

# Virtual Mentor

American Medical Association Journal of Ethics  
March 2009, Volume 11, Number 3: 207-214.

## CLINICAL CASE

### Is There a Duty to Inform Patients of Phase I Trials?

Commentary by Courtenay R. Bruce, JD, Anne Lederman Flamm, JD, Thomas W. LeBlanc, MD, MA, and Philip M. Rosoff, MD, MA

Andrew, a 15-year-old boy, was diagnosed with acute lymphocytic leukemia. He underwent standard chemotherapy treatments and a bone-marrow transplant, none of which produced remission. No other standard therapies were available for Andrew to try. Dr. Wilson, Andrew's oncologist, knew of a phase I trial of an experimental oncology therapy going on at the hospital where Andrew was being treated. Participants in these types of trials have end-stage cancer and often a prognosis of months to live, criteria that Andrew fit. Phase I trials test the safety of the experimental agent and determine the dosage that will be used in later-phase trials.

Dr. Wilson knew that phase I trials did not aim for efficacy and did not demonstrate very favorable response rates for outcomes such as tumor shrinkage. Yet he felt he should inform Andrew and his family about this study, giving them the option to decide whether or not Andrew would participate. He was concerned that, in presenting this option to them, they may think that he was advocating for Andrew's participation.

### Commentary 1

by Courtenay R. Bruce, JD, and Anne Lederman Flamm, JD

In 2007, approximately 10,400 children under the age of 15 were diagnosed with cancer. Of them, 1,545 will die from the disease [1]. Despite these sobering figures, pediatric-cancer survival rates are increasing, most likely as a result of clinical research that includes pediatric-oncology participants in the hopes of finding new therapies.

### Ethical Issues

Standard phase I studies are first-in-human trials in which successive cohorts of three to six patients receive increasing doses of an investigational agent to evaluate the drug's toxicity, maximum tolerated dosage, and pharmacokinetics. While investigators may note clinical responses and outcomes, phase I trials are not designed to test efficacy, a target reserved for subsequent phase II testing. Studies estimate only a 4 to 5 percent response rate in phase I cancer trials, which historically used highly toxic drugs with unknown long-term effects; thus, they are typically offered only to patients who have exhausted all established therapeutic options [2]. The combination of toxic drugs, dying subjects, and the low likelihood of direct benefit raises concern that phase I trials subordinate individual participants'

well-being to the interests of science. Phase I studies in end-stage pediatric-cancer patients like Andrew are particularly ethically controversial in light of society's special duty to protect children. Historical examples of serious abuses of children in the name of scientific advancement are experiments in Nazi concentration camps and, in the United States, the infamous Willowbrook study in which investigators deliberately infected institutionalized children with the hepatitis virus [3].

Dr. Wilson recognizes the inherent tension between the scientific purpose of phase I studies and a physician's ethical obligation to promote his patient's best interest. The case does not indicate that Dr. Wilson has direct involvement in the phase I trial to which he may refer Andrew, but, even without such involvement, physicians can face pressure to support research, and that pressure might influence their decision about whether participation is appropriate for a patient.

Promoting patient best interest and enhancing autonomy require physicians to disclose the risks and benefits of participation and nonparticipation. Despite the low likelihood of direct benefit, patients often perceive the phase I option as therapy [4]. The dependent nature of the patient-physician relationship encourages this "therapeutic misconception" inasmuch as the patient trusts the physician's medical judgment and may believe that the physician offers only what is best [5]. Influences outside this relationship can exacerbate therapeutic misconception. The media readily disseminates early favorable research results, and research institutions often advertise trial participation as being a form of treatment or the best chance for a cure [6].

Concern about therapeutic misconception led to recommendations to improve the informed-consent process in order to enhance participants' understanding of phase I purpose, design, and risk-benefit ratio [6]. More recently, however, patients and advocacy groups have disavowed exclusion from research as a means of protecting patients with incurable diseases, arguing that individuals with terminal cancer, not healthy physicians or paternalistic research oversight bodies, should determine whether the risk-benefit ratio is acceptable [7]. Full disclosure throughout the consent process enables prospective participants to make this risk-benefit assessment.

This informed-consent process also includes a discussion of nonclinical benefits. The patient may benefit psychologically from participation by fulfilling the need to gain some control over his or her illness or contributing to society. The patient might derive a sense of hope as well, thinking that if there were no hope, the drug would not be tested [3, 4].

Patients express that participation offers hope even when they understand the trial's purpose. In contrast, when therapeutic options are absent, both patients and physicians often view an alternative to trial participation—palliative care—as giving up. Some physicians are uncomfortable with ceasing curative efforts because this seems contradictory to the role of healer [4, 6]. Nonetheless, information about

alternatives to participation is necessary for the patient to make a risk-benefit assessment. The physician may want to discuss the advantages and disadvantages of both participation and nonparticipation concurrently to mitigate concerns about physician influence. Discussing palliative care within the context of a comprehensive care plan that provides symptom control and comfort while living with cancer, and not just as a transition to dying, may limit the patient's and the physician's apprehension about the topic. The physician may also want to discuss hospice care and its benefits, including pain palliation and provisions for spiritual or social needs of the patient and his family [3].

Because patients have a right to be informed of and make autonomous choices about appropriate care, physicians have an ethical obligation to inform patients who meet eligibility criteria for phase I trials of that option. The information given to prospective phase I participants depends on the physician's involvement in the trial. If the physician is not actively part of the trial, he or she may not be obligated or even able to provide explicit information about its particulars. In all cases, the trial investigator should be the one to present detailed information at the time of enrollment. The referring physician can supply general information about phase I studies and discuss whether participation is an appropriate choice for the patient [2, 4, 6]. The referring physician can also ensure that the consent process contains adequate information and that the patient's choice is voluntary.

### **Adolescent Assent**

Adolescent patients must be able to comprehend the information they receive and to assent or dissent voluntarily to participation in research. Legally, adults are presumed to be autonomous and competent to consent to become research participants, while unemancipated minors are generally presumed to be legally incompetent to consent [8]. In such instances, parents have a legal right to make health care decision in behalf of their child. In this case, although it might be legally sound to confine decision-making powers to Andrew's parents, Dr. Wilson has an ethical obligation to Andrew. In an attempt to reconcile Andrew's interest in autonomy with parental authority, Dr. Wilson should seek Andrew's assent and his parents' permission for Andrew to participate in the trial [3].

To assent, Andrew must have a basic understanding of the study's purpose and procedures and must be able to state whether he wishes to participate or not [8]. Psychological studies have indicated that, by age 14, most minors have attained the cognitive skills necessary for reasoning and decision making [8, 9]. Andrew should demonstrate maturity, understand what is being asked of him, and be able to communicate his thoughts about participation. The physician can seek assistance in assessing a patient's capacity, such as the expertise of a psychiatrist or developmental psychologist [8].

Andrew's assent or dissent must be voluntary, and he should know his assent is being sought independent of parental permission. The tendency for children to defer to their parents can be mitigated by controlling the consent process. Dr. Wilson

might consider talking to Andrew without his parents, or, in their presence, addressing questions specifically to Andrew and encouraging him to speak [8, 10].

If Andrew dissents, it is reasonable for Dr. Wilson to inquire about the bases for his decision. He may be dissenting on grounds of misconceptions that can easily be clarified. Dr. Wilson should also evaluate whether his dissent reflects age-appropriate nonconformity, because a patient's true preferences may be obscured by nonconformist attitudes. If Andrew continues to dissent after undertaking a thorough decision-making process, he is likely demonstrating his true values and preferences [8].

Divergent conclusions between parents and their adolescent can also present ethical challenges. Parents are legally obligated to promote their child's best interests [3, 8, 10]. If Dr. Wilson has reason to believe Andrew's parents are not considering his best interests, he might petition a court to appoint a guardian for Andrew, though guardianship is typically pursued as a last resort when a child lacks an appropriate representative. Dr. Wilson should use his professional judgment in determining whether the parents are competent to contribute to the decision making.

Parents may disagree with each other or their child. Federal regulations, state law, and institutional research policy provide guidance on whether one or both parent(s) must give permission for trial participation. In general, where the child can expect no direct benefit from the trial drug, federal law allows him or her to be exposed to only minimal risk. If Andrew's parents want him to participate and Andrew objects, his objection should be weighed heavily since phase I trials offer little chance of a clinical benefit [8, 10].

## References

1. National Cancer Institute. Childhood cancers: questions and answers. 2008. <http://www.cancer.gov/cancertopics/factsheet/Sites-types/childhood>. Accessed December 30, 2008.
2. Roberts TG Jr, Goulart BH, Squitieri L, et al. Trends in the risks and benefits to patients with cancer participating in phase 1 clinical trials. *JAMA*. 2004;292(17):2130-2140.
3. Kodish E. Pediatric ethics and early-phase childhood cancer research: conflicted goals and the prospect of benefit. *Account Res*. 2003;10(1):17-25.
4. Miller M. Phase I cancer trials: a crucible of competing priorities. *Int Anesthesiol Clin*. 2001;39(3):13-33.
5. Henderson G, Churchill LR, Davis AM, et al. Clinical trials and medical care: defining the therapeutic misconception. *PLoS Med*. 2007;4(11):e324.
6. Miller FG, Rosenstein DL. The therapeutic orientation to clinical trials. *N Engl J Med*. 2003;348(14):1383-1386.
7. *Abigail Alliance for Better Access to Developmental Drugs v von Eschenbach*, 445 F.3d 470 (DC Cir. 2006).
8. Leikin S. Minors' assent, consent, or dissent to medical research. *IRB*. 1993;15(2):1-7.

9. Daugherty C, Ratain MJ, Grochowski E, et al. Perceptions of cancer patients and their physicians involved in phase I trials. *J Clin Oncol*. 1995;13(5):1062-1072.
10. Committee on Bioethics, American Academy of Pediatrics. Informed consent, parental permission, and assent in pediatric practice. *Pediatrics*. 1995;95(2):314-317.

Courtenay R. Bruce, JD, is a postdoctoral fellow in the Cleveland Fellowship in Advanced Bioethics program. Her research interests include pediatric and surgical ethics.

Anne Lederman Flamm, JD, is an associate in the Bioethics Department at the Cleveland Clinic. She spent 7 years as a clinical ethicist at The University of Texas M.D. Anderson Cancer Center in Houston, and is currently developing a research program on ethics and cancer.

## **Commentary 2**

by Thomas W. LeBlanc, MD, MA, and Philip M. Rosoff, MD, MA

This case raises a number of difficult ethical issues, in both the clinical and philosophical realms. Owing to their complexity, a thorough analysis is impossible in a short commentary; so we will highlight the most salient questions in the hopes that this piece will serve as a springboard for further discussion.

One must begin with some background information about Andrew's condition. Acute lymphoblastic leukemia (ALL) is the most common childhood leukemia, accounting for upwards of 30 percent of all pediatric cancers [1]. Due in no small part to participation of children and their families in organized clinical trials over the last 30 years, it is now a readily treatable disease in the majority of cases, with cure rates averaging roughly 80 percent [2]. Nonetheless, relapse following therapy for ALL remains the second leading cause of cancer deaths in children. Unlike most adults with cancer, the majority of children with cancer are enrolled in a clinical trial. Clearly, clinical research involving pediatric malignancies is of paramount importance. Children enrolled in so-called therapeutic trials derive direct benefits from their participation, ranging from the Hawthorne effect, to positive effects of the experimental therapy [3-6]. Moreover, the clinical research enterprise bestows a social good that benefits future patients.

Andrew appears never to have been in remission, which portends a dismal prognosis. While myeloablation with stem-cell transplant may offer some possibility for long-term survival, patients must be in remission for the best chance of success. At this point, having failed first- and second-line therapies, options for Andrew's care include palliation or participation in another clinical trial (if he is eligible), but neither of these is curative. It is a common misconception that therapeutic clinical trials always seek a cure, so we must be careful to clearly distinguish between different types. In this case, Dr. Wilson feels obligated to inform Andrew about a

phase I trial. This is a very specific subtype of clinical trial and is quite different from the multicenter cooperative studies that led to today's improved cure rates for ALL. Rather, the purpose of a phase I study is "to evaluate [a drug's] safety and identify side effects" [7]. Hence, there can be no reasonable expectation of any direct benefit to a participant.

Unfortunately, it seems that the mere suggestion of a phase I trial as an option lends credence to, or generates a false hope for, a cure or some form of beneficial outcome, especially if it is offered by the treating physician. Dr. Wilson knows (or should know) that such studies aim to collect data regarding safety, pharmacokinetics, and other *in vivo* drug properties, but these details are easily misconstrued by patients and families, regardless of a physician's intentions [8]. Some have termed this false hope for cure the "therapeutic misconception" [9, 10]. In this setting, a phase I study may be viewed as a last-ditch effort for a cure, and can be difficult to refuse when presented as an option. Compared to palliation, which is often perceived by families as "giving up hope," participation in the trial feels like a way to keep fighting. But properly understood, a phase I study stands to yield no such benefit to the subject, and thus cannot rightfully be thought of as a reasonable choice in the quest for a treatment.

The therapeutic misconception presents Dr. Wilson with a difficult dilemma, inasmuch as it may conflict with other physician duties, including the Hippocratic requirement to "do no harm," and its unwritten prescriptive corollary to "do good" for individual patients. It is particularly problematic if a phase I study is pursued at the expense of palliation, or if the study medication hurts the child. One might argue that the bioethical principle of beneficence mandates a "duty to palliate" whenever there is no remaining hope for a cure. Since a phase I study presents no such hope, it might be considered tragic for Andrew to participate in this trial instead of just going home, spending quality time with family and friends, and living out his remaining weeks on his own terms with the help of a home hospice or similar program.

Insofar as this study provides no reasonable expectation for cure, there can be no legitimate duty to inform a patient or family about the phase I study. One might even argue that raising such a study as an option contributes to the fostering of false hope and inappropriate delay of rightful palliation. The simple act of an oncologist's presenting a study as an option commonly leads to the presumption that it will benefit the patient. Yet for phase I studies, there can be no reasonable expectation of *any* direct benefit to the patient, regardless of how promising a new drug or technology might seem. There are too many variables and risks to assume any chance of benefit, and most certainly not a chance of cure. Not surprisingly, pediatric oncologists are conflicted and confused about the nature and role of phase I studies [11].

Unfortunately, even the process of phase I studies can be misleading with CT scans, blood counts, and bone-marrow biopsies often being part of the protocols. If one has no expectation of a tumor response, why should these measurements be a part of the

study? Yet these tests further facilitate unrealistic expectations from participants and confuse families. So if participation delays palliation, one must wonder whether presenting the study as an option is ethical in itself. It would seem that the only ethically reasonable option, then, is to allow participation in phase I studies *only* when rightful and appropriate palliation is also provided and when participants and families fully understand the aims of the trial. This is quite a tall order, to say the least.

On the other hand, if doctors did not enroll their (and others') patients in phase I trials—be they children or adults—we would never be able to gather the vital information about new drugs and treatments that fuels the advance of medicine. Thus, there may be a social duty, if you will, for doctors to offer patients the option of participation in these trials (and for patients to volunteer), even when there is no expectation of individual benefit. While outside the scope of this commentary, this point raises the complex questions of the proper role and societal obligations of oncologists in the clinical research enterprise. Less obvious is the fact that, if the patient-doctor relationship remains intact, any recommendation for treatment or care of a condition must be viewed as both potentially beneficial by (and for) the patient and endorsed by the doctor. Therein lie the major dilemmas which remain unresolved.

#### Notes and References

1. National Cancer Institute. *SEER Cancer Statistic Review, 1973-1999*. Bethesda, Maryland: National Cancer Institute; 2000: 467.
2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin*. 2008;58(2):71-96.
3. These are phase III clinical trials open to patients with primary, previously untreated disease. Often, they are a randomized, controlled design in which the experimental therapy is compared with the standard of care.
4. Braunholtz DA, Edwards SJ, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a “trial effect.” *J Clin Epidemiol*. 2001;54(3):217-224.
5. Roethlisberger FH, Dickson WJ. *Management and the Worker: An Account of a Research Program Conducted by the Western Electric Company, Hawthorne Works, Chicago*. Cambridge, Massachusetts: Harvard University Press; 1939.
6. The Hawthorne effect is the poorly understood phenomenon whereby patients enrolled in clinical trials do clinically better than those with comparable disease who are not enrolled in the trial. It was originally described in the setting of behavioral research from the early 20th century.
7. NIH & Clinical Research. How does clinical research work? 2008. <http://clinicalresearch.nih.gov/how.html>. Accessed Jan 15, 2009.
8. Oberman M, Frader J. Dying children and medical research: access to clinical trials as benefit and burden. *Am J Law Med*. 2003;29(2-3):301-317.

9. Kimmelman J, Palmour N. Therapeutic optimism in the consent forms of phase 1 gene transfer trials: an empirical analysis. *J Med Ethics*. 2005;31(4):209-214.
10. Glannon W. Phase I oncology trials: why the therapeutic misconception will not go away. *J Med Ethics*. 2006;32(5):252-255.
11. Estlin EJ, Cotterill S, Pratt CB, Pearson AD, Bernstein M. Phase I trials in pediatric oncology: perceptions of pediatricians from the United Kingdom Children's Cancer Study Group and the Pediatric Oncology Group. *J Clin Oncol*. 2000;18(9):1900-1905.

Thomas W. LeBlanc, MD, MA, is a senior medical resident at Duke University Medical Center and a graduate of Duke University School of Medicine in Durham, North Carolina, where he also earned a master's degree in philosophy, focusing on medical ethics. He will begin fellowship training in medical oncology in July 2009. Dr. LeBlanc's career interests include palliative care, oncology, medical ethics, medical education, and literature in medicine.

Philip M. Rosoff, MD, MA, is the director of clinical ethics at Duke University Hospital and a faculty scholar in the Trent Center for Bioethics, Humanities and History of Medicine at Duke University School of Medicine in Durham, North Carolina. Dr. Rosoff is a professor of pediatrics (oncology) and medicine.

#### **Related in VM**

[Helping Patients Decide Whether to Participate in Clinical Trials](#), January 2007

[Hoping for the Best, Preparing for the Worst](#), August 2005

[Clinician and Researcher](#), July 2003

*The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental.*

*The viewpoints expressed on this site are those of the authors and do not necessarily reflect the views and policies of the AMA.*

Copyright 2009 American Medical Association. All rights reserved.