

COMMENTARY

Pediatric oncology as a Learning Health System: Ethical implications for best available treatment protocols

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Abstract

Introduction: Pediatric oncology is often considered as a field in which research and care are highly integrated. We believe that this integration can be seen as a so-called Learning Health System, a system in which research is considered an important means to continuously improve the practice of care. In order to substantiate our assumption of pediatric oncology as an LHS, we will analyze so-called “best available treatment protocols.” These protocols always contain research elements, even if the main goal of these protocols is to treat children diagnosed with cancer.

Methods: We will analyze the implications for ethical review and informed consent if these protocols had to function as exponents of pediatric oncology as an LHS.

Results: An analysis of best available treatment protocols teaches us how these protocols integrate care and research and how these protocols can be seen as exponents of a system where care and research need no longer be sharply distinct practices.

Discussion: Further intervention in the field of pediatric oncology is essential to also meet the requirements for an ethically responsible LHS.

Conclusion: Best available treatment protocols, which combine research and care, can be seen as examples of pediatric oncology as an LHS. However, in order to prevent that research elements in these protocols will be overlooked, we will have to find new ways to accommodate for the oversight of these protocols, such as multifaceted review and risk-adapted approaches. Moreover, informed consent process must be changed in order for patients to understand how care and research are integrated in these protocols.

KEYWORDS

ethics, Learning Health Systems, pediatric oncology

1 | INTRODUCTION

Pediatric oncology is often considered as a field where research and care are highly integrated.¹⁻⁴ 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.^{3,4} In addition, parents and (older) children are highly motivated to help to improve the diagnosis and treatment of childhood cancer in general.⁵ Second, 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

List of abbreviations: EU, European Union; LHS, Learning Health care System; REC, Research Ethics Committee

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are needed, followed by guideline development and evaluation.⁶ Third, for many diseases, there are collaborative group or international (eg, European or even TransAtlantic) phase III studies, and sometimes also open phase I/II studies.⁷ 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. Fourth, 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 and to implementation of new radiological techniques.^{3,5} Fifth and finally, for many cancers, children will be treated according to so-called *best available treatment protocols*.⁸ These protocols provide children with the best currently available treatment, which is usually an optimized version of the previous treatment regimen.⁹ While evidence resulting from one or more randomized controlled trials may be lacking, the protocols are developed based on data collection, experience, and (inter)national consensus among pediatric oncologists.⁹

The enormous drive to improve the field by integrating learning activities in daily care and treatment, the high rate of research participation, and in particular the best available treatment protocols that truly integrate care and research may turn pediatric oncology into a so-called Learning Health System (LHS), a system in which research is embedded in the practice of care to ensure “the best evidence for the collaborative healthcare choices of each patient and provider” and “innovation, quality, safety, and value in health care.”¹⁰ The LHS starts from the presumption that the practices of research and care are no longer sharply distinct as they usually are.^{2,10,11} 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.² Giving up the distinction has implications for ethical review and informed consent procedures since traditionally, research practices have been subject to more stringent (inter)national laws and ethics regulations than other medical learning activities involving human beings, such as quality improvement studies.^{2,11,12}

Thus far pediatric oncology has not been officially coined as an LHS, and proper analyses are lacking. To start this analysis of pediatric oncology as an LHS, in this paper, we will ethically analyze the *best available treatment protocols*. We will consider how and to what extent they contribute to the conception of pediatric oncology as an LHS. In particular, we will focus on the implications for ethical review and informed consent processes.

2 | ANALYSIS

2.1 | 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.^{2,8} The protocol may also involve centralized pathology or

What is known

- Pediatric oncology is often seen as a practice in which care and research are intertwined

What is new

- So-called best available treatment protocols are examples that clearly illustrate the integration of care and research.

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 new treatment strategy that is already considered the standard of care*. This uncertainty is typically 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.⁸ 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 Acute Lymphoblastic Leukemia-7 protocol resulted in worse outcome compared to the Berlin-Frankfurt-Münster study it was based upon and was stopped prematurely.⁷

2.2 | Review

Ethical review of best available treatment protocols currently depends on its categorization. In Figure 1, we describe 4 examples of classification of (Dutch) best available treatment protocols. The protocol in the first example underwent ethical review since it was classified as research; the protocols in the other examples were exempted from review since they were classified as care. 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 seems to be a sheer impossibility. Instead, we propose to more explicitly remove the boundary between research and care for these protocols and to *require ethical scrutiny for all best available treatment protocols*, regardless of the question whether the protocol can be classified as research or care.

Box 1 Example of best available treatment protocol as research

In 2003, 6 months of beta-interferon maintenance treatment was added to treat paediatric nasopharyngeal carcinoma, without prior evidence for its efficacy in a randomized controlled trial, concurrent with the implementation of radio-chemotherapy and the omission of methotrexate from the chemotherapy courses.¹⁸

Box 2 Example of best available treatment protocol classified as care

The DCOG NBL 2009 Treatment Protocol for Risk Adapted Treatment of Children with Neuroblastoma was based on the German GPOH protocol to which Dutch oncologists added two cycles of MBIG (meta-iodobenzylguanine) in high-risk patients. The rationale for adding these cycles of MBIG was a series of successful pilot studies conducted in the Netherlands (objective response rate 66% in 44 newly diagnosed neuroblastoma patients).¹⁹ At the same time, the risk of side effects was increased (one of the stopping rules was toxicity) and potentially adding the additional cycles could affect the ability to administer intensive chemotherapy due to bone marrow toxicity. Therefore, adding the cycles was a clear modification from the standard of care as defined by GPOH. Furthermore, another stopping rule was failure to deliver 6 cycles of chemotherapy after treatment with MBIG. There was also a potential safety risk whether adding MBIG would allow for collecting sufficient cells for autologous transplantation after the standard treatment with chemotherapy. The REC in charge of this protocol did not classify this study as research. The study was stopped early because in the end the number of high-risk patients suitable to undergo MIBG at diagnosis was too limited.

Box 3 Example of best available treatment protocol classified as care

In 2004, pediatric oncologists of the Dutch Childhood Oncology Group (DCOG) developed a new protocol for the treatment of children with acute lymphoblastic leukemia (ALL). This DCOG ALL-10 protocol was based on previous DCOG ALL protocols and on the findings of national and international ALL studies. The ALL-10 protocol also contained a significant modification compared with previous ALL protocols. After initial treatment, patients in the ALL-10 protocol were assigned to different risk groups based on minimal residual disease (MRD) levels. Risk stratification with accompanying tailoring of therapy had not been done in previous protocols. The results of the ALL-10 protocol were systematically collected, analyzed, and compared with historical controls. Patients were not randomly assigned prospectively. Stopping rules were established, and a data and safety monitoring board had access to data on side effects and serious adverse events, to assess whether the protocol should still be followed. Both the pediatric oncologists and the REC members regarded the intervention provided by ALL-10 as the best available (standard) treatment and therefore not as a research intervention to which patients were subjected.⁸

Box 4 Example of best available treatment protocol classified as care

In 2016, the Renal Tumour Study Group of the International Society of Paediatric Oncology (SIOP-RTSG) developed a new protocol for the diagnosis and treatment of childhood renal tumors, the UMBRELLA SIOP-RTSG 2016 (the UMBRELLA protocol), to continue international collaboration in the treatment of childhood renal tumors. This protocol combines research with care since it will also support integrated biomarker and imaging research, focusing on assessing the independent prognostic value of genomic changes within the tumor and the volume of the blastemal component that survives preoperative chemotherapy. The recommendations in the protocol have been established by a multidisciplinary panel of leading experts on renal tumors within the SIOP-RTSG. The UMBRELLA protocol is coined as a best available treatment standard. It was not subjected to ethical review in the Netherlands.²⁰

FIGURE 1 Examples of best available treatment protocols

2.3 | Informed consent

Another ethical challenge is the informed consent process for best available treatment 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.⁸ 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.¹³

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 presented and understood.

3 | DISCUSSION

An analysis of best available treatment protocols teaches us how these protocols integrate care and research and how these protocols can be seen as exponents of a system where care and research need no longer be sharply distinct practices. However, further intervention in the field of pediatric oncology is essential to also meet the requirements for an ethically responsible LHS.

3.1 | Ethical review

We propose a twofold review strategy for ethical review. First, we should create a multifaceted review system. Largent and colleagues have recently proposed a similar system of research ethics review for comparative effectiveness studies in an LHS.¹ In their model, several advisory boards, ethics committees, scientific committees, and even patient advisory boards review and approve research protocols, depending on the level of risks involved. Translated to pediatric oncology as an LHS, we may adopt a system for pediatric oncology in which the number of reviewing bodies will increase but formal ethics review by the Research Ethics Committee (REC) will decrease, in particular for studies with low risks (see the second tier of our approach described below). In pediatric oncology, we may think of a first round of internal review by scientific and ethical committees consisting of peers. They may determine that further review is essential, but also that full review by an REC would be overly demanding. One might object that this round of internal peer review creates potential conflicts of interest. However, currently, the research review system largely depends on the discretion of individual researchers to submit their protocols for review to RECs. Therefore, a first layer of internal review may lead to intensified review of the content of protocols.

Second, we should take a more *risk-adapted approach*,¹⁴ requiring more stringent or full review for protocols that contain changes that are *highly innovative* or *substantially deviate* from the current

standard treatment, such as in examples 1 and 2. But for other protocols ethics, review can be less stringent. Although in pediatric oncology, almost all treatments are high-risk treatments, this does not imply that full review is always essential. Usually best available treatment protocols are based on years of experience. They are not first in man studies or entirely new treatment strategies. Moreover, in principle, there are sound reasons to change current protocols. In a true Learning Health care System, the transition from the one protocol to the next may also be more continuous. Pediatric oncologists do not have to postpone submission to RECs until a protocol has been substantially changed, but can make continuous changes where necessary which are continuously being assessed. Hypothetically, we may then 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 best available treatment protocols.

This approach to the review of best available treatment 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. At the same time, if risk-adapted approaches are adopted, other ethical oversight protection mechanisms will have to play a role to ensure scientific validity and that patients are not exposed to unreasonable risks. For instance, it will then be essential to ensure quality of data, monitoring of the approved protocol by Data and Safety Monitoring Boards, and scientific validity by means of clearly formulated hypotheses and prospectively defined statistical plans, and to formulate stopping rules.

3.2 | Informed consent

Best available treatment protocols may lead to compromises to voluntary informed consent, which cannot be easily mitigated. But they may be considered as acceptable when the social value of the study 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.¹⁶ They might explain that even though the treatment is considered the best available alternative according to the medical professional standard, its relative merits may still be uncertain. In the same vein, a form of “scientific citizenship”¹⁷ 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.¹¹ 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.

4 | CONCLUSION

Best available treatment protocols, which combine research and care, can be seen as examples of pediatric oncology as an LHS. However, in order to prevent that research elements in these protocols will be overlooked, we will have to find new ways to accommodate for the oversight of these protocols, such as multifaceted review and risk-adapted approaches. Moreover, 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 informed consent processes for these protocols, in which patients are meaningfully engaged. Patients and their parents have to understand that research and care in pediatric oncology may be inextricably intertwined.

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ETHICAL APPROVAL

This article does not contain any studies with human participants performed by any of the authors.

COMPETING INTERESTS STATEMENT

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare no financial relationships with any organization that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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TRANSPARENCY DECLARATION

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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