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Ethical Challenges in Cancer Research in Children

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Key Words. Ethics • Pediatrics • Cancer • Clinical trials

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the ethical challenges in cancer clinical trials that are particularly important when children are research subjects.
2. Describe the process of obtaining assent and consent for a child to participate in a cancer clinical trial.
3. Identify the different ethical challenges that arise in different phases of oncology studies.

ABSTRACT

Clinical research has led to great advances in cancer therapy for children, and a greater proportion of children than adults with cancer participate in clinical trials. Despite this success, there remain important ethical challenges in conducting this research. There are challenges in obtaining informed consent and assent when children are research subjects; challenges arising from study design issues in phase III, II, or I clinical trials; and challenges related to the development of new classes of drugs, especially molecularly targeted therapies. It is important for researchers and clinicians to understand these challenges so that progress in cancer treatment is achieved in a sound ethical and regulatory fashion. The Oncologist 2007;12:1336–1343

INTRODUCTION

The improvements in outcomes for children with cancer over the last five decades are often held up as a model of the importance of the organized, consistent application of clinical research approaches to therapeutic challenges. For example, whereas childhood leukemia was nearly universally fatal before 1960, approximately 80% of children with leukemia are now disease free 5 years after diagnosis [1]. In contrast to adults, a high percentage of children with cancer are enrolled into clinical trials, and indeed, it is generally considered standard of care to do so. Despite the incontrovertible successes of this approach, however, the ethical challenges of conducting clinical trials in children with cancer remain formidable. In this article I review the special challenges related to obtaining informed consent and assent when children are research subjects; challenges arising from study design issues in phase III, II, or I clinical trials; and challenges related to innovations in basic science, such as the development of molecularly targeted therapies.

INFORMED CONSENT

It has long been recognized that performing a medical procedure on a patient without the patient’s consent is legally tantamount to battery. In 1915, Benjamin Cardozo, in the
case of a woman who underwent surgery against her will, famously stated that “Every human being of adult years and sound mind has a right to determine what shall be done with his own body” [2]. However, what needed to be disclosed for a patient’s consent for treatment to be valid remained unsettled. In 1957, the term “informed consent” was first used to describe the result of a physician’s deliberation after a physician has disclosed the facts that are material to the patient’s decision about treatment [3]. The subsequent trend, at least in the U.S., has been toward an increasingly patient-centered approach in which the physician may recommend, but the patient ultimately decides.

The standard is even higher for informed consent for participation in biomedical research than it is for consent to undergo medical treatment. The Nuremberg Code [4] states that “the voluntary consent of the human subject is absolutely essential” for permissible medical experiments, and further elaborates that the subject “should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision” whether to participate. The Belmont Report [5] grounds these requirements in the principle of respect for persons, which requires that individual autonomy be respected. Thus, potential research subjects with the capacity to make decisions for themselves must be given sufficient information to make a considered determination about their desire to volunteer. The requirement for informed consent from research subjects is now the standard starting point for discussion of ethical conduct of human subject research.

Adequate informed consent to participate in research requires a number of key elements. First, certain key information must be provided (Table 1). The prospective subject must be told, at a minimum, the purpose of the research and the procedures to be followed, and identification of any procedures which are experimental.

Table 1. Requirements for informed consent (Title 45 Code of Federal Regulations Part §46.116)

<table>
<thead>
<tr>
<th>Basic elements</th>
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<tbody>
<tr>
<td>1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject’s participation, a description of the procedures to be followed, and identification of any procedures which are experimental</td>
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<td>2. A description of any reasonably foreseeable risks or discomforts to the subject</td>
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<td>3. A description of any benefits to the subject or to others which may reasonably be expected from the research</td>
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<td>4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject</td>
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<td>5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained</td>
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<tr>
<td>6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained</td>
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<tr>
<td>7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects’ rights, and whom to contact in the event of a research-related injury to the subject</td>
</tr>
<tr>
<td>8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled</td>
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<tr>
<th>Additional elements to be provided when appropriate</th>
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<tbody>
<tr>
<td>1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable</td>
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<td>2. Anticipated circumstances under which the subject’s participation may be terminated by the investigator without regard to the subject’s consent</td>
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<tr>
<td>3. Any additional costs to the subject that may result from participation in the research</td>
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<tr>
<td>4. The consequences of a subject’s decision to withdraw from the research and procedures for orderly termination of participation by the subject</td>
</tr>
<tr>
<td>5. A statement that significant new findings developed during the course of the research which may relate to the subject’s willingness to continue participation will be provided to the subject</td>
</tr>
<tr>
<td>6. The approximate number of subjects involved in the study</td>
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VULNERABLE SUBJECTS

CONSENT, PERMISSION, AND ASSENT IN VULNERABLE SUBJECTS

Obtaining consent from vulnerable subjects, whose ability to decide autonomously about research participation may be compromised, is even more complicated. These vulnerable subjects require special protections, which revolve around the consent process and how to preserve voluntariness and autonomy. The federal regulations [12] specify additional protection for three classes of vulnerable subjects: pregnant women, fetuses, and neonates (45 CFR 46 subpart B); prisoners (subpart C); and children (subpart D). Mentally disabled persons and economically or educationally disadvantaged persons are also mentioned in the federal regulations (§46.111(b)), and racial minorities, the economically disadvantaged, the very sick, and the institutionalized are mentioned in the Belmont Report as being potentially vulnerable.

In the case of children, both the legal and developmental aspects of competence and capacity to give informed consent must be considered. By law, most children (individuals under the age of majority in the state where the research is being conducted) are not considered competent to give consent to medical treatment, let alone to consent to participation in medical research. Perhaps more importantly, regardless of the law, most children do not develop a cognitive capacity that approaches an adult’s ability to give appropriate informed consent until somewhere in the middle of the teenage years. The development of children’s capacity to comprehend research participation is reviewed in the Institute of Medicine’s report Ethical Conduct of Clinical Research Involving Children [13].

In order to overcome these competence and capacity issues, the usual mechanism for obtaining informed consent for a legal minor consists of providing the same information to the parents as would be given to an adult potential research subject, with developmentally appropriate information being given to the child in most cases. The parents then provide consent, or permission, for their child to participate in the research. The child provides assent, or agreement to participate, without this agreement rising to the level of informed consent. Although this approach sounds straightforward, implementing it can be quite challenging. In particular, recent issues of whether there are, or should be, limits to parents’ ability to give permission for a child to participate have arisen in the context of nontherapeutic research. This topic is discussed further below. In addition, parents are under considerable stress at the time of diagnosis or relapse of a child with cancer. This stress may interfere with their ability to comprehend or retain information as well as they normally would, even if they are otherwise completely competent. This in turn may raise issues about whether the consent or permission they provide on behalf of their child is fully informed [14–16].

The meaning of “assent” can also be problematic. The federal regulations remind us that “assent means a child’s affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent” (§46.402(b)). Nonetheless, how this affirmative agreement can be measured, how seriously dissent should be taken, and at what developmental stage the child’s wishes should take precedence over all else are controversial. The regulations require the IRB, in determining whether assent is necessary, to “take into account the ages, maturity, and psychological state of the children involved” (§46.408(a)). Although the age of 7 years is often used as a rough guideline for when it is reasonable for investigators to begin to explain to children what will be done to them and to ask them to agree [17], there is a wide variation in IRB practices on this topic, demonstrating that interpretation of the regulations is quite difficult in reality [18–20]. In addition, if the research presents the prospect of an important direct benefit to the child that is available only in the context of the research, the federal regulations permit the requirement for assent to be waived (§46.408(a)). In pediatric oncology, where treatment offered in research protocols is often considered standard of care, the question of whether a potential benefit is available only through participation in the research is particularly germane and thoroughly scrutinized by IRBs.

RISKS RELATED TO STUDY PHASE

The nature of cancer therapy itself also raises distinct complicating issues in research. Because the disease is often life-threatening or fatal, and because its treatment is often fraught with toxicity and adverse events, many studies of cancer therapy carry with them the potential for serious risk to the individual subject, as well as the potential for the subject to have personal benefit from participating. As part of
Table 2. Research risk categories (Title 45 Code of Federal Regulations, Part 46 Subpart D)

<table>
<thead>
<tr>
<th>Paragraph</th>
<th>Category</th>
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<tr>
<td>§46.404. Research not involving greater than minimal risk</td>
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<tr>
<td>§46.405. Research involving greater than minimal risk but presenting the</td>
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<tr>
<td>prospect of direct benefit to the individual subjects</td>
<td></td>
</tr>
<tr>
<td>§46.406. Research involving greater than minimal risk and no prospect</td>
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<tr>
<td>of direct benefit to individual subjects, but likely to yield generalizable</td>
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<tr>
<td>knowledge about the subject’s disorder or condition</td>
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<tr>
<td>§46.407. Research not otherwise approvable which presents an opportunity</td>
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<tr>
<td>to understand, prevent, or alleviate a serious problem affecting the health</td>
<td></td>
</tr>
<tr>
<td>or welfare of children</td>
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</table>

There are specific challenges related to the phase of study that a child may be enrolled in. In phase III studies, the overall contribution of a new agent or approach is evaluated, often in a large, randomized trial setting in which the new agent is compared with the previous best standard therapy. In phase II studies, the effectiveness of the drug in a particular setting or disease is studied; in pediatric oncology, these studies are usually single-agent, nonrandomized trials. In phase I studies, a drug is given for the first time to normal humans or, more commonly in the case of toxic anticancer drugs, to patients with advanced disease, primarily in order to learn about the drug’s pharmacology and toxicities. Biologic correlative information about the new agent, such as the degree to which it inhibits a molecular target in the host or tumor, is also frequently included in early-phase studies in particular.

Most “front-line” pediatric cancer studies are phase III studies. These studies commonly involve the addition of a new drug that has shown some single-agent activity in the disease being treated to an already-proven regimen in order to determine whether the addition improves outcome. The ethical issues in these studies can be subtle and often revolve around which components of the treatment actually represent research and how much potential risk and benefit those individual components present [21, 22]. For example, patients with newly diagnosed leukemia might be enrolled in a study incorporating a new monoclonal antibody into a standard therapy backbone. A bone marrow aspiration might be performed at a particular point after the antibody is administered, at a time when bone marrow examination would not usually be indicated. It is fairly evident that administration of the antibody is experimental, and that its risks and benefits must be weighed carefully. The component analysis approach argues that the risks and benefits of the bone marrow aspiration and any part of that procedure, such as sedation, must be weighed separately and assigned their own risk category [21, 22]. In this scenario, therefore, apparently minor differences of opinion about how much greater risk the procedure presents and how much potential benefit to the child there is of the procedure can lead to major differences in the approvability of that part of the research from an IRB’s point of view. Nonetheless, phase III research in children with cancer does not usually involve major ethical controversies.

Phase II studies are usually conducted in patients who have had the known standard therapy for their cancer and whose disease has recurred, or less commonly, in patients with a newly diagnosed disease for which there is no standard therapy. These studies most often have, as their goal, to establish the response rate, with a reasonable confidence interval, of a particular tumor to a particular treatment. In pediatric oncology, most phase II studies are not randomized because the goal is not to determine how active the new agent is compared with something else, but rather, simply to describe the response rate, adverse events, and sometimes biologic correlates of response or toxicity of the new agent [23–27]. Among the ethical challenges, however, are issues pertaining to investigator bias and to determining exactly what information about the current status of a trial a prospective subject needs in order to make an “informed” decision whether to participate.

Investigator bias in early-phase studies may arise when physicians or families develop enthusiasm for a treatment before the actual risks and benefits of the treatment have been fully described. Such enthusiasm often is based on anecdotes or popular press reports of encouraging results with
a new agent. For example, when the angiogenesis inhibitor endostatin was discussed on the front page of The New York Times, not only did patient demand for access to the initial trials far exceed the number of subjects needed, but also, the stock price of the company developing the agent increased fivefold within days [28–31]. Similarly, a deep-seated belief on the part of physicians and advocates that high-dose chemotherapy and bone marrow transplant should be better than conventional chemotherapy in advanced breast cancer resulted in high-dose treatment of >40,000 women in the 1990s, mostly outside of clinical studies, before randomized clinical trials demonstrated that there was little, if any, benefit to this approach (reviewed in Mello and Brennan [32]).

Similar problems with bias can create difficulty in pediatric oncology. Pressure to make an investigational agent available to a particular patient may result in enrollment of subjects of questionable eligibility into studies. In addition, when an agent is approved for some other indication but its role in pediatric cancer is not yet determined, bias that it is beneficial may result in treatment of a large number of patients off study. This has several disadvantages. First, many patients may be exposed to an agent that will eventually be discovered not to be helpful, and their risk will not have been offset by the information that would have been gained in a clinical trial. Second, these patients may lose the opportunity to receive other agents currently under study, some of which may turn out to be active. Third, clinical trials of the agent in question, and of other agents, may suffer from slow accrual because potential subjects are diverted into off-study treatment. Conversely, if there is bias that an agent is inactive or unlikely to be active, even though the relevant phase II studies are not yet complete, accrual to the trials may be slow. Either situation results in a delay in determination of the actual activity of the new agent. Paradoxically, if many physicians are using a drug off study, this may result in a larger number of children receiving the agent before it is definitively shown to be inactive than would have if the negative study had been completed in a more timely fashion. In order to mitigate investigator and patient bias as much as possible, the response rate in phase II studies is usually masked until accrual is complete.

The opposite ethical dilemma arises when phase II studies are nearing completion and activity has not yet been observed. Most phase II studies in pediatrics involve a multistage approach, in which activity is initially assessed in a small (9–22 subjects) cohort, which is expanded only if the observed activity exceeds a preset threshold. If all patients in the first cohort were enrolled at the same time, there would be little issue because the response rate could fairly be said to be unknown at the time of study entry for all subjects. However, as the study proceeds, an overall response rate can be estimated based on each subject’s individual outcome. Although the confidence interval will be wide, the estimate of the response rate will decrease with each subject who does not have a response to therapy. Thus, toward the end of a study of an agent that turns out to be inactive, patients will be enrolled when the response rate is predicted to be low, although not as low as the study design defines as inactive. Ratain et al. memorably formulate this problem as “what do we tell the fourteenth patient?” [25, 33]. Table 3 shows the odds of consecutive nonresponses, and the upper limit of the 90% confidence interval around the estimated response rate after each consecutive subject does not respond, in a cohort of 14 subjects, for an agent whose true response rate is 20% (the lower limit is always a response rate of 0).

![Table 3](image)

For example, when the response rate really is 20%, the probability of getting five nonresponders in a row is 33%, and the corresponding 90% confidence interval is 0%–45%.

Table courtesy of Susan Hilsenbeck (supported in part by NIH P30CA12).
challenges of phase I studies arise from the apparent conflict between the primary goal of the study, which is usually to determine the maximum tolerated dose (MTD) of an agent to be used in future studies, and the primary goal of the patient, which is almost always to be helped by the experimental treatment. The “therapeutic misconception,” or belief that a clinical trial is designed for the subject’s benefit, is widespread and persistent, and may create difficulties with informed consent [37–41]. In addition, although IRBs must consider the potential for direct benefit when reviewing pediatric research, there is some debate about whether such potential exists in early-phase studies [13, 42, 43]. Reviews of phase I study outcomes have shown that the response rate is generally 5%–10% [44–46]. Symptom control and quality of life improvement, which could also be beneficial, have not been assessed regularly in these studies. Furthermore, response is not spread evenly among all trials. Most trials have few or no responses, whereas trials of an agent that turns out to be active may have a high proportion of responders [44]. The most extreme example of the latter is probably the phase I trial of imatinib in patients with chronic myelogenous leukemia, where the hematologic response rate was 98% [47]. Most responses in phase I trials, at least of cytotoxic agents, occur in patients receiving >80% of the eventual MTD [46].

Phase I trials in children often begin after there are some data available from adult studies. Thus, there may be some hints regarding drug activity, at least against adult tumor types. In addition, because the starting dose for phase I studies in children is usually close to the adult MTD [48], children have the advantage of being less likely to receive “subtherapeutic” doses of new drugs. Nonetheless, it is difficult to assess in advance how likely any drug is to produce responses. Overall, although there is not complete consensus, it is reasonable to consider that phase I trials of new anticancer agents do offer a prospect of direct benefit to the children participating.

CHALLENGES OF MOLECULARLY TARGETED THERAPY

There are other ethical challenges in pediatric cancer research that may not be related directly to the subject and his or her treatment. For example, the new paradigm for anticancer drug development has moved away from identification of generally cytotoxic agents to development of agents, like imatinib, that specifically target a critical pathway within cancer cells. Inherent in this approach to drug development is the concept that different tumors are likely to have different critical pathways, and that treatment may eventually be tailored to a specific tumor type. It is reasonable to expect that, at some point, agents could be developed that target pediatric tumors without an analogous target in adult tumors. For example, if an agent were developed that targeted the EWS-FLI1 fusion protein in Ewing’s sarcoma, it is unlikely that there would be adult studies of the drug. Thus, there might be situations in which an anticancer drug could first be given to children, with no prior experience in adults. This situation might exacerbate many of the controversies discussed above, especially in the phase I setting, although for now it remains hypothetical.

The development of molecularly targeted agents invariably includes assessment of the effect of the drug on the target. This brings into sharp focus the problem of more than minimal risk, nontherapeutic components included in therapeutic trials, such as tumor biopsies. Competent adults may volunteer for such studies, but it is less clear whether parents may give permission for their children to participate in them. Two court cases addressed this issue for otherwise healthy children. In T.D. v. New York, a New York court found “unacceptable the provisions that allow for consent to be obtained on behalf of minors for participation in greater than minimal risk non-therapeutic research from the minor’s parent or legal guardian” [49]. In Grimes v Kennedy-Krieger, the court held that “in Maryland a parent . . . cannot consent to the participation of a child or other person under legal disability in nontherapeutic research or studies in which there is any risk of injury or damage to the health of the subject” [50]. (The court later clarified that “any risk” meant any more than minimal risk.) These cases have raised concerns in the research community about whether new limits will be imposed on nontherapeutic research in healthy children that currently would fall into categories §46.406 or §46.407 [51]. Because most pediatric oncology studies, however, fall into category §46.405, there has been little impact so far of these decisions on research in children with cancer.

The scientific need to obtain biologic specimens for correlation with drug activity can also create the potential for coercion if a patient’s ability to get an agent he hopes to benefit from is contingent on his willingness to undergo a procedure to which he might otherwise not consent. On the other hand, if the scientific goals of the study cannot be achieved because the specimens are not obtained, then the study may not meet the ethical requirement of contributing to advancements in knowledge. The Children’s Oncology Group Phase I Consortium has taken the stance that such correlative biology sampling should generally be optional, arguing that if there is insufficient willingness of families to participate in the sampling when it is truly voluntary, then perhaps the procedures are more burdensome than they might appear to the researchers. The participation rate in optional correlative studies is being monitored by this group [52].
CONCLUSION
Clinical research has been and will continue to be essential to improving survival and decreasing disease- and treatment-related morbidity in children with cancer. In parallel, the complexity of designing such research and obtaining informed consent and assent for children to participate in it, especially when it has nontherapeutic components, will continue to challenge pediatric oncologists, IRBs, parents, and children even as new therapies emerge. It is important for researchers and clinicians to understand these challenges so that progress in cancer treatment is achieved in a sound ethical and regulatory fashion.

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