Ethical Considerations in Research Involving Children

Theresa A. O’Lonergan, MA, and Henry Milgrom, MD

Address
Pediatric General Clinical Research Center, University of Colorado at Denver Health Sciences Center, 1056 E. 19th Avenue, B218, Denver, CO 80218, USA.
E-mail: O’Lonergan.Theresa@tchden.org

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Introduction
Occasionally, a review of ethical considerations in human subject research promotes satisfactory discharge of the obligations of researchers to human subjects and contributes to the continued evolution of the research enterprise. This is most important in pediatric research, given the emanan
t changes in this field. Unique ethical issues face the pediatric researcher as more studies in children are mandated by federal initiatives, the gap between available marketed drugs and those labeled for pediatric use widens, pediatric genetics research advances, and departments of pediatrics embrace translational research. Our intention is to articulate some of these issues, which the authors have pondered as an ethicist and clinical researcher, respectively. As ethical considerations in the conduct of clinical research arise from diverse disciplines reflecting ethics, regulatory, legal, policy, or empirical perspectives, we draw upon all fields that inform the ongoing discourse. We reference selected materials from anthologies, cited by national commissions and institutes, and relied upon by those teaching biomedical ethics. We also examine current literature written from three loosely defined categories: full-on ethics, regulation and law, and policy or position statements, which we deem pivotal or at least provocative and timely.

Children: A Vulnerable and Protected Class
Among vulnerable populations, children are unique in that there is a well-established precedent of considering them entitled to protection. The principles that comprise the foundation of biomedical ethics—respect for persons, autonomy, beneficence, nonmaleficence, and justice—all apply to children, and are reflected in the regulatory approach [1]. The standard set by the Declaration of Helsinki—that concern for the interests of the subject must always prevail over those of both science and society—is the foundation of regulations governing clinical research in pediatrics [2]. Both the National Institutes of Health (NIH) and the US Food and Drug Administration (FDA) operate under the Common Rule that aims to protect research subjects and specifies conditions for inclusion of children [3]. Risk assessments are made with lower thresholds for the youngest subjects, and some research simply is not permissible in pediatrics. There is far less discretion in what parents can permit with regard to their children compared with what they could permit for themselves. Inclusion of healthy children in research is more restrictive than inclusion of healthy adults [4]. There are very limited risks to which a healthy child can permissibly be exposed—no matter how significant the potential gain in generalizable knowledge. Children may not choose to act in altruistic ways when it involves clinical research, and, more importantly, no one else can make this decision on their behalf. An excellent articulation of the historical legal reasoning about this is Purdy’s 1992 book [5].

The goal of federal regulations governing the protection of vulnerable subjects is the preservation of the moral standing of subjects who may not be in a position to assert that natural right. Vulnerable subjects are those who, for reasons of environmental, cognitive, or custodial factors, might easily have their rights or preferences overridden by those to whom they are in a subordinate position. In the case of fetuses, they have no legal standing in the United States but may have moral standing. Infants have legal standing, but have no ability to form or express preferences. Children (beginning at about 4 years old) clearly have moral and legal standing, can form and express preferences, but are subordinate to adults with regard to having
those preferences respected. Children can be consulted to determine their preferences; hence, the requirement for assent. We are morally obliged to take a conservative approach to the research we conduct on infants, children, and adolescents because we must, as much as possible, maintain and respect the child’s right to an open future. This means that we must not intervene in ways that would likely limit the range of options that would be available to the child upon reaching adulthood.

The First Question: Should Children Be Included in Clinical Research?
The most fundamental question is “Should clinical research ever be conducted on children/adolescents?” Before the mid-1900s, it was thought that exposing children to the risks of clinical research was ethically unjustifiable because children are a vulnerable and protected class. As the discipline of pediatric medicine came to recognize physiologic differences between children and adults, the ethics of treating and prescribing medications for children based on data from research on adults was questioned [6,7]. A moral pull exists between protecting children from the risks of research and exposing them to the dangers of imprecise dosing extrapolated from adult studies [8].

Historically, Immanuel Kant and J.S. Mill have represented the two primary approaches to judging the ethical acceptability of actions. Kant, a deontologist, asserts that humans have an inviolable worth that necessitates adherence to a categorical imperative by which all actions must be judged. It requires that rational beings never be used as mere means to some end [9]. Thus, “using” persons—including children—to test scientific hypotheses is ethically unjustifiable. Mill’s system is based strictly upon utility and does not assert that humans have any inviolable worth. Whether or not an action is ethically justifiable is determined by the balance of utility and disutility that results. Thus, human suffering that produces great benefit for others—on balance—may be ethically justifiable [10]. Redmon [11] asserts that children can be used in research without necessarily compromising their inviolable worth, and this is justifiable on both Kantian and Millian grounds. Federal regulations and Institutional Review Boards (IRBs) rely on a composite of these two views; some actions are simply impermissible, whereas others may be permissible relative to potential benefits. In the case of pediatric research regulations, IRBs and researchers in general are more Kantian than Millian.

Leikin [12] believes that it is permissible to include children in research based on the moral obligation to help others when the cost to oneself is small. This piece is informed by both moral and psychological development theories. The most recent comprehensive authoritative source to exclusively address the ethical issues in pediatric research is the 2004 Institute of Medicine’s report, which takes the view that research in children is necessary [13].

The report gives support to ethical principles as the driving force and proper foundation for regulations governing pediatric research.

The necessity of conducting pediatric clinical research is also clearly stated by the Royal College of Paediatrics, which asserts:

1. Research involving children is important for the benefit of all children.
2. Children are not small adults; they have an additional, unique set of interests.
3. Research should only be done on children if comparable research on adults could not answer the same question.
4. A research procedure that is not intended to benefit the child subject directly is not necessarily either unethical or illegal.
5. All proposals involving medical research on children should be submitted to a research ethics committee.
6. Legally valid consent should be obtained from the child, parent, or guardian, as appropriate [14].

Although federal texts do not explicitly state that there is governmental approval for research in children, the regulations, initiatives, and legislation addressing their inclusion provide implicit de facto acceptance of such research [15,16]. The relevant portion (45CFR46 Subpart D) of the regulations not only draws on the ethical principles cited in the most prominent of governmentally sponsored reports, commissions, and committees but instantiates those principles in regulations thus requiring or forbidding certain actions based upon the status of the child [3]. The FDA website provides a useful and extensive list of material and legislation concerning pediatric research [17].

Ethical Concerns in Conducting Clinical Research in Pediatric Populations
General considerations
What we consider ethical treatment of children is changing with evolving standards of decency and rapidly advancing medical technology. Of the multiple ethical considerations that must be weighed in pediatric clinical research, most important are the age and health of the child. Children who are healthy, those with chronic conditions, and those who are acutely ill or dying all present different sets of considerations. Likewise, ethical concerns that arise with children are different from those with adolescents.

The treating pediatrician’s role is clear; he is an advocate (in the health context) for his patient—the child. The pediatrician’s dual duties as a researcher are more complex. Children (and, to a lesser extent, adolescents) are not legally empowered to consent on their own behalf. Pediatricians must sometimes pursue the best interests of their patients when these interests are not shared by the parents or even compete with the parents’ interests. When