



Ethical Considerations in Pediatric Research

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LEARNING OBJECTIVES

1. Apply the ethical principles described in the Belmont Report.
2. Demonstrate the concepts of beneficence, justice, and respect for persons as they relate to pediatric research.
3. Discover study design issues that are implicated by the inclusion of pediatric subjects.
4. Evaluate challenges to conducting research in pediatric populations.

ABBREVIATIONS IN THIS CHAPTER

CFR	Code of Federal Regulations
IRB	Institutional review board
NI	Noninferiority

[Table of other common abbreviations.](#)

INTRODUCTION

The conduct of research in pediatric subjects is crucial to optimizing clinical care in this diverse patient population. Although the demand for pediatric research remains high, the logistical implementation is complex. Many factors have led to a lack of pediatric research, including lack of agreed-on end points, informed consent issues, and the general perception that pediatric patients are vulnerable study subjects. This perceived vulnerability of children is based on several factors: (1) their decision-making capacity may be immature, (2) their lives are still subject to the authority of others, (3) their underlying dissent may be masked for fear of upsetting authority figures, and (4) their rights and interests may be undervalued by society.

To ensure that pediatric patients are provided the best clinical care, it is important that thoughtful, efficient research be conducted that has the scientific merit to answer important clinical questions. The fundamental challenge to pediatric research is risk: what is the risk of conducting (or not conducting) the research, and who has the right to decide the level of risk exposure to the child? What “say” does a child have in agreeing to participate in research? What “say” does the legal guardian have in agreeing for a child to participate in research? What is the ultimate goal of the research? Finally, does the goal of the research justify the risks associated with the study?

This chapter outlines the ethical factors affecting the successful conduct of pediatric research. Ethical considerations and their relationship within the context of informed consent and assent are discussed. The discussion of clinical research design focuses on ethical challenges inherent to researchers, especially those unique to pediatric patients. Finally, additional confounders to pediatric research, such as compensation and the role of the pharmaceutical industry, are discussed.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of terms associated with conducting clinical research
- Basic anatomic and physiologic differences between adults and adolescents
- Fundamental principles of medical ethics

[*Table of common pediatric laboratory reference values.*](#)

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Caldwell PH, Murphy SB, Butow PN, et al. [Clinical trials in children](#). *Lancet* 2004;364:803-11.
- Fleischman AR. [Ethical issues in neonatal research involving human subjects](#). *Semin Perinatol* 2016;40:247-53.

HISTORY OF HUMAN SUBJECTS RESEARCH

The exploitation of subjects by researchers has a long and dark history. One of the most graphic exploitations was that conducted by the Nazi regime during World War II. Prisoners of war were forced to participate in research experiments against their will, often with no benefit. After the war, during the trials in Nuremberg, German physicians were charged with crimes against humanity for experiments in the concentration camps that led to murders, tortures, and other atrocities. The Nuremberg trials outlined areas in which permissible medical experiments can be conducted, with the findings ultimately becoming the Nuremberg Code.

Several high-profile research studies showing questionable ethics occurred after the Nuremberg Code was established. The most famous was the U.S. Public Health Service “Study of Untreated Syphilis in Negro Males,” often called the Tuskegee Syphilis Study. African American males who had contracted syphilis were prohibited from knowing their infection status as well as from receiving appropriate treatment so that researchers could track the natural course of the disease. This study occurred when a known treatment for syphilis was available. In 1972, public awareness of the study led to an outcry and eventual study discontinuation.

Unfortunately, lapses in ethical judgment are not limited to adult subjects. History has shown cases in which the interest of the child’s legal guardian conflicted with the best interest of the child. For example, the cases surrounding Willowbrook State School showed that legal guardians allowed their child to be enrolled in questionable hepatitis studies to ensure

their child would be enrolled in the school for mentally handicapped children. Although the legal guardians knew it was questionable to allow their child to participate in this study, they feared that declining participation would not allow their child to be enrolled in Willowbrook, a notoriously difficult school to gain admittance to. The Willowbrook example shows how the rights of children can be compromised by guardians and health care communities alike.

A second example of ethical wrongdoing in pediatric subjects can be extracted from the human radiation experiments conducted at the Walter E. Fernald Developmental Center in Waltham, Massachusetts. In these experiments, young male wards of the institution were exposed to trace levels of radioactive calcium and iron in an attempt to discern issues of mineral absorption. Parents of the children enrolled in the studies were given incomplete information regarding the study when providing their consent. The parents were never told the children would be receiving any radiation, whereas the children were led to believe they were simply joining a science club. The experiments raised important issues of what is truly “informed consent” and whether institutionalized children should ultimately be able to enroll in clinical research, given that they are by nature a vulnerable population.

The U.S. Senate Committee on Labor and Public Welfare met in 1973 to address human experimentation as a result of the public outcry associated with the Tuskegee Syphilis Study and the Willowbrook cases. In 1974, the National Research Act was passed by Congress. The National Research Act was instrumental in two important acts: (1) the establishment of the National Commission, which would develop the ethical principles associated with human subjects research; and (2) the requirement for institutional review boards (IRBs). About the same time that the National Research Act was passed, the Public Health Service implemented “Regulations for the Protection of Human Subjects of Biomedical and Behavioral Research.” These regulations (45 Code of Federal Regulations [CFR] 46) continue to serve as the basis for federal-specific requirements in the conduct of human subjects research (Services 2005).

The National Commission meeting occurred in 1975–1978 to deliberate regulations governing human subjects research. Topics ranged from IRB governance to research in vulnerable subjects (e.g., fetuses, prisoners, children, and the developmentally delayed). As part of these proceedings, the committee met in 1976 at the Belmont Conference Center to discuss the basic ethical principles that would serve as the framework for human subjects research. The findings of the committee (the Belmont Report) were incorporated into the National Commission’s final report in 1979. The NIH published guidelines in 1998 titled “Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.” The basis for these guidelines stemmed from the lack of clinical studies involving pediatric patients. To receive NIH funding for a clinical drug study, children must be included in research

protocol unless (1) the research is not applicable to children, (2) the knowledge sought is already available in children (or will be obtained from a currently funded study), (3) an age-specific separate study is warranted and preferred, or (4) insufficient data exist in adults to determine whether children are at potential risk. The NIH guidelines continue to state that including children in NIH-sponsored studies should follow the regulations of 45 CFR 46 (Services 2005; National Commission 1978).

ETHICAL CONSIDERATIONS

The Belmont Report identified three ethical principles that serve as a framework for human subjects research: beneficence, justice, and respect for persons. One principle is no more or less important than the others; rather, all three must be considered when conducting research. Under some circumstances, all three principles may be in conflict with one another, and the researcher must choose the appropriate direction that best answers the scientific question. Applying these principles can be challenging in both adult and pediatric subjects. However, unique differences in pediatric subjects will be discussed in the sections that follow.

Beneficence

Beneficence is the ethical principle that is founded in kindness and acts of charity. It is a moral obligation to act for the other's benefit, help them further their interest, and prevent or remove possible harm (*primum non nocere*). As it applies to health care and biomedical research, it is often summarized as "do no harm." In pediatric research, it is important that research does not exploit the vulnerability of minors who may be unable to give true assent for study participation. Therefore, the researcher must ensure that the research question is scientifically sound and that no "unnecessary" harm is done to the study subject. A key aspect of harm as it relates to research is "risk," which serves as a basis for research review by the IRB. As discussed later in the chapter, the IRB assesses the risk to the research subject and any potential benefit to the patient or future patients. There is considerable debate regarding the role of beneficence for a patient when the patient will not receive any direct benefit from the research. In the adult population, it is widely accepted that a researcher can risk a small level of harm to the research subject if the subject willingly consents to treatment that will benefit humanity. The ability of a child to comprehend the risk in the larger picture of human health and the child's willingness to assent to such risk are subject to significant research debate.

Justice

Justice is the ideal distribution of risk and benefits throughout a population when conducting research. The selection of subjects should be equitable, and vulnerable subjects should not be exploited for the benefit of the general population. The inclusion and exclusion of subjects in research protocols

should be based on a valid scientific question and not based on discriminatory factors or ease of enrollment. One aspect of biomedical research is to determine whether an intervention improves, does not improve, or has no effect on a pathophysiologic condition. The principle of justice states that individuals within a population should have equitable access to the potential benefits of the intervention and share in the potential risks. Factors that may disrupt the equitable distribution of participation include demographic differences (e.g., minority and wealth differences, primary language), mental status, and coercion by investigators based on financial incentives. This last aspect is of particular relevance in the pediatric population because of concerns that investigators may coerce children to provide assent because of financial incentives such as a gift card to a toy store or fast food restaurant. The value of such financial incentives is often reviewed by IRBs to ensure that it is consistent with community standards and not a source of potential enticement.

Respect for Persons

The third ethical principle of "respect for persons" can underscore an important challenge in pediatric research: paternalism versus autonomy. Autonomy is the belief that a rational individual has the capacity to make an informed decision. Paternalism, however, is the belief that an individual is incapable of making an informed decision and that a surrogate must make the decision in the best interest of the individual. A classic example of the struggle of autonomy versus paternalism lives in the house of every teenager. A key tenet in human subjects research is the subject's ability to make an informed decision regarding whether to participate, given the perceived risk. The autonomous decision of a coherent adult is obvious, but at what point can an autonomous decision be made by a child? Do children have the ability to make autonomous decisions, or does a paternalistic decision need to be made in the best interest of the child? Societies perceive "adulthood" (or the ability to make autonomous decisions) according to a variety of factors such as age, sexual development, and schooling. In the United States, the "age of majority" is 18 years in most states, with 19 years in others. It is widely accepted that a child can make an autonomous decision at this age.

INFORMED CONSENT AND ASSENT

The informed consent process is based on the ethical principle "respect for persons." As discussed in the National Commission's 1979 report, research subjects "shall be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied." The standards of informed consent include that (1) information should be provided to the potential subject such that they can decide whether to participate; (2) the information should be presented in such a way that it can be easily understood; and (3) the potential subject should understand that consent is voluntarily given and the

individual is free to withdraw at any time. The applications of these standards to the pediatric patient can be challenging. For example, what is the appropriate way to ensure that a 10-year-old understands the information being presented by the researcher? Thus, it becomes imperative that researchers work with the child's guardian to meet the informed consent standards to the best of their ability. Informed consent is typically a legal document; thus, the age required to give consent is the age at which one is considered an adult. In the United States, the age is typically 18 years. Written assent is often required from teenagers in addition to consent from parents; some IRBs have required the use of consent forms for older teenagers (16–17 years) whereby both the teen and the parent/guardian ascertain consent. The National Commission's report "Additional Protections for Children as Research Subjects" was published in 1977 and serves as the basis for regulations 45 CFR 46 (Subpart D) (Jonsen 1978).

Overview of Risk Categories

The regulations contained within 45 CFR 46 describe the various levels of risks in research involving children. These risks are classified in levels according to the risk-benefit ratio provided directly to the child. The greater the risk-benefit ratio, the more protections that are required for the child. These levels were implemented in sections 45 CFR 46.404, 46.405, 46.406, and 46.407 of Subpart D of the Health and Human Services regulations. A summary of the pediatric research risk is provided in Table 1-1.

Minimal risk is often defined as harm or discomfort similar to that encountered in everyday life during physical or psychological examinations or tests. Thus, research activities are compared with the likelihood of minimal risk or greater. Risk is further delineated regarding whether the subject has the prospect of direct benefit by participating in the study (see Table 1-1). Consent or assent can be waived according to 45 CFR 46.116(d) when subject information is collected but de-identified and no correlation exists between the information presented and an individual subject because the risk is considered negligible.

Institutional review boards are responsible for assessing the levels of risk in conjunction with the principal investigator. This assessment is done after reviewing the study protocol. A common misconception is that the IRB is responsible for research study design when, in fact, the IRB's primary responsibility is to protect the study subject. It can be implied that a poorly designed research study does not answer the research question and places the subject at unnecessary risk. Regardless, it remains the IRB's primary focus to protect the rights of the research subject through the assessment of risk, the appropriate execution of informed consent, and the appropriate review and execution of assent.

Informed Consent

Informed consent is the legal permission that a patient voluntarily agrees to participate in a research study. Informed consent must be signed by the legal guardian(s) of the child

Table 1-1. Risk Categories in Pediatric Research

45 CFR 46 Code	Descriptor	Examples	Consent
404	Research involving no greater than minimal risk	Venipuncture Chest radiograph Psychological risk Classroom observation	One parent Child assent
405	Research involving greater than minimal risk but presenting the prospect of direct benefit	Shortened course of therapy compared with conventional practice	One parent Child assent
406	Research involving greater than minimal risk and no prospect for direct benefit	Urine catheterization Skin or bone marrow biopsy Radiocontrast with sedation	Both parents Child assent
407	Research otherwise not approvable	Research not approvable by previous sections but presents an opportunity to understand, prevent, or alleviate a serious problem	Both parents Child assent HHS panel of experts
116	Waiver of consent or assent	De-identified patient information for performance improvement or research publication	Not applicable

HHS = Health and Human Services.

with the number of signatures needed, depending on the risk of the research (see Table 1-1). Informed consent must be written in a manner that satisfies the IRB standard that “the information must be provided in a form that is understandable.” An eighth-grade reading level is generally accepted to be appropriate for general adult comprehension. Adults who serve as a child’s legal guardian must sign the informed consent, and this step cannot be delegated to other family members or friends unless legally certified. Children who are wards of the state have additional safeguards because previous exploitations often involved orphans. Regulation 45 CFR 46.409 limits the involvement of wards in research that is greater than minimal risk and without direct subject benefit. In addition, regulations stipulate that children who are wards of the state must be appointed an advocate who has the background and experiences consistent with serving in this capacity.

Informed Child and Adolescent Assent

The concept of informed assent for children is similar to that of obtaining informed consent for adult research subjects. Although informed assent is not legally binding, it remains an ethical cornerstone in that a child or adolescent is giving his or her permission to voluntarily participate as a research subject and understands the risk of doing so to the best of his or her ability. As such, the child/adolescent should be given the rights outlined in Box 1-1.

Assent is generally divided into three categories: children too young to properly give informed assent (neonate to age 6 years), youth assent (children age 7–12 years), and adolescent consent (given to children age 13–18 or 19 years, depending on each state). Children younger than 7 years should be given simple verbal explanation of what the research study entails, what will happen to them, and what they may be asked to do. It is important to document this conversation either on the parental permission form or in the study records.

The youth and adolescent assent forms differ in the scope and context of information provided to the child. The adolescent assent form is slightly more complex than the youth

form. Both assent forms should be brief and study-specific, with subheadings or numeric paragraphs, and contain language that is appropriate to both the child’s development and age. The assent form should have a simple format that is easy to read and, when possible, should be limited to one page.

Children are not required to sign the assent form, but investigators are required to document in the research record that child assent has either been obtained on the parental permission form or retained separately within the study records. It may be necessary to use two assent forms written to accommodate subjects at either end of the age range or to accommodate different maturity levels of the participants.

Even when the researcher and the IRB determine that the children are capable of assenting, the IRB may grant a waiver of the assent requirement in accordance with 45 CFR 46.116(d). This would include when the capability of the child is so limited that he or she cannot reasonably be consulted or the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research. In circumstances such as a child’s dissent, which should normally be respected, the dissent may be overruled by the child’s parents.

Ultimately, the institutional IRB is responsible for determining that appropriate provisions are made in obtaining assent from the child and adolescent. If the IRB determines that a pediatric research subject is capable of providing informed assent, the study protocol must include this information. It is important that researchers work closely with their respective IRB to conduct actions of assent and consent.

ETHICAL STUDY DESIGN IN THE PEDIATRIC PATIENT POPULATION

It is critical in all aspects of research to specifically target the research question. This takes on particular relevance in the pediatric patient population because children have historically been perceived as vulnerable study subjects. Therefore, children should not participate in clinical research unless it is necessary to answer an important scientific question that is pediatric-specific. It is well described that research should be conducted in adults before pediatric patients unless the disease is unique to pediatric patients. This stems from the belief that most adults can assess the risk and benefits of being associated with a study, whereas a child may not fully comprehend the expectations associated with participating in a study.

Inversely, not conducting pediatric research can be equally unethical. If a health care practitioner is forced to make clinical decisions on a case-by-case basis, pediatric patients could be faced with unnecessary harm because of the lack of a cohesive, evidence-based approach that benefits the entire population. Thus, the best way to balance the risk-benefit

Box 1-1. Rights of Pediatric Assent

1. Conducting the process in a manner and location that ensures participant privacy
2. Giving adequate information about the study in a language understandable to the participant
3. Providing adequate opportunity for the participant to consider all options
4. Responding to the participant’s questions
5. Ensuring the participant has understood the information provided
6. Obtaining the participant’s voluntary agreement to participate
7. Continuing to provide information as the participant or research requires

ratio in pediatric research is for the health care practitioner to be aware of confounding factors affecting the risk-benefit ratio as it applies to pediatric research.

Targeting the Research Question

The importance of minimizing risk and maximizing benefit centers on establishing an answerable research question. The question should be direct and based on the concept of clinical equipoise. Clinical equipoise states that a research subject should not be provided inferior treatment by participating in the research study. Therefore, the scientific question must be based on scientific “uncertainty”: the interventions must be perceived as equitable rather than conducting a study with a known inferiority. The nature of the research question should be specific and should clearly enumerate the scientific uncertainty leading to the study design. Therefore, each group (including the control group) should be vetted for ethical and scientific rationale before the research protocol is initiated.

Control Group and Placebo Controls

The choice of an appropriate control group should be based on both scientific and ethical principles. The primary focus should be on using the appropriate comparator to show the safety or efficacy of the intervention. Thus, having an intervention studied versus placebo is often perceived as the ultimate comparator. It is commonly thought that the individuals assigned to the placebo group are receiving inferior treatment, thereby compromising clinical equipoise. However, another option to consider is that the placebo group could be limited to the exposure of a potentially ineffective or toxic intervention. Treatment (or nontreatment) of patent ductus arteriosus (PDA) shows this clinical equipoise. Historically, the standard of care for neonatal PDA was either surgery or pharmacologic treatment with indomethacin or ibuprofen. The research question was raised: What if there was no intervention for PDA and the duct was able to resolve on its own? Although groups of health care practitioners argued that it would be unethical not to intervene, proponents of the research challenged that the pharmacologic treatment could be considered a greater risk than benefit and the study should proceed. Studies showed that the no-intervention group (essentially a placebo group) had better outcomes than the pharmacologic intervention group. This example shows that a perceived intervention may not be clinically advantageous to the placebo group.

Alternatives to Placebo-Controlled Trials

The complexity of the scientific and ethical questions regarding pediatric placebo-controlled studies makes this approach somewhat limited in practice. Thus, investigators have explored a “placebo-like” experience without the scientific and ethical concerns associated with a placebo-controlled trial. A common approach, both in children and adults, is the noninferiority (NI) study. An NI study is intended to show that a new treatment is

no worse than the active control (typically, the current standard of care) by a specified margin. It is important that sufficient historical data exist to define the effect of the control regimen with which the alternative regimen can be compared.

The ethical challenge when using an NI study design is the effectiveness of the active control. If an active control is not very effective, the experimental therapy only has to be equally effective to an ineffective option. This is particularly problematic when examining interventions for life-threatening events. For example, if a cardiovascular medication has been used in pediatric patients with 20% effectiveness, an NI study design would have to show that the experimental therapy achieves a minimum of 20% effectiveness. Most researchers and clinicians would state that 20% effectiveness is disappointingly low. It is important that researchers understand the baseline of active control before embarking on an NI study design.

First-in-Human Pediatric Clinical Trials

Certain disease states are unique to the pediatric patient population (e.g., Kawasaki disease and neuroblastoma). Therefore, experimental therapies for pediatric-specific diseases must first be introduced directly to pediatric patients rather than to adults. These first-in-human interventions are based on previous in vitro, in silico, and preclinical work in animal models. Although significant scientific work is done before use in patients, the ethical dilemma remains regarding whether the intervention offers a direct benefit to the patient. Ethicists often contend that patients are misled with first-in-human studies because it implies that the patient will receive direct benefit from the study; rather, patients should be informed that this is truly an experimental intervention and no direct benefit may be provided.

Another ethical challenge associated with pediatric first-in-human trials is the initial starting dose of the experimental agent. Dosing is often a result of pharmacokinetic modeling in addition to toxicity studies. An initial dose is designed to target the therapeutic effect while reducing the likelihood of toxicity. This becomes even more challenging in pediatric patients because doses need to be adjusted by weight or body surface area rather than a standard adult dose. Maturation rates of drug-metabolizing enzymes and drug transporters, as well as differences in the ontogeny of organs in neonates and infants, make it difficult to predict drug disposition in the pediatric population. Investigators often “err” on the conservative side of a dosing regimen in first-in-human studies to avoid adverse effects, which may lead to undertreatment and therapeutic failures. Thus, any potential benefit to the patient is unrealized in these initial studies.

CHALLENGES IN CONDUCTING PEDIATRIC RESEARCH

As we have described, conducting research in pediatric populations is inherently difficult. In addition to the common hurdles associated with general clinical research, conducting

studies in pediatric patients comes with a unique set of challenges. Issues of guardianship, researcher competencies, barriers to recruitment, the role of compensation, and commercial sponsorship all have magnified roles in pediatric research. We will briefly consider each of these hurdles in more detail.

Guardianship

Guardianship is a term used to describe someone who is either chosen or appointed to make legal decisions for another person unable to make these decisions on his or her own. Guardianship issues with children can quickly become legally complex, and guardianship can occur with or without the termination of parental rights. If parental rights remain in the presence of alternative guardianship, it can be unclear to the investigator who can legally make decisions regarding a child's involvement in pediatric research. One such example may arise from issues of consent. When conducting research in children for whom issues of guardianship arise, it is often difficult to ascertain issues of consent (who can consent, do both parents and guardians need to consent, etc.). For this reason, researchers often avoid approaching or enrolling pediatric patients when the guardianship is either involved or unclear. By doing so, large groups of pediatric patients often may not be well represented in pediatric clinical trials and pediatric research in general.

Adopted children as well as orphans and vulnerable children are often excluded from participating in research that may offer them substantial medical benefit because of complexities arising from guardianship. With an estimated 153 million orphans worldwide and 380,000 children in the United States living without families, a significant population of children are void of evidence-based medical interventions when they are underrepresented in clinical research because of barriers of guardianship (Kelley 2016). One common approach in pediatric research is not to allow children to enroll in studies when neither a parent nor a legal guardian is available to consent on their behalf. This approach is based on the assumption that children, by their dependent nature, are a vulnerable population. Although this approach seeks to do no harm to the patient, it may not benefit the patient in the long run. A newer approach being implemented in countries such as the United States and South Africa names the population of orphaned and vulnerable children as a special vulnerable population while allowing them to participate in clinical research using additional protective measures such as incorporating study advocates. This approach, although often costlier and more time-consuming, allows children from vulnerable populations to be represented in clinical research (Kelley 2016).

Role of Compensation

The role of compensation in medical research has been, and remains, controversial, regardless of study participant age. Opponents of participant compensation argue that

compensation reduces the voluntariness of informed consent. Proponents of compensating participants offer that it is unethical to have a patient participate in research and not be paid in some manner. It is estimated that 25% of pediatric studies currently offer some form of compensation for study participation (Caldwell 2004). Compensation for participating in pediatric trials is currently allowed in the United States; however, many countries, including those in Europe, do not allow compensation for pediatric trial participants (Caldwell 2004). Compensation issues become confounded in pediatric studies because the participants by law cannot consent to enrollment. United States federal regulations offer no guidance on compensating pediatric research participants; however, the American Academy of Pediatrics (AAP) argues that the practice of paying adolescents for participating in research is consistent with the "traditions and ethics of society." The AAP advocates for two safeguards relative to compensation in pediatric research. First, parents should receive no more than a token gesture of appreciation, and second, payments to children should not be disclosed until the study's end (Wendler 2002).

Participant compensation for medical research is quickly becoming standard practice in the United States. As it becomes more common, the issues around compensating pediatric study participants are slowly being addressed. Payments to parents must be sufficient to compensate for excess hardships incurred by study participation, such as excess costs for transportation, medical care, or food and nutrition. However, the compensation to parents or guardians must not exceed an amount that would render the payment coercive to the parents' decision to enroll the child in the clinical study.

Commercial Sponsorship

Many obstacles are responsible for the lack of pharmaceutical company involvement in pediatric studies. Costs associated with conducting trials in pediatric patients are substantially greater than costs associated with conducting similar trials in adults (Li 2007). In addition, fewer patients are often available to participate in pediatric trials, making recruitment a challenge for pediatric studies. Ultimately, the market for the end product determines whether a pharmaceutical company is willing to participate in pediatric studies because profit often drives product development. Potential return on investment in pediatric product development is often less than ideal because of smaller target patient populations for the end product relative to adult formulations. In addition, failed trials and unexpected safety issues that may arise in younger patients can quickly drive up the costs associated with conducting trials in children.

The complexity of ethical issues surrounding pediatric trials is often reason enough for pharmaceutical companies to avoid participating in pediatric trials. The dearth of investigators comfortable with participating and conducting pediatric research makes it difficult for pharmaceutical companies to

enroll enough participants to conduct trials with the power necessary to obtain statistical or even clinical relevance. Many strategies have been used in an attempt to overcome these barriers to commercial involvement in pediatric research. Formation of large pediatric clinical trial networks such as the IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials) Network helps ensure the availability of well-trained and qualified investigators while offering access to more pediatric patients from more geographically diverse populations. Similar pediatric clinical trial networks exist for other disease states such as oncology, cardiology, and rare or genetic-associated diseases. These networks lend a framework for pediatric studies, reducing barriers for industry involvement. A second strategy often used by commercial pharmaceutical companies is to incorporate a pediatric sub-study into a larger, predominantly adult-focused study. By doing so, investigators can ascertain the role of age as a confounding variable in treatment outcomes. In addition, with this piggyback trial design approach, operational costs can be substantially lower because existing study infrastructure is used for both the adult and pediatric portions of the study.

Research Competencies

There remains a deficit of trained clinician-investigators focused on pediatric studies. Many times, pediatric clinicians choose not to participate in clinical studies, believing that it may interrupt the patient-provider relationship. Clinicians may worry about the impressions of parents or guardians if they approach them about the possibility of enrolling their child in a pediatric trial. Other times, clinicians simply believe they lack the training and skill set to participate in clinical research. To this end, large federally funded initiatives have focused efforts on making training available in the responsible conduct of research. The NIH offers various programs directed at training clinicians to conduct pediatric clinical research. These programs consist of fellowships, training grants, continued education, and certificate programs. In addition, academic medical centers have begun to implement postgraduate training opportunities in clinical and translational research with the intent of bolstering involvement in clinical research as part of their institutional missions. Still, however, there is a deficit of clinicians and clinical staff trained and comfortable with conducting pediatric research. Often, the clinicians with training in conducting pediatric research migrate to dedicated children's hospitals with hopes of having more involvement with pediatric studies. However, this leaves a paucity of competent researchers outside these children's hospitals and academic medical centers to both enroll and fully participate in pediatric research.

CONCLUSION

Pediatric clinical research provides valuable information to clinicians, imparting to them the tools and knowledge they need to provide optimal care to their patients. With proper planning and study oversight, ethical research may be conducted in children who are often considered a vulnerable population. In this chapter, we have outlined the ethical factors affecting the successful conduct of pediatric research as well as some of the barriers to conducting research in children. We have described the regulations that govern clinical research and provided general considerations that must be made when designing and conducting research in this patient population. Although training programs for pediatric clinicians desiring to conduct clinical research have grown in number and size, a need remains for strategies to increase the number of clinicians actively involved in pediatric research.

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Self-Assessment Questions

- In the Public Health Service syphilis study, participants were not informed that they were participating in a research study. Which one of the following ethical principles outlined in the Belmont report best describes the ethical principle most violated in the Public Health Service syphilis study?
 - Justice
 - Beneficence
 - Respect for persons
 - Clinical equipoise
- Researchers intend to conduct a pediatric study evaluating a new broad-spectrum antibiotic for the treatment of otitis media. Because of the cost of the antibiotic, the inclusion criteria of the study include individuals who have third-party insurance because the cost of the medication will not be covered within the research protocol. Which one of the following best describes the ethical principle most violated?
 - Justice
 - Beneficence
 - Respect for persons
 - Clinical equipoise
- A 16-year-old male adolescent who is HIV positive develops an adverse effect while taking abacavir. The medical team researches and discovers that this adverse effect has not been published in the literature. You have been asked to facilitate the publication of this case study. Which one of the following is the most appropriate next step?
 - Ascertain a waived consent through an institutional review board (IRB).
 - Obtain adolescent assent from the teenager.
 - Obtain adolescent assent from the teenager and informed consent from one parent.
 - Obtain adolescent assent from the teenager and informed consent from two parents.
- The IRB receives a research protocol that examines the pharmacologic response to palivizumab using a new biomarker that has been validated by the company and several clinical trials. Throughout the discussion, a pulmonologist raises concerns that the investigator should be using an older biomarker for the study instead of the new one. Except for the pulmonologist's objection, the protocol is appropriate. Which one of the following is the most appropriate action?
 - Deny the IRB application until changes in the biomarker are made in study protocol.
 - Deny the IRB application because the research subjects are at risk of harm.
 - Approve the IRB application because the research subjects are not at risk of harm.
 - Approve the IRB application because the new biomarker is a better predictor of response than the older biomarker.
- A novel fifth-generation cephalosporin receives FDA label approval. The agent covers vancomycin-resistant *Enterococcus* (VRE) spp. in addition to gram-negative organisms and anaerobes. A collaboration of researchers intends to submit an NIH research grant protocol to examine its use in the ICU. The study excludes pediatric patients because the researchers prefer not to worry about assent issues. Which one of the following is the NIH most likely to do?
 - Fund the study as currently written because understanding the pharmacokinetics (PK) in the adult ICU setting is important.
 - Fund the study as currently written because it addresses a serious health care concern related to VRE.
 - Not fund the study because sufficient data should have been obtained during the FDA approval process.
 - Not fund the study because there is no scientific explanation for why children are excluded from the study.

Questions 6 and 7 pertain to the following case.

The P-KIST study is planned for children younger than 10 years to assess the pharmacokinetic profile of a single dose of a new intravenous antihistamine. Children in the study will receive intravenous maintenance fluids, followed by the injection of the intravenous antihistamine into the running intravenous line. Serial blood sampling will take place every 2 hours for 8 hours, followed by discontinuation of the intravenous maintenance fluids.

- Which one of the following is the best classification for the P-KIST study?
 - Research involving no greater than minimal risk and the prospect of direct patient benefit.
 - Research involving greater than minimal risk but the prospect of direct patient benefit.
 - Research involving greater than minimal risk but no prospect of direct patient benefit.
 - Eligible for waived consent.

7. Which one of the following best depicts who is ultimately responsible for assessing the appropriate level of risk in the P-KIST study?
- Institutional IRB
 - Principal investigator
 - NIH
 - FDA

Questions 8–10 pertain to the following case.

G.G. is a neonatal intensive care specialist who wishes to evaluate a practice change for term infants who are born to group B *Streptococcus*-positive mothers. Current standard of practice is to administer intravenous ampicillin for 10 days to ensure that exposed infants born vaginally do not develop late-onset group B *Streptococcus* sepsis. The medical team wishes to administer the first 3 days of ampicillin therapy intravenously, followed by 7 days of oral therapy. Blood samples will be obtained during intravenous and oral therapy to ensure that ampicillin serum concentrations are equivalent.

8. Which one of the following best describes the appropriate risk level for G.G.'s study?
- No risk category; this is a standard of practice, albeit in a different dosing form.
 - Research involving no greater than minimal risk.
 - Research involving greater than minimal risk but direct benefit to patient.
 - Research involving greater than minimal risk but no direct benefit to patient.
9. G.G.'s research protocol is initiated, and subject recruitment is going well. The team would like to enroll an infant in the study, but the mother is sole guardian, and she is currently in the adult ICU. The infant's grandmother offers to sign the informed consent because she wants the child to be home while the mother is recovering in the hospital. Which one of the following is the best course of action regarding G.G.'s study?
- Allow the grandmother to sign the informed consent as a surrogate for the incapacitated mother.
 - Exclude the infant from study participation.
 - Continue with the plan to change the infant from intravenous to oral ampicillin, as planned, without informed consent.
 - Enroll the infant now and obtain informed consent from the mother when she is medically able to do so.
10. G.G.'s research team is notified that the mother has rapidly improved and is now able and willing to discuss the study protocol. However, English is her second language, and she has difficulty communicating with the research

team. Which one of the following is the best action for the research team to take?

- Provide adequate information (written and verbally) about the study in a language understandable to the participant.
- Note in her medical chart that she provides verbal informed consent.
- Exclude the infant from the study because the informed consent sheet is not available in the mother's native language.
- Continue to transition the infant from intravenous to oral therapy.

Questions 11–14 pertain to the following case.

The DOPPTOP research team wishes to examine the relationship between traumatic brain injury (concussions) and cerebral blood flow. Cerebral blood flow will be measured using an innovative Doppler ultrasound "helmet" that measures blood flow velocity. Those with concussions will be matched with controls to examine potential differences in blood flow between the two groups. To obtain the best results and avoid the co-variable of anxiety affecting cerebral blood flow, all patients enrolled in DOPPTOP will receive a small dose of oral midazolam before measurements are taken.

11. Which one of the following is the most appropriate risk category for DOPPTOP?
- Research involving no greater than minimal risk
 - Research involving greater than minimal risk but the prospect of direct benefit to patient
 - Research involving greater than minimal risk but no prospect of direct benefit to patient
 - Not eligible for waived consent
12. The DOPPTOP study is approved by the institutional IRB. A 14-year-old girl volunteers to serve as the control in the study, and the appropriate informed consent is obtained. In reviewing the adolescent assent form, the researcher becomes concerned that the teenager does not understand the risks associated with the study. Which one of the following would be the most appropriate next step for the DOPPTOP research team?
- Do not enroll the patient because she does not understand the risk associated with the study.
 - Use the youth assent form because it may more clearly convey the risks associated with the study to the patient.
 - Document in the chart that the patient understands the scope of the research protocol, even though she cannot understand the adolescent assent form.
 - Encourage the patient to sign the adolescent assent form because she understands the risks sufficiently.

13. While conducting DOPPTOP, a 16-year-old male adolescent with a history of concussions agrees to participate in the study. The appropriate assent and consent forms are filled out, and later the teenager attends the outpatient clinic to have the cerebral ultrasound. After consuming the oral midazolam at the outpatient clinic, the research subject objects to participating in the study. His mother states that “it is just the medicine talking” and urges the researchers to proceed. Which one of the following is the best course of action for the DOPPTOPP research team?
- Proceed with the study because the mother, who signed the informed consent sheet, said it was appropriate to proceed.
 - Discontinue to study because the teenager revoked assent.
 - Discontinue the study because the mother said it was appropriate to do so.
 - Wait several hours until the drug effects wear off and ask him to participate again without re-obtaining assent.
14. A parent wishes to enroll his child to serve as a control in the DOPPTOPP study. As the research team discusses the protocol with the parent, it becomes apparent that the parent is most interested in the \$200 gift card that is provided as compensation for the child participating in the study. Which one of the following best describes the ethical principle most compromised in this situation?
- Justice
 - Beneficence
 - Respect for persons
 - Clinical equipoise
15. An infectious disease physician wants to study two-drug therapy for HIV infection in treatment-naive adolescents for whom the current standard of care is triple-drug therapy. The physician believes the added risk of adverse effects from three drugs does not outweigh the efficacy benefit of the third drug. Which one of the following study designs would best answer this question?
- A randomized controlled trial in which the control arm is placebo and the active arm is two-drug therapy.
 - A non-inferiority trial in which two-drug therapy is studied against three-drug therapy for HIV.
 - A cohort study of patients receiving two-drug therapy comparing efficacy with historical control data of three-drug therapy.
 - A non-inferiority trial of two separate regimens consisting of two drugs active against HIV.
16. Which one of the following best describes pharmaceutical companies’ involvement in pediatric clinical trials?
- Pharmaceutical companies eagerly participate in studies focused on pediatric drug development because the return on investment is often greater than in adult clinical trials.
 - Pharmaceutical companies are mandated by federal law to enroll equal numbers of adults and adolescents in any trial expected to garner FDA approval.
 - The barriers to pharmaceutical company involvement in pediatric clinical trials are greater for pediatric trials than for adult trials and thus often discourage industry involvement in the pediatric trials.
 - Pharmaceutical company involvement in pediatric clinical trials is strong because recruiting patients is easier than in an adult trial, and there are more trained investigators for pediatric research than for adult studies.
17. A 6-year-old girl, an orphan, lives in a suburban group home in southern California. She has a rare genetic disease that would make her eligible for a clinical trial at a nearby children’s hospital. Which one of the following would be the biggest concern regarding this child’s involvement in the study?
- She would not be considered for enrollment because she is an orphan, and her biological parents would be unable to consent to the study.
 - She can enroll in the study as long as she meets the inclusion and exclusion criteria for the study; she must provide consent before enrolling because she has no parents to assent for her.
 - She can enroll in the study if she meets the inclusion and exclusion criteria but must provide assent; the assent form used for the study should be written at a level she can understand. No further consent is needed.
 - For her to enroll into the study, a legal guardian would need to provide consent.
18. Which one of the following best describes the training requirements of investigators involved in pediatric clinical trials?
- Pediatric trials are managed similarly to adult trials; thus, the investigators need no special training.
 - Investigators involved in pediatric clinical trials are required to have a special certification from an academic medical center justifying their competency in conducting pediatric research.
 - Pediatric clinicians are often hesitant to participate in pediatric clinical trials because they often

believe they lack the training needed to manage the complex issues that arise from enrolling pediatric patients.

- D. Physicians for adult patient populations are often used to carry out pediatric clinical trials because there is a lack of trained pediatricians to participate in pediatric trials.
19. A 12-year-old boy recently received a diagnosis of neuroblastoma. The pediatric oncologist managing the boy's care would like to enroll him in a study in which biopsied tissue from the tumor will be studied by a local pathology laboratory to determine the genetic characteristics underpinning the tumor's characteristics. Results from the study will not affect the immediate care of the patient. Which one of the following best describes the child's enrollment in the study?
- A. The study will not need IRB approval because no intervention is occurring for the patient; he is simply providing a tissue sample to the investigator.
- B. The study will need IRB approval; the patient will need to provide assent, and his parents will need to provide consent for him to participate.
- C. The oncologist managing the boy's care will be responsible for signing the consent form for his involvement in the study because the oncologist is the most knowledgeable provider regarding study procedures.
- D. Neither the boy nor his parents should receive any type of compensation for participating in the study because the tumor biopsy would have occurred at some point in his care anyway.
20. Which one of the following best describes the conduct of first-in-human trials in pediatric populations?
- A. They may never be conducted in pediatric populations. Adult clinical trial data must first be available so that investigators can scale dosing appropriately for children.
- B. Dosing in these trials may be based on preclinical studies.
- C. They are unethical to conduct in pediatric populations.
- D. To conduct first in human trials in children, the dose selected for the study must be proven to provide efficacy for the pathophysiologic state being studied.