Safeguards for Minors in Clinical Research: An IRB Perspective

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Clinical trials evaluate the effectiveness of one or more interventions in treating, preventing, or diagnosing a disease or condition. A 2013 memo from Robert Temple, the deputy center director for clinical science with the U.S. Food and Drug Administration (FDA), emphasizes the importance of conducting clinical research in the specific populations for which the drug is intended and minimizing unnecessary exclusions,[1] thus helping to assess the treatment risks and benefits in this population.

With this theme in mind, including minors in clinical research is essential, as extrapolation of results from adult studies for application in younger patients is often inaccurate. The pathophysiology, severity, course, and treatment response of conditions such as influenza and certain forms of cancer are different in adults and children. Additionally, some conditions, such as prematurity, are specific to a pediatric population, and other genetic conditions, such as phenylketonuria, could lead to disability or death in childhood if untreated.

Despite the importance of clinical trials, minors are traditionally underrepresented in clinical research because of their higher vulnerability to exploitation and increased protection under federal regulations governing research.[2] Due to the lack of clinical data in minors, physicians often must decide whether it is ethical and beneficial to prescribe a medication "off-label" (intended for a use not included in the approved labeling of the drug) to a child based on adult studies or anecdotal evidence in children.

Although many benefit from off-label prescriptions, others may not because the medicine was ineffective, toxic, or administered at the wrong dose. Physiologically, children are not "little adults," and their inclusion in research is necessary

to establish scientific evidence for safety and efficacy of drugs used in this age group.

Although the passage of the Best Pharmaceuticals for Children Act[3] and the Pediatric Research Equity Act[4] resulted in more than 500 pediatric labeling changes over the past 12 years,[5] only 41% of the molecular entities approved between 2002 and 2008 included pediatric labeling.[6] Improving knowledge about these treatments will help to determine a more effective diagnosis, prevention, and/or treatment of conditions in a wide range of age groups.

However, clinical trial research in minors also presents unique ethical challenges. Institutional review boards (IRBs) must ensure that

- any prospective study involving minors is scientifically necessary to perform in that age group,
- the study intends to increase knowledge about diagnosis, prevention, or treatment of the condition, and
- the risks do not exceed those of other groups.[7]

In most studies, one or both parents or legal guardians must provide informed consent. Minors must also agree to participate in the research if the IRB determines—based on age, maturity, and psychological state—that the participants are capable of providing assent.

This article discusses historical and current trends in clinical research involving minors and provides suggestions on how IRBs should establish additional safeguards to protect minors, while facilitating potentially beneficial clinical research.

Methods and Review

Although the concept of research ethics was not widely addressed until after World War II, medical experimentation involving children dates back several centuries. Physicians often used their own children, their servants' children, and/or institutionalized children to investigate infectious disease or immunization procedures because these children were available and convenient for such experimentation.[8]

As controversy grew regarding questionable 19th- and early 20th-century research practices in children—such as deliberate infection with sexually transmitted diseases, lumbar punctures, and invasive investigation of digestive processes—legislative proposals were implemented requiring legal consent (which minors were unauthorized to provide) to participate in research. This implicitly banned researchers from using children in their studies, although enforcement of such proposals was inconsistent.

Specific guidelines on ethical research in minors were not widely implemented until the 1964 Declaration of Helsinki, which stated that legal guardians must provide consent for child participants.[9] Nevertheless, controversial research practices continued, even in studies in which guardian consent was obtained.

From 1963 to 1966, researchers deliberately infected children at the Willowbrook State School, a state institution for "mentally defective persons" in New York, with hepatitis to study the natural history, prevention, and treatment of the disease.[10] Although the institution was closed to new residents during the course of these studies, parents could still enroll their child in the hepatitis program at the institution. Even though parental consent was technically obtained, many parents were coerced into enrolling because their child's admission to the institution was contingent on study participation.

Such controversial practices led to the development of policy statements by the U.S. Surgeon General in 1966 that required research institutions to have IRB committees to assess study methods for obtaining informed consent, assessing risks and benefits, and ensuring participant welfare.[11]

In 1973, the U.S. Department of Health, Education, and Welfare, now known as the Department of Health and Human Services (HHS), issued a document addressing special protections of children in research trials.[12] The document noted that, in trials, children 6 years or older must provide "assent," an "ethical review board" must review research protocols involving children, and a "protection committee" must monitor the research after it is initiated.

In 1983, the HHS included special regulations for research involving children based on the National Commission report on children issued in 1977 (Subpart D).[13]

The Children's Health Act of 2000 requires the FDA regulations to be consistent with those of the HHS, further increasing the protection of child research participants.[14] This act, which includes a pediatric research initiative in the National Institutes of Health, reflects the trend toward increasing research and treatment of health conditions affecting children and including diverse populations to verify the effectiveness of potential therapies.[14]

This trend has also introduced ethical issues that IRB members must consider in their review process. For example, they should ensure that the investigators effectively communicate (in written and/or verbal form) the research methodology and participation risks and benefits to parents and children,[15,16] and that the parents understand their child is receiving appropriate care when participating in a placebo-controlled or randomized controlled trial.[16]

Committees should also address possible discrepancies between the parent and child in the

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desire to participate in the study,[17] and the possible relationship between low verbal communication between the patient and the physician during the informed consent process and difficulty in the patient's understanding of the study.[18]

Finally, the IRB must set standards for financial compensation for parents and children that is sufficient but not substantially coercive.[19]

To promote ethical, efficient clinical research in minors, the IRB must emphasize clear communication of the procedures, risks, benefits, and appropriate compensation in the proposals they receive from investigators, as well as consent/assent documents appropriate for the social, cultural, economic, educational background, age, and psychological capacity of the participants.

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Discussion and Recommendations

The relevant IRB must assess the risks and benefits of any human trial, and the regulations guiding research in children are understandably more stringent than in adults. In fact, Subpart D of the HHS regulations governing research states that any study in children involving greater than minimal risk must:

- provide prospective direct benefits to the participant;
- improve generalized knowledge about a disorder or condition; and/or
- provide an opportunity to understand, prevent, or treat a serious problem affecting the child's health or welfare.[13]

However, IRB committees frequently vary in terms of their definitions of "minimal risk" and "direct benefits," which could be problematic for gaining consistent approval among research institutions in a multisite study. Furthermore, risk assessment of common study procedures, such as blood draws, electromyograms, and allergy skin testing, have been found to vary among IRB chairpersons, as did their identification of direct benefits, such as psychological counseling and participant payment.[20]

Such discrepancies in analyzing risks and benefits are particularly important in multicenter studies, in which variations in the IRB review process may affect study approval and/or patient participation at certain research sites, thus limiting generalizability of the results. In one assessment of the IRB review process for a multicenter observational study in children, the committees varied on their recommendations of approval, conditional approval, and deferral, even though the study protocol was essentially identical across the centers.[21]

The number of days from submission to approval of the IRB application varied from five to 172 days for another multisite health services study.[22] The variability in the IRB review and approval process among the centers may limit potentially valuable research at certain centers if

- such studies cannot receive approval,
- investigators find the review process too burdensome, or
- certain groups of individuals (e.g., low-income) are discouraged from participating.[22]

Therefore, universal criteria of defining minimal risk and direct benefits among IRB committees will help establish consistent methods of assessing the ethical and scientific value of clinical studies in children.

Informed consent and assent procedures should also go beyond simply dispensing information and forms to parents and children. Multiple studies[16,23–25] indicate that parents do not fully understand the proposed treatment their child is about to undergo, even after investigators obtain informed consent from them. Parents often want more decision-making time[26–29] and information about the procedures[26,28] before consenting.

The child's involvement in the decision to participate is important, even if he or she cannot legally provide consent. IRB committees typically require research investigators to obtain assent from children by communicating the prospective procedures at a level appropriate for the child's age, maturity, and psychological state. Greater communication between the physician and child patient is associated with increased understanding of the study procedures in one study; however, levels of patient-to-physician communication are low.[18]

IRB committees should ensure that, after establishing that the consent/assent procedures and information provided are suitable for the target population, researchers provide sufficient opportunity for parents and children to understand the study procedures, communicate their questions and concerns to the investigators, and discuss participation with one another (in the absence of the investigator) before making a decision.

Children who are wards (under the legal custody of the state or other agency, institution, or entity) may not be able to obtain parental consent for research participation. Research that involves a greater than minimal risk and offers no direct benefits can be conducted in wards only if (a) the study is investigating a topic for which their status as wards is required for participation, or (b) the study is conducted in a setting in which most children are not wards (e.g., children under legal custody of the state could participate in a study at a public school that they attend, provided they have a pediatric advocate, because most of the other children in such a setting are under direct custody of a parent or guardian).[13] If these criteria are

met, IRB committees must ensure that pediatric advocates—individuals who have the expertise and competence to act in the best interest of the child and are not otherwise associated with the research study—are appointed throughout the child's participation in the research.

Conclusion

In summary, clinical research in minors is important for establishing efficacy of drugs and other treatments, thus improving therapeutic options in a wide range of pediatric populations. However, the history of exploitative research practices and the vulnerability of children require that additional safeguards be employed before undertaking research in this population. IRB committees should adopt universally consistent and methodical procedures for assessing risks and benefits, evaluate consent/assent processes, and assign pediatric advocates when appropriate to facilitate ethical research that promotes the health, welfare, and interests of children and their families.

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