

Ethical Considerations in Research Involving Children

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Ethical concerns and medical advances unique to children and adolescents make pediatric research an evolving endeavor. The child's changing physiology from infancy to maturity requires understanding of the benefits and risks of medical therapies currently available, but often not tested in children, as well as the risks and benefits of inclusion of children in clinical research. Recent mandates from the US Food and Drug Administration (FDA) require that drugs be tested for safety and efficacy in children. Growing concern for the prevalence of chronic disorders and increasing understanding of distinct phenotypes of these disorders points to a likely need for unique interventions matched to specific phenotypes. All contribute to the increasing complexity of ethical considerations in pediatric research.

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 emanant 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

the pediatrician is both the treating provider and the researcher, his duties are further conflicted, as he must promote the best interests of the child and fulfill his research duties while dealing with the correlative interests of parents. This complicated set of obligations makes ethics in pediatric research a perennial topic and the justification for very specific regulations that protect and promote the interests of children. Parental permission and pediatric assent, assessment of risk compared with benefit, and the long-term interests of the child are the most important issues. One excellent resource addressing regulatory and ethical issues is the NIH Clinical Center text edited by Emanuel *et al.* [18•]. This is an examination of healthy children of short stature in clinical trials to mitigate social and psychological harm but not a disease, which led to the conclusion that the study utilizing growth hormone did not comply with the regulations [19]. A second piece examines the minimal risk threshold frequently criticized as vague and lacking in utility [20••]. The authors assert that the term embodies considerations of both magnitude and probability, which other proposed terms do not. Furthermore, they argue that “minimal risk” is a socially defined term and as such is operative across time and cultures.

Gidding *et al.* [21] propose a new method for assessing pediatric research risk for healthy children. The primary ethical issue is that healthy children (unlike children with a condition under study) cannot benefit medically from inclusion. The authors suggest that the standard for inclusion of healthy children be based on the probability, severity, and reversibility of risks, and on whether a medical intervention would be needed to treat the adverse events. For some studies, there might be no possibility of risk; for others, there might be the possibility of mild-to-severe risks that could occur immediately or be delayed and may or may not require medical intervention. Although these considerations make risk-assessment more complicated, they also make the assessment more accurate.

Consent and assent in pediatric research

An essential issue in both pediatric treatment and clinical research is who speaks for the child [22]. Dworkin's [23] chapter on proxy consent details the difference between representation, surrogate, and proxy consent asserting that what parents do on behalf of their children is presumed to be a representation of the best interests of the child, and what the child would choose if she or he were able to do so. He leaves the reader with an appropriate level of disquiet; consenting on behalf of anyone is problematic. Issues arise about minors assenting or consenting to treatment. Standards for assessing minors' competence are inadequate and imprecise, inchoate autonomy is not equal to rebellion, and adolescents are not a homogenous group with regard to capacities [12]. One should tie capacity assessment of a minor to a Piaget-related rating of the child's conception of illness [24]. Koocher and DeMaso

[25], in consideration of the difference between the de facto presumption of competence in adults and the presumption of de jure incompetence in children, give suggestions for the pediatrician that are of equal utility for the researcher. They stress that although a child is incompetent from a legal perspective, she or he is differentially capable of intellectually and emotionally participating in making decisions. Furthermore, the physician is responsible for both assessing and facilitating the child's understanding.

Studies have been conducted to collect data about the informed consent/assent process in children and adolescents. Several have found that pediatric subjects understood well the parts of the assent form that dealt with concrete information (rights and benefits) and less well understood those aspects dealing with more abstract information (scientific purpose of the study, alternative treatments) [26,27]. Most studies of the consent process assess comprehension/recall; the Weithorn study [28–30] examines the process by measuring the inferential ability of children and adolescents. The ability to infer the significance of possible events and side effects of treatment for one's life is more important than rote recall of those possible events. Zinner [31], in an examination of informed consent by adolescents, argues that failure to recall details of the consent process is not ipso facto failure to understand. She distinguishes the utilitarian and deontological dangers of not allowing adolescents to consent for themselves.

A classic article about the maturity of children to assent to medical research examines the incongruity between not allowing children and adolescents to consent on their own behalf to medical research when those same children are entrusted with the care and protection of children for whom they baby-sit [32]. Lindeke *et al.* [33] provide guidelines for conducting pediatric research assent, including some example standard language. Erb *et al.* [34] include discussions of different models of assent, the importance of understandable language, and strategies to improve and respect the voluntary nature of research participation. Sigman and O'Connor's [35] examination of the mature minor doctrine used by pediatricians and the law in dealing with adolescents contains a discussion of the distinctly moral and legal issues in adolescent assent.

Risk and benefit assessment

A useful article on risk assessment examines vulnerability from a developmental perspective as it pertains to inclusion of children and adolescents, asserting that risk assessment must be tied to development to be meaningful [36]. With regard to research protocols, both the definition and measurement of outcome variables must be age-appropriate, with design of long-term studies considering the developmental progress of the study population.

The usual assumption that research involves inherent risk—which is generally the case in studies involving adults—does not necessarily apply to pediatric research. The closer supervision and monitoring that occurs in

research is balanced against the fact that many drugs routinely used for children were not tested in children. Usage and dosing based on inadequate information potentially place the pediatric patients/subjects at higher risk in the treatment setting than the research subject in a controlled setting [37]. Therapeutic research can be considered as primarily intended to benefit the participants (although this cannot be asserted unqualifiedly in placebo-controlled trials) [36]. Conversely, nontherapeutic research is primarily aimed at furthering medical knowledge. This distinction is an essential factor involved in the assignment of risk levels. Factors that affect a child's ability to give assent include age, maturity, and psychological state as well as role constraints that result from socialization factors and the child's family situation [38]. Strategies useful for ensuring voluntary assent include using multiple media in a setting that minimizes parental influence and providing the child with a clear plan to follow if he or she decides to withdraw from the study.

The current risk-assessment methods for pediatric psychiatric research on biologically based mental illness are inadequate. This has prompted Arnold *et al.* [39] to suggest that an age-gradual consent process be utilized to avoid the danger of overprotection. They also support the Institute of Medicine call for national insurance for subjects injured in research [40].

Clinical trials

The American Academy of Pediatrics guidance on evaluating drugs in pediatrics is comprehensive and useful; it details the relevant considerations for the pediatric researcher from study design through recruitment, payment, and inclusion of vulnerable children [41]. Of special interest is the guidance for inclusion of dying children and those with potentially fatal or progressive disease. Because parents of such children likely have impaired decision-making capacities, researchers should consider timing and asking a colleague not affiliated with the study to speak with the parents. A role for advocacy groups for research in this population is acknowledged. One of the authors (TAO) works closely with investigators and participants in oncology research at a large tertiary-care children's hospital. It is useful to both investigators and families to have an impartial person familiar with both the science and the ethical issues of pediatric oncology trials—especially when adolescents in end-stage disease are involved, which requires consideration of the preferences and needs of parents, family, the adolescent, and the researcher.

From an almost obsessive adherence to the placebo-controlled trial to the drive to eliminate such trials altogether as unethical, we have, perhaps, come to a middle ground at which to carefully consider the appropriateness of placebo controls for some, but not all, scientifically rigorous studies. Stang *et al.* [42] question whether placebo controls are always unethical. They raise issues with the robustness of the assumptions employed in arguing both

for and against the use of placebos. Among these is the idea of proven therapy. The term "assumed effective therapy" might be more accurate. Onder [43•] includes these same considerations with regard to placebo-controlled trials in asthma research. He lists five scientifically sound reasons for such trials: (1) ensuring scientific validity; (2) evaluation of new therapies less effective than the gold standard; (3) reduction of the number of subjects exposed to new agents; (4) clinical situations in which withdrawal of treatment is an option; and (5) assessing the true incidence of side effects. He also argues that lack of equipoise is not a sufficient reason to make placebo-trials unethical.

Miller and Shorr [44] examine the use of placebo controls where effective treatment exists. After refutation of the assertion that the debate is one between science and ethics—because lack of scientific rigor in a clinical trial makes the trial itself unjustifiable—they assert that consent alone cannot justify placebo-control use. They make two suggestions: that any investigator proposing the use of placebo controls where effective therapy is available provide compelling justification, and that master databases be developed from historical placebo-control trials for use in validation of results of contemporary trials. The Declaration of Helsinki, 2000, stated that benefits, risks, and effectiveness of new therapies must be tested against the best current therapy, effectively banning the use of placebo-controls in clinical trials [45•]. Following heated objections from clinical researchers, the World Medical Association issued a "clarification" that qualified its earlier position. Use of placebo was deemed justifiable for compelling and scientifically sound methodological reasons or when the therapy being investigated is for a minor condition. Saunders and Wainwright [46] examine other blanket statements against the use of placebo and oppose these as simplistic.

Flynn [47•] makes recommendations for the use of placebo in antihypertensive trials in children. Potential subjects must be asymptomatic, with mild-to-moderate hypertension; subjects can have no hypertension-related target-organ damage; trials must be of short duration; no standard of care exists or it is common practice not to initiate drug therapy; and there must be close monitoring. Coffey *et al.* [48•], in a review article of placebo-controlled trials in asthma that included children, assert that trials that involve arms that do not receive daily anti-inflammatory medication following the National Heart, Lung, and Blood Institute (NHLBI) standard are subjecting children to unacceptable risk and are unethical. Furthermore, trials involving both children and adults are of no benefit to children unless separate analyses of the data are conducted.

Newburger *et al.* [49] examine the problem of adolescents being enrolled in oncology group clinical trials affecting morbidity and mortality at far lower rates than either adults or children. It is of note that participation in a

clinical trial may improve safety for a child with a malignancy, calling into question the therapeutic/nontherapeutic distinction that Thompson [36] or Nelson [37] would employ as part of risk assessment. Olechnowicz *et al.* [50] examine children's participation in the consent process in leukemia trials and observe that usually someone other than the patient was most important in deciding about trial participation.

Glantz [51] focuses on regulatory and ethical issues in pediatric psychopharmacology, raising the concern that relapse (as might occur in the subjects receiving placebo) might not only cause immediate distress and morbidity but also lead to irreversible additional injury. Conducting psychiatric pharmacology research in children and adolescents is necessary as few psychopharmacologic agents have been tested in children/adolescents. Psychopharmacologic trials should require that psychosocial interventions be tried and found unsuccessful before children are allowed to participate [52].

Epidemiologic research

Although epidemiologic research must apply the four principles of medical ethics (autonomy, beneficence, non-maleficence, and justice), ethical priorities may differ from those in clinical research. The model of public health may require some sacrifice of individual rights for the protection of the public [53–55]. The opposite point of view contends that epidemiologic research imposes additional ethical concerns—for example, that the principle of avoiding harm must include consideration of group stigmatization as well as individuals, and that the definition of harm must include embarrassment, ostracism, or time spent in the research [56–60]. Research questions should be selected and participants chosen to equitably distribute the benefits and burdens of research [60,61••], and findings should be reported responsibly, avoiding sensationalism resulting in harm to groups [59].

Genetics

Juengst [61••] challenges the hyperbole about the ethical perils of using genetics information and asserts that the issues are not nearly as far-ranging as has been claimed, but the four essential areas of concern are profound indeed and affect primarily our public identities. These ethical issues involve familial role, ancestral origins, community membership, and ethnic affiliation and the use of these in determining social status. He denies that the moral challenge of genetics is either the disclosure of essential secrets about ourselves or a therapeutic gap.

Kodish [62••] examines the ethical issues in genetic testing for children and articulates the rule of earliest onset (not prior to the earliest possible age of onset) as a method to determine when testing should occur. He applies the rule to oncology research, suggesting that research employing genetic testing be exempted from the rule for three reasons: (1) knowledge gained is likely to prevent or ame-

liorate the condition; (2) our changing understanding of the genetic basis of cancer justifies ambiguity regarding benefit to research participants; (3) additional protections for research participants mitigate the risks of testing. He asserts that it is a parental obligation (where there is familial history) to seek such testing as a preventive measure, much like immunizations.

Leeder and Kearns [63] also see inclusion of pharmacogenetic tools in pediatric clinical trials as justified by the opportunity to make significant contributions to clinical pediatrics. Ross and Moon [64] consider genetic testing of children and provide three algorithms to aid decision-making based on: the symptomatology of the child, consideration of public health, and familial risk. These algorithms lend themselves to use as inclusion/exclusion criteria for clinical trials using genetic testing. The AAP recommends that the risks and benefits of carrier testing be evaluated in carefully monitored clinical trials before broad population screening is contemplated [65].

Asthma

As part of a series of articles about early intervention in asthma, Silverman *et al.* [66] discuss the design issues for those at risk for asthma but who are asymptomatic. Significantly, they assert that the risk/benefit assessment must be between risk to individual children and benefit to the population. Risk to individual subjects cannot be adequately defined, because early pharmacologic intervention may present risks that do not manifest until adulthood. The sharp increase in the incidence of asthma is cited as justification for early intervention trials. Children often do not experience full control of asthma and suffer the consequences of progressive disease. Milgrom [67] calls for new therapies to be assessed in children well before the fifth birthday. Holt and Sly [68] state that the value of new therapeutic agents with potential for blocking progression from trivial allergy to persistent asthma is most likely to be recognized if these new drugs are tested in children before disease becomes permanently established.

Use of invasive procedures in pediatric research affects approvability. One such procedure is bronchoscopy. It is asserted that given the paucity of information from bronchoalveolar lavage in both normal and asthmatic children, it might well be unethical not to collect such data routinely at the time of clinically performed bronchoscopy, which would involve very little additional risk. The skill and experience of the bronchoscopist is a factor in risk assessment of research bronchoscopies [68]. Davies *et al.* [69] examined the safety (and ethics) of performing bronchoscopy in children with difficult asthma to inform clinical management. The procedure is more easily and safely conducted under general anesthesia compared with conscious sedation. Salva *et al.* [70] report on a study of 170 children in which no safety issues arose. These authors did not consider the additional risk of anesthesia for research-only bronchoscopies, which must be included in risk assessments and may increase the risk to unapprovable levels.

Conclusions

Because investigators have shied away from enrolling children in clinical studies, many of the drugs physicians prescribe for children are not labeled for pediatric use and are given on a trial and error basis [71•]. The alternative to studying pediatric drug regimens in children is to have uncontrolled methods of treatment, where best opinions are used, but the information is not shared or built upon [72].

It is important to consider the broad health and social needs of the population and how it may benefit from better treatment or prevention of allergic disorders. Young children comprise the segment of society most susceptible to develop allergic disorders and most likely to suffer their manifestation. If we are to learn to identify children who are going to have asthma and to prevent this by treating them at an early age, then we have to conduct studies in pediatric subjects. In the not-too-distant future, physicians may be able to treat conditions years before they develop. This must be accomplished in the context of highest ethical standards and with broad societal support.

We may be at a point in time when more ethical issues arise in pediatric research than are resolved. This could be attributed to increasing awareness of physiologic factors that are unique to children, which drives the push to conduct more pediatric research. Other factors include vast new possibilities and awareness of the need for early intervention in increasingly common conditions such as asthma and diabetes. If progress is to be made, we will have to involve children in research. Thus, the dialogue may be expected to increase in both frequency and intensity.

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