participate in medical research. This varies from observational studies, to laboratory research on different types of tissue, to drug research, to supportive care studies. As such, pediatric oncology is a field where treatments are often provided in the research context, thereby integrating research with care. This thesis evaluates the challenges and advantages that come with the integration of research and care in pediatric oncology. The first part concerns the informed consent that parents (and older patients) provide for a child's research participation, and to what extent this can be voluntary in an environment where the treating physician is often the one to obtain informed consent for a child's research participation (within a dependent relationship). The second part analyzes whether research and care can and should be distinguished, and investigates the implications of the integration of research and care for ethical review and the informed consent procedure. Hence, the two main themes of this thesis are, 'Dependent relationships and voluntary informed consent' and 'The distinction between research and care'.

Part I: Dependent relationships and voluntary informed consent

Chapters 2, 3 and 4 of this thesis focus on inclusion for medical research within a dependent relationship. Within the treating relationship, children with cancer together with their parents are dependent on the treating physician for the necessary treatments and thereby for the chance of a cure. Due to the integration of research and care in pediatric oncology, it is often the case that physicians enroll their own patients in research. It is assumed that the situation of dependency may have a negative influence on the voluntariness of consent, because patients might not feel free to refuse their treating physician performs the informed consent procedure, due to concerns regarding consequences for their treatment or the relationship with the physician. Since voluntariness is one of the pivotal pillars of informed consent for research, it is important to assess whether voluntariness is indeed compromised within a dependent relationship, and what kind of safeguards could be valuable to implement.

Therefore, **Chapter 2** explores which strategies or safeguards for voluntary consent in a dependent relationship are mentioned by ethical guidelines for human subjects research. From a review of a variety of ethical guidelines, two different approaches towards protecting voluntariness of consent when it is obtained by the own treating physician were identified, the 'process approach' and the 'content approach'.
The 'process approach' focuses on the process within which informed consent is obtained and on ways to diminish the physician's presumed influence during the informed consent procedure. The most common form is to have another qualified professional, who is independent of the treating relationship, obtain informed consent instead of the treating physician (usually a research nurse). Instead, the independent person can also function as counselor, who is present during informed consent

conversations and is available for questions and advice. The second approach, the 'content approach' focuses on the information that patients receive during the informed consent procedure. The voluntary nature of research participation and the right to withdraw should be explicitly addressed towards patients.
Although both approaches may be able to safeguard voluntariness to a certain extent, we argue that both approaches are suboptimal, as the influence of the treating physician can never be fully removed. Therefore, we advise to always combine these two approaches. At the same time, it is important to realize that inclusion for research in a dependent relationship does not entail compromised voluntariness. In some cases the own physician may even be in the best position to obtain informed consent, for example if the research is the means through which treatment is delivered or if a study is too detailed and specialized for research nurses to explain. The informed consent can then be signed in the presence of a research nurse or an equally qualified colleague.

Chapter 3 describes the results of our qualitative study for which we interviewed a variety of actors from pediatric oncology, to explore their experiences with voluntary informed consent in a dependent relationship. The study consisted both of group interviews (focus groups) and of individual interviews, with pediatric oncologists, research coordinators, parents of a child with cancer, and adolescents with cancer. The study shows that the dependent relationship between physicians and families was seen in three different ways: as a potential negative influence, as having no or minimal influence, and as a potential positive influence on voluntary informed consent. In addition, three strategies to protect voluntary informed consent in a dependent relationship were suggested, two of which are the same as those identified in **Chapter 2**, involving an independent individual and emphasizing the voluntary nature of research participation. The third strategy aimed to ensure that parents and older patients gain a sense of responsibility by making clear that they are the ones in charge.
We conclude that the dependent relationship between pediatric oncologists, patients and parents need not be problematic for, and involvement of the treating physician during informed consent may even have a positive impact on voluntary informed consent.

Chapter 4 provides a conceptual analysis of voluntary informed consent in the integrated research-care context of pediatric oncology. Two key scenarios are identified in which voluntary informed consent for pediatric oncology studies is potentially compromised due to the intertwinement of research and care. The first scenario is inclusion by the treating pediatric oncologist, which has also been addressed more empirically in the first two chapters. The second scenario concerns treatments that are only available in the research context. This chapter examines whether voluntary informed consent of parents for research is compromised in these two scenarios, and if so whether this is also morally problematic, using the conceptual account of voluntariness and voluntary consent of Nelson and colleagues. This account asserts that consent for research is no longer voluntary when there are substantially controlling influences on a person's decision-making process.

There are three types of influences, that is, persuasion, manipulation and coercion, with increasing influence on voluntariness.
We conclude that although the dependent relationship in itself does not constitute a controlling influence on voluntary informed consent, it does qualify as a risk factor for controlling influence as it defines the conditions within which decisions have to be made. In addition, if physicians intentionally frame study related information, this is a controlling influence, as it is a form of informational manipulation. In the second scenario, protocols with an inherent research component qualify as controlling, since the options available to patients and their parents are restricted through manipulation of options. None of the substantially controlling influences is morally problematic in itself. However, an accumulation of different influences that are each morally acceptable could create situations that become morally problematic influences on informed consent of parents for their child's research participation.

Part II: The distinction between research and care

Chapters 5, 6, 7 and 8 take a closer look at the distinction between research and care and the ways in which these two activities are intertwined in pediatric oncology. As is often mentioned in research (ethics) literature, this integration has contributed to major improvements in the treatment of children with cancer in the past decades. However, traditionally, research and care have been distinguished, due to their different objectives: research aims to develop generalizable knowledge for groups of (future) patients, whereas care is concerned with the health and wellbeing of individual patients. Combining these two different activities may pose problems, in particular with respect to review and consent for protocols that integrate the provision of treatment with the conduct of research.

Chapter 5 describes the results of a qualitative study on the experiences of those involved in pediatric oncology with the intertwinement of research and care and the dual role of pediatric oncologists as researchers and treating physicians. Respondents are partly the same as those of **Chapter 3**. Four themes characterize how these respondents experience the intertwinement of research and care in pediatric oncology. First, research is considered of major importance to improve the field of pediatric oncology, and pediatric oncology professionals convey this message to patients and their parents. Second, the pediatric oncologists considered it difficult to categorize studies into cancer therapy as either research or treatment. This difficulty in particular concerned best available treatment protocols, which are seen as a seamless combination of research and care. Third, role conflicts appear within the work of the pediatric oncologists, who generally function both as a physician and as a researcher. Finally, the various benefits of combining treatment with research are emphasized. These benefits include therapeutic benefits for participating patients, due to close monitoring, following strict protocol guidelines, and the use of innovative interventions, but also benefits for future patients by increasing survival chances and minimizing side-effects. Pediatric oncology professionals, parents and patients have a very positive outlook on combining research and care, but may not reflect critically enough on potential conflicts that arise when research and care are intertwined.

Yet, potential conflicts of combining research and care should also receive appropriate attention, since managing conflicts between treatment and research is only possible if they are recognized as such by relevant actors.

Chapter 6 further explores the best available treatment protocols that were identified in **Chapter 5**. These protocols form a grey area between research and treatment; such protocols are considered state-of-the-art treatment, while these are simultaneously designed to evaluate whether the protocol's modifications of previously used treatment regimens have improved survival rates. Recently, two Dutch protocols for the treatment of children with Acute Lymphoblastic Leukemia (ALL) have been categorized in two different ways, one as research (ALL-11) and the other as treatment (ALL-10). Whereas the two protocols were largely similar, only ALL-11 received full ethics review by a Research Ethics Committee.
To explore whether the distinction between research and care in pediatric oncology is morally relevant, we applied several characteristics of research to the ALL-10 and 11 protocols. First, the goal of producing generalizable knowledge on ALL treatment and the advancement of therapy for children with ALL is clearly present in both protocols. However, the protocols are also developed to provide state-of-the-art treatment for patients with ALL. Second, to achieve the aim of producing generalizable knowledge and improve ALL treatments systematic collection of data is performed in both protocols. Third, the two protocols contain modifications compared to previous protocols that produce potentially high and uncertain risks. Fourth, due to the addition of several research studies, both protocols involve burdens and risks unrelated to the treatment that children with ALL receive. Finally, both ALL-10 and ALL-11 provide treatment to patients according to detailed protocols and thereby satisfy the fifth characteristic of research. However, protocol-controlled treatment is very common in pediatric oncology and has been shown to be beneficial to individual patients.
Thus, even though research and treatment are being combined for the benefit of the individual and groups of patients, both ALL-protocols should now be regarded as research protocols since they satisfy five characteristics of research. Yet, in the future it remains to be discussed how to review hybrid protocols that integrate a research goal with the objective of providing individual patients with best current treatment. A change in both research ethics regulation and oversight of conventional care is needed.

Chapter 7 takes up the challenge from the conclusions of **Chapter 6** by examining appropriate review and consent procedures for best available treatment protocols. These protocols contribute to the depiction of pediatric oncology as a so-called Learning Health care System (LHS), a system in which research is considered an essential means to continuously improve the practice of care. Since best available treatment protocols are hybrid protocols, they always contain research elements, even if the main goal of these protocols is to treat children diagnosed with cancer. As long as oversight systems do not sufficiently embed hybrid protocols, it seems best to qualify these studies as research.

This classification will prevent that research elements in treatment protocols will be overlooked and will ensure that patients understand the research components. In theory, however, risk-adapted approaches may be adopted in order to determine the level of review needed, for example by applying less stringent rules for ethical review of these protocols if risks are minimal. Another ethical challenge is the informed consent process for hybrid protocols, (as was already introduced in **Chapter 4)** since children and their parents cannot meaningfully opt out of best available treatment protocols. Physicians are usually reluctant to provide patients with the treatment of the previous protocol as it is considered outdated. Compromises to voluntary informed consent cannot be easily mitigated. But they may be considered as acceptable, when the social value of the research is compelling, and the study is the best available medical alternative for the child. At the same time, the level of understanding of best available treatment protocols can be improved. If there were regulatory oversight for hybrid protocols, physicians might use an integrated form of consent. They might explain that on the one hand the treatment is considered the best available alternative according to the medical professional standard, but on the other hand may be relatively uncertain.
Since research elements are embedded in the treatment of patients, even in protocols that are predominantly care-orientated, oversight systems may want to accommodate for protocols that involve minimal risk and to require transparency about the sometimes inextricable intertwinement of research and care in pediatric oncology.

Chapter 8 is based on the three previous chapters and provides ethical guidance for pediatric oncology professionals and Research Ethics Committees with respect to best available treatment protocols. It consists of three recommendations.
First, pediatric oncologists should clarify to patients and their families that the research component of the protocol is an inherent part of receiving treatment. They should explain that best available treatment protocols combine treatment and scientific goals, and clarify what is novel or changed to the prior best available treatment. Second, despite the research component, it may be acceptable for the child's treating pediatric oncologist to obtain informed consent instead of an independent physician, because of the treatment context in which the protocols are offered. Third, pediatric oncology professionals should recognize that best available treatment protocols with research elements need ethical review. Research Ethics Committees should learn to discern this type of protocols as special cases, should be aware that treatment protocols may contain research elements, and should be prepared to review these protocols.

Finally, **Chapter 9** is the General Discussion and provides an overview of the findings from this thesis. Here, several perspectives on medical research and research oversight are used to further morally evaluate the integration of research and care in pediatric oncology. These perspectives are 'Researcher Paternalism', 'Regulatory Protectionism', 'Participant Access', and 'Collaborative Partnership'. Especially the first two perspectives seem inherently conflicting, as the first states that oversight and

regulation can be left to the pediatric oncology profession itself, whereas the second perspective emphasizes external and independent forms of regulation. However, it is important to keep in mind that elements of all perspectives can be simultaneously present in a certain practice, as they do in pediatric oncology. The third and fourth perspectives take an entirely different approach, by focusing on patients (and parents) themselves, and what they regard as desirable and worthwhile. Because from these perspectives research and care are increasingly seen as intimately linked, regulations to protect research participants are regarded as obstacles rather than as safety measures. Collaborative partnership, which takes patient engagement as the starting point, could mitigate dilemmas around the integration of research and care in pediatric oncology, due to its strong focus on what patients and parents themselves consider important. Consequently, a shift of focus occurs: from the power and authority of physicians to the choices and (developing) autonomy of children and their parents. Although it is recognized that children are dependent and vulnerable, these characteristics are not what completely defines them. I conclude that the perspective of patient engagement combined with the valuable elements of the other perspectives seems preferable to optimally safeguard the interests of children with cancer and their families, without compromising the conduct of research and advancement of pediatric oncology.

As such, our research project has strived to contribute to the ethically sound integration of research and care in pediatric oncology.

SAMENVATTING

Het merendeel van de kinderen met kanker neemt deel aan medisch-wetenschappelijk onderzoek. Dit varieert van observationele studies, tot laboratorium onderzoek met weefsel zoals bloed of beenmerg, tot geneesmiddelenonderzoek en studies naar ondersteunde zorg. Dit betekent dat behandelingen vaak worden aangeboden in een onderzoekscontext, waardoor zorg en onderzoek vermengd raken. Dit proefschrift biedt een morele evaluatie van de uitdagingen en voordelen van de vermenging van zorg en onderzoek zoals die plaatsvindt in de kinderoncologie. Het eerste deel richt zich op de geïnformeerde toestemming (ook wel 'informed consent') die ouders (en oudere patiënten) geven voor de deelname van kinderen aan onderzoek, en bekijkt in hoeverre deze toestemming vrijwillig is en kan zijn in een omgeving waar de behandelend arts vaak degene is die toestemming vraagt voor deelname van het kind (dus, binnen een afhankelijkheidsrelatie). In het tweede deel wordt geanalyseerd in hoeverre zorg en onderzoek gescheiden kunnen en moeten worden. Ook worden de gevolgen onderzocht voor ethische toetsing en voor de toestemmingsprocedure van protocollen waarin zorg en onderzoek volledig geïntegreerd lijken. De twee hoofdthema's van dit proefschrift zijn dus 'Afhankelijkheidsrelaties en vrijwillige toestemming' en 'Het onderscheid tussen zorg en onderzoek'.

Deel I: Afhankelijkheidsrelaties en vrijwillige toestemming

Hoofdstukken 2, 3 en 4 van dit proefschrift gaan over de situatie waarin patiënten in onderzoek worden geïncludeerd binnen de afhankelijkheidsrelatie die zij hebben met hun arts. Kinderen met kanker en hun ouders zijn binnen de behandelrelatie afhankelijk van hun arts voor het verkrijgen van de nodige behandelingen en voor de kans op genezing. Als gevolg van de vermenging van zorg en onderzoek in de kinderoncologie, is het vaak zo dat artsen hun eigen patiënten includeren in onderzoek. Meestal wordt aangenomen dat inclusie binnen een situatie van afhankelijkheid aan de kant van de patiënt een negatieve invloed heeft op de vrijwilligheid van de door de patiënt gegeven toestemming voor deelname aan onderzoek. Dit omdat patiënten zich wellicht niet vrij voelen om toestemming te weigeren tegenover hun eigen behandelend arts, omdat ze bang zijn dat dit gevolgen heeft voor de onderlinge relatie of voor hun behandeling. Aangezien vrijwilligheid een van de kerncomponenten is van geïnformeerde toestemming, is het van belang om te onderzoeken of vrijwilligheid inderdaad onder druk staat in een afhankelijkheidsrelatie, en wat voor waarborgen ingebouwd zouden moeten worden.

Hoofdstuk 2 kijkt naar de manier waarop ethische richtlijnen voor medisch-wetenschappelijk onderzoek met mensen proberen de vrijwilligheid van toestemming te beschermen, als deze toestemming binnen een afhankelijkheidsrelatie gegeven wordt. In deze richtlijnen vonden we twee verschillende benaderingen ten aanzien van het beschermen van de vrijwilligheid, de 'procesbenadering' en de

'inhoudsbenadering'. De procesbenadering richt zich, zoals de naam al zegt, op het proces waarbinnen toestemming wordt gevraagd, en daarbij op manieren waarop de invloed van de behandelend arts op deze toestemming verkleind kan worden. Meestal houdt dit in dat iemand anders dan de behandelend arts toestemming vraagt voor deelname aan onderzoek (dit is dan vaak een research verpleegkundige). Deze persoon dient volledig onafhankelijk te zijn van de behandelrelatie met de patiënt. Deze onafhankelijke persoon kan ook aanwezig zijn tijdens de toestemmingprocedure, als een soort counselor, en beschikbaar zijn voor vragen en advies.
De tweede benadering, de inhoudsbenadering, gaat over de informatie die patiënten ontvangen tijdens de toestemmingprocedure. Er moet benadrukt worden dat deelname aan onderzoek alleen geldig is als het vrijwillig is en dat patiënten altijd het recht hebben om hun deelname weer in te trekken.
Ook al kunnen beide benaderingen gedeeltelijk waarborgen dat patiënten ook binnen een afhankelijkheidsrelatie vrijwillige toestemming geven, dan nog zijn beide benaderingen niet optimaal, omdat de invloed van de behandelend arts aanwezig blijft. Daarom raden we aan om beide benaderingen altijd te combineren. Tegelijkertijd moeten we ons realiseren dat inclusie voor onderzoek binnen een afhankelijkheidsrelatie niet noodzakelijkerwijs de vrijwilligheid van de toestemming aantast. De behandelend arts zou in sommige situaties wellicht zelfs de aangewezen persoon kunnen zijn om toestemming voor onderzoek te vragen. Bijvoorbeeld als onderzoek de vorm is waarin de behandeling wordt aangeboden, of als een studie te gedetailleerd en specialistisch is voor research verpleegkundigen om uit te leggen. Het daadwerkelijke tekenen van de toestemmingsformulieren kan dan echter wel het beste worden gedaan in het bijzijn van een research verpleegkundige.

In **Hoofdstuk 3** worden de resultaten beschreven van onze kwalitatieve studie met verschillende betrokkenen uit de wereld van de kinderoncologie naar hun ervaringen met vrijwillige toestemming binnen een afhankelijkheidsrelatie. De studie maakte zowel gebruik van groep interviews (focusgroepen) als van individuele interviews, met kinderoncologen, research coördinatoren, ouders van een kind met kanker en jongeren met kanker. De studie laat zien dat de afhankelijkheidsrelatie op drie verschillende manieren werd ervaren: als een potentieel negatieve invloed op vrijwillige toestemming, als iets dat heel weinig tot geen invloed heeft op de vrijwilligheid en als een potentieel positieve invloed.
Daarnaast werden er drie manieren geopperd om vrijwilligheid binnen een afhankelijkheidsrelatie te beschermen. Twee daarvan waren dezelfde als die besproken zijn in **Hoofdstuk 2**, namelijk de betrokkenheid van een onafhankelijke professional, en het benadrukken van de vrijwilligheid van deelname aan onderzoek. De derde strategie had tot doel om ouders en oudere kinderen duidelijk te maken dat zij degene zijn die de regie hebben en de keuzes maken ('empowerment').
We concluderen dat de afhankelijkheidsrelatie tussen kinderoncologen, patiënten en ouders geen problematische invloed hoeft te hebben op vrijwillige toestemming, en dat betrokkenheid van de eigen arts zelfs een positieve invloed kan hebben op de toestemmingsprocedure.

Hoofdstuk 4 geeft vervolgens een conceptuele analyse van vrijwillige toestemming in de context van de kinderoncologie en de vermenging van zorg en onderzoek die daar plaatsvindt. Er worden twee scenario's beschreven waarin de vrijwilligheid van toestemming van ouders voor de onderzoeksdeelname van hun kind onder druk staat vanwege de vermenging van zorg en onderzoek. Het eerste scenario behelst inclusie voor onderzoek door de behandelend arts (wat in de vorige hoofstukken al bekeken is vanuit empirisch perspectief). Het tweede scenario betreft behandelingen die alleen in een onderzoekscontext aangeboden worden.
In dit hoofdstuk bepalen we of de vrijwilligheid van de toestemming van ouders negatief beïnvloed wordt in deze twee scenario's, en zo ja, of dit dan ook moreel problematisch is. Hierbij maken we gebruik van de invulling die Nelson en collega's hebben gegeven aan vrijwilligheid en vrijwillige toestemming, die stelt dat toestemming voor onderzoek niet meer als vrijwillig kan worden gezien zodra er invloeden zijn die 'substantieel controlerend zijn'. Ze onderscheiden drie vormen van invloeden, namelijk overtuigen, manipuleren en dwingen, die in oplopende mate controlerend zijn.
We concluderen dat de afhankelijkheidsrelatie op zichzelf geen controlerende invloed op vrijwillige toestemming heeft, maar dat het wel een risicofactor is, omdat het de omstandigheden definieert waarbinnen ouders keuzes moeten maken. Als artsen met opzet de informatie over een studie op een bepaalde manier verwoorden ('framen') vormt dit ook een controlerende invloed, omdat de informatie dan gemanipuleerd wordt. In het tweede scenario worden behandelprotocollen met een ingebouwde onderzoekscomponent gedefinieerd als controlerend, omdat hierin de mogelijke opties waaruit ouders kunnen kiezen beperkt worden (en daarbij is het een vorm van manipulatie). Geen van de invloeden die als controlerend worden beschouwd zijn op zichzelf moreel problematisch. Echter, als er tegelijkertijd op meerdere manieren invloed wordt uitgeoefend op de keuze van ouders voor onderzoeksdeelname van hun kind kan dit problematisch worden.

Deel II: Het onderscheid tussen zorg en onderzoek

Hoofdstukken 5, 6, 7 en 8 bieden een nadere bestudering van het onderscheid tussen zorg en onderzoek en de manieren waarop deze twee activiteiten geïntegreerd zijn in de kinderoncologie. In de literatuur wordt er vaak op gewezen dat deze vermenging heeft bijgedragen aan de vooruitgang die de kinderoncologie de afgelopen decennia heeft geboekt in de genezing van kinderen met kanker. Van oudsher worden onderzoek en zorg echter beschouwd als twee aparte domeinen, vanwege het feit dat ze twee verschillende doelen nastreven: onderzoek heeft tot doel om generaliseerbare kennis te ontwikkelen voor groepen van (toekomstige) patiënten, terwijl zorg zich richt op de gezondheid en het welzijn van individuele patiënten. Indien beiden toch gecombineerd worden, zorgt dit voor ethische vragen, met name op het gebied van toetsing van en toestemming voor protocollen die het geven van zorg integreren met het doen van onderzoek.

Hoofdstuk 5 beschrijft de resultaten van onze kwalitatieve studie naar de ervaringen van betrokkenen uit de kinderoncologie met de vermenging van zorg en onderzoek, en met de dubbele rol van arts-onderzoeker die veel kinderoncologen hebben. Deelnemers aan deze studie zijn deels hetzelfde als die van **Hoofdstuk 3**. Vier thema's laten zien hoe de vermenging van zorg en onderzoek in de praktijk ervaren worden. Ten eerste, onderzoek wordt gezien als essentieel voor het verbeteren van de kinderoncologische praktijk, en deze boodschap wordt ook actief uitgedragen door kinderoncologen, naar ouders en kinderen. Ten tweede bleek dat kinderoncologen het lastig vinden om studies nar antikankermedicijnen te classificeren als zorg of onderzoek. Dit geldt met name voor zogenaamde 'best available treatment' protocollen, die worden gezien als volledige integratie van zorg en onderzoek. Ten derde, omdat kinderoncologen over het algemeen zowel arts als onderzoeker zijn, treden er op verschillende momenten rolconflicten op in hun werk. Tenslotte wordt er nadruk gelegd op de voordelen die het combineren van zorg en onderzoek kan brengen. Deze voordelen zijn deels therapeutisch van aard, door de strikte monitoring die onderdeel is van onderzoek, het geprotocolleerd handelen, en het toepassen van innovatieve behandelingen, maar ook de voordelen voor toekomstige patiënten worden benadrukt.
Zowel professionals in de kinderoncologie als kinderen en hun ouders hebben een positieve kijk op het combineren van onderzoek en behandeling, maar hierdoor dreigt het gevaar dat eventuele belangen conflicten die kunnen ontstaan niet voldoende aandacht krijgen. Het is dus belangrijk om het bewustzijn van mogelijke nadelen van de vermenging van zorg en onderzoek te vergroten, om hiermee de belangen van patiënten te beschermen.

In **Hoofdstuk 6** gaan we dieper in op de 'best available treatment' protocollen die beschreven worden in **Hoofdstuk 5**. Deze protocollen vormen een grijs gebied tussen zorg en onderzoek, aangezien ze beschouwd worden als 'state-of-the-art' behandeling, maar tegelijkertijd ontworpen zijn om te evalueren of een nieuw protocol een verbetering inhoudt ten opzichte van voorgaande protocollen. Onlangs zijn twee opeenvolgende Nederlandse protocollen voor de behandeling van kinderen met Acute Lymfatische Leukemie (ALL) op twee verschillende manieren geclassificeerd: ALL-10 werd gezien als standaardbehandeling en ALL-11 als onderzoek, terwijl beide protocollen voor een groot deel overeenkomen. Eerstgenoemde werd niet getoetst door een Medisch Ethische Toetsingscommissie (METC) en de andere wel. Om te onderzoeken of het onderscheid tussen zorg en onderzoek moreel relevant is in de kinderoncologie hebben we een aantal kenmerken van onderzoek toegepast op deze twee protocollen.
Ten eerste blijkt dat beide protocollen duidelijk tot doel hebben om generaliseerbare kennis te ontwikkelen over de behandeling van ALL en het verbeteren van de bestaande behandelingen. Echter, ze zijn ook ontwikkeld om de beste behandeling te bieden aan patiënten die op dit moment ALL hebben. Ten tweede, om wetenschappelijke kennis op te kunnen leveren, wordt er bij beide protocollen gebruik gemaakt van de systematische verzameling en opslag van data. Ten derde, beide protocollen zijn zodanig gewijzigd ten opzichte van voorgaande protocollen, dat hierdoor onzekerheid ontstaat over de omvang en ernst van de risico's die

patiënten lopen als gevolg van de behandeling. Ten vierde, het toevoegen van extra studies aan de protocollen zorgt voor belasting en risico's die niet gerelateerd zijn aan de behandeling die patiënten met leukemie krijgen. Tenslotte is het zo dat behandeling volgens ALL-10 en ALL-11 strikt geprotocolleerd verloopt, wat het vijfde kenmerk van onderzoek is. Deze manier van behandelen is echter zeer gangbaar in de kinderoncologie en er is zelfs aangetoond dat dit voordelig kan zijn voor de behandeling van patiënten.
Beide ALL-protocollen bevatten algemene kenmerken van wetenschappelijk onderzoek. Tegelijkertijd voldoen ze ook aan het doel om de best mogelijke behandeling te bieden aan patiënten. Er is dus nog zeker discussie nodig over de vraag hoe dergelijke 'hybride' protocollen getoetst moeten worden.

Hier gaat **Hoofdstuk 7** dieper op in. In dit hoofdstuk onderzoeken we welke toetsings- en toestemmingsprocedures het meest geschikt zijn voor best available treatment protocollen. Deze protocollen zijn een van de redenen dat de kinderoncologie beschouwd wordt als een zogenaamd 'Learning Health care System' (LHS). Dit is een gezondheidszorgsysteem waarin onderzoek gezien wordt als een belangrijk middel om de bestaande zorgpraktijk continu te verbeteren. Aangezien best available treatment protocollen hybride protocollen zijn, bevatten ze altijd onderzoekselementen, ook als het belangrijkste doel is om behandeling te bieden aan kinderen met kanker. Daarom is het logisch om deze protocollen te categoriseren als onderzoek en altijd te laten toetsen door METC's, in ieder geval zolang ons systeem van toezicht en toetsing niet is toegerust om hybride protocollen op een aparte wijze te toetsen. Door best available treatment protocollen als onderzoek te beschouwen wordt voorkomen dat onderzoekselementen van protocollen over het hoofd worden gezien en wordt ervoor gezorgd dat patiënten de onderzoekscomponent herkennen. Puur theoretisch gezien zou toetsing afhankelijk kunnen worden gemaakt van het risiconiveau, bijvoorbeeld door minder strenge eisen voor monitoring te stellen aan protocollen met een minimaal risico.
Een ander belangrijk aspect is de toestemmingprocedure voor hybride protocollen, zoals deze ook al deels aan bod kwam in **Hoofdstuk 4**, en in het bijzonder de vrijwilligheid van de toestemming die ouders geven om hun kind deel te laten nemen aan een dergelijk protocol. Artsen zijn over het algemeen terughoudend in het aanbieden van de behandeling zoals die in een voorgaand protocol werd gegeven, omdat die als verouderd wordt gezien zodra het nieuwe protocol geïntroduceerd is. Problemen ten aanzien van vrijwillige toestemming kunnen dus niet eenvoudig opgelost worden. We zouden het echter als acceptabel kunnen beschouwen dat toestemming niet volledig vrijwillig is, onder voorwaarde dat de relevantie van het onderzoek zeer groot is, en de studie het best beschikbare medische alternatief biedt voor kinderen met kanker. Wel kan het begrip van best available treatment protocollen vergroot worden bij ouders, door expliciet te maken dat het protocol door de beroepsgroep gezien wordt als de beste behandelingsoptie, maar dat er ook onzekerheden over bestaan die nog onderzocht moeten worden.
Aangezien onderzoek en zorg in hybride protocollen geïntegreerd zijn, ook in protocollen die in eerste instantie vooral zorg lijken te bieden, moet ons systeem van toezicht zich richten op differentiatie naar risiconiveau.

Daarnaast is het belangrijk dat betrokken professionals transparant zijn over het feit dat behandelingen in de kinderoncologie soms onlosmakelijk verbonden zijn met een vorm van onderzoek.

Hoofdstuk 8 is gebaseerd op de drie voorgaande hoofdstukken en biedt een leidraad voor professionals in de kinderoncologie en voor Medisch Ethische Toetsingscommissies ten aanzien van best available treatment protocollen, in de vorm van drie aanbevelingen.
Ten eerste moeten kinderoncologen aan patiënten en hun ouders duidelijk maken dat de onderzoekscomponent onlosmakelijk verbonden is met het krijgen van een behandeling. Ze moeten dus uitleggen dat best available treatment protocollen wetenschappelijke en behandeldoelen combineren, en aangeven wat er nieuw of anders is ten opzichte van het voorgaande protocol en waarom. Ten tweede, het kan voor dergelijke protocollen aanvaardbaar zijn dat de behandelend arts het protocol uitlegt en toestemming vraagt voor deelname van het kind, omdat deze protocollen worden aangeboden in een behandelsetting. Ten derde, het is belangrijk dat kinderoncologen de onderzoeksaspecten van best available treatment protocollen herkennen, en erkennen dat toetsing door een METC geboden is. Dit geldt ook voor METC's en zij moeten daarnaast toegerust zijn om dergelijke protocollen te toetsen.

Hoofstuk 9 tenslotte, is de Algemene Discussie van dit proefschrift en biedt een overzicht van de verschillende bevindingen die hierin naar voren komen. Verschillende perspectieven op medisch-wetenschappelijk onderzoek en ethische toetsing komen hier aan bod, om daarmee de vermenging van zorg en onderzoek in de kinderoncologie verder moreel te evalueren.
Deze perspectieven zijn 'Paternalisme van onderzoekers', 'Bescherming door regulering', 'Toegang tot medicijnen', en 'Samenwerkingsverbanden'. Vooral de eerste twee perspectieven lijken niet goed samen te gaan, aangezien de eerste ervan uit gaat dat de kinderoncologische beroepsgroep autonoom is in het stellen en controleren van regels, terwijl de tweede juist het belang van extern en onafhankelijk toezicht benadrukt. Het een sluit het ander echter niet uit, aangezien elementen van alle perspectieven naast elkaar kunnen bestaan in een en dezelfde praktijk. Het derde en vierde perspectief gooien het over een andere boeg, en richten zich op patiënten (en ouders) zelf, en op wat zij als belangrijk en waardevol beschouwen. Vanuit beide perspectieven worden onderzoek en zorg als twee nauw verweven praktijken gezien en hierbij worden van bovenaf opgelegde maatregelen om patiënten te beschermen gezien als overbodig. Het actief betrekken van patiënten en hun families bij het ontwikkelen en uitvoeren van onderzoek zou dilemma's van de vermenging van zorg en onderzoek kunnen verminderen, vanwege de focus op wat mensen zelf van waarde achten. Dit biedt een hele andere benadering, namelijk uitgaande van de keuzes en autonomie van patiënten/ouders in plaats van de macht en autoriteit van artsen en METC's. Hoewel nog steeds erkend wordt dat kinderen en hun ouders in een afhankelijke positie (kunnen) zitten en daardoor kwetsbaar zijn, zijn dit niet de kenmerken die hen definiëren.

Het combineren van actieve betrokkenheid van kinderen met kanker en hun ouders met de waarborgen van de andere perspectieven lijkt daarmee de beste manier om de belangen van ouders en kinderen te beschermen, zonder belangrijk onderzoek in de kinderoncologie tegen te houden.

Op deze manier heeft dit proefschrift gepoogd een bijdrage te leveren aan een ethische verantwoorde manier van het integreren van zorg en onderzoek in de kinderoncologie.

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List of publications

SAS Dekking, R van der Graaf, JJM van Delden. Strengths and weaknesses of guideline approaches to safeguard voluntary informed consent of patients within a dependent relationship. BMC Medicine. 2014 March 24;12:52.

SAS Dekking, R van der Graaf, AYN Schouten-van Meeteren, MC Kars, JJM van Delden. A qualitative study into dependent relationships and voluntary informed consent for research in pediatric oncology. Pediatric Drugs. 2016 April;18(2): 145-156.

SAS Dekking, R van der Graaf, JJM van Delden. Voluntary informed consent in pediatric oncology research. Bioethics. 2015 Dec 21.

SAS Dekking, R van der Graaf, MC Kars, A Beishuizen, MC de Vries, JJM van Delden. Balancing research interests and patient interests: a qualitative study into the intertwinement of care and research in pediatric oncology. Pediatric Blood & Cancer. 2015 May;62(5):816-22.

SAS Dekking, R van der Graaf, MC de Vries, MB Bierings, JJM van Delden. In: D Strech, M Mertz editors. Discriminating between research and care in pediatric oncology: ethical appraisal of the ALL-10 and 11 protocols of the Dutch Childhood Oncology Group (DCOG). Ethics and Governance of Biomedical Research: Theory and Practice. Springer; 2016. In press.

SAS Dekking, R van der Graaf, MC de Vries, MB Bierings, JJM van Delden, E Kodish, JD Lantos. Is a New Protocol for Acute Lymphoblastic Leukemia Research or Standard Therapy? Pediatrics. 2015 Sep;136(3):566-70.

R van der Graaf, SAS Dekking, MC de Vries, CM Zwaan, JJM van Delden. Pediatric oncology as a Learning Health care System: ethical implications of best available treatment protocols. Submitted.

SAS Dekking, R van der Graaf, MC de Vries, CM Zwaan, JJM van Delden. Best available treatment protocols in pediatric oncology: recommendations for practice. Forthcoming.