

Pediatric Consent and Clinical Trials

a report by

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Uniqueness of Pediatric Trials

Pediatric clinical trials are considerably inimitable compared with adult trials. Moreover, the complexities of the approval and consenting process for pediatric trials qualify them as a unique entity in the clinical research discipline.¹ There are explicit federal regulations that an Institutional Review Board (IRB) employs to determine risk in pediatric studies. The IRB must possess the ability to be sensitive to those issues specific to the pediatric population. As a result, an IRB that comprises both clinical personnel and the lay community, who serve as a voice for children and their families, is imperative. Many characteristics of a clinical trial are scrutinized when the IRB assigns a risk category. For instance, some areas of concern are the type of study, whether the benefits to the patient are greater than the risks, whether healthy volunteers are part of the study, or whether it is a treatment or genetic study. Pediatric consent forms require readable lay language; most IRBs require that the consent form not exceed the sixth grade reading level. Since parents/guardians are customarily the consenting authority to enroll their child into a research study, it is important for them to understand what they are consenting to and why. Assent may be obtained from a child who is able to understand the trial and is of a specific age that is predetermined by the local IRB. Some parents may be content to allow their child to participate in a clinical trial for the sake of advancing medical knowledge in a specific discipline, which is considered an indirect benefit. However, this perception is notional and, ergo, the exception; most parents prefer something more concrete. Consequently, more parents/guardians are likely to enroll their child in a clinical research trial if there are obvious direct benefits.^{2,3}

Determinants of Risk

There are concerns in pediatric trials that are unfathomable in adult trials. For instance, to recruit healthy pediatric subjects into a trial, it must be determined by the IRB that the proposed study poses no additional risk to that which would normally be encountered in everyday life. The determination may be dependent upon a number of issues; one IRB may

interpret risk differently than another. Some may compare it with riding in a car, while others may compare it with crossing the street. A drive in a vehicle may be very safe in the Midwest, but risk assessment may be significantly altered if the same scenario were evaluated in a big city on the East Coast. The same holds true with crossing a street. These analogies reiterate the point that the composition of an IRB be representative of both lay and clinical staff. Lay persons are a critical component of the IRB; they address practical issues that clinicians may not have considered or perhaps have overlooked.

Importance of Pediatric Trials

Phase I trials in pediatrics are important, given that they provide fundamental data for pediatric drug labeling. By providing accurate dosing to children there is a potential for more effective treatments, which may reduce hospital stays and, ultimately, insurance costs. According to the Code of Federal Regulations (CFR), pediatric trials with greater than minimal risk must confine research to children who have a condition or disorder, and the trial cannot pose any additional risks than would normally be encountered in their clinical care.⁴ Pediatric studies involving healthy subjects are generally more difficult to recruit because there is usually no direct benefit associated with this type of study.^{1,5}

From an ethical perspective, there are important facets of a phase I trial that demand consideration. Serial blood samplings, blood drawing access, and trial design are specific topics of concern. It is important that parents plainly recognize this when informed consent is obtained. Blood drawing access is another substantial issue—if it is a requisite for a two-year-old to have a peripheral intravenous (PIV) catheter placed for blood drawing, this will necessitate stabilization to avoid multiple PIVs. This procedure is replete with ethical issues. Consequently, an IRB may define the number of sticks permissible per subject. When a phase I trial is designed, blood volumes need to be considered, especially for children less than two years of age. Many sites obtain consent, but are largely ill equipped to entertain a two-year-old subject for 8–12 hours in the interest of adherence to a pharmacokinetic sampling schedule. The protocol should also be designed



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to address the needs of today's family. Childcare may be required, the subject may miss school, or a parent may need to take a day off from work to be with their child. Time, travel, and sundry expenses that might not be incurred if the child were not a participant in a clinical trial are vital issues that need to be broached.

Informed Consent and Child Advocacy

Informed consent in the pediatric setting is more complex than the adult consent process. If it is an outpatient study, visit schedules and time commitments are crucial, particularly for school-age children or families with multiple siblings. Pediatric studies are expensive to conduct because in some ways you are not only consenting an individual, you are consenting an entire family unit, and any additional demands on them should be considered carefully. The subject is a patient first, particularly for disease-specific studies; clinical issues cannot be ignored. As a result, it is imperative that the clinical research team carefully assesses whether or not to approach a subject. The family may be emotionally devastated as a result of clinical circumstances, which may in turn affect the candidate viability. This could be perceived as an auxiliary burden on the family.

There are also several other ethical considerations indigenous to pediatric studies. The importance of timing cannot be over-emphasized. The research team must be sensitive to the family's state of mind. Another area of concern is the clinical team caring for the child. When there are multiple clinically indicated procedures performed on a child, it is imperative that the research team be considerate of the demands already placed on the family. The research team is obliged to ensure that parents/guardians understand the procedures that are clinically indicated, and that being approached about a clinical trial may cause undue stress and confusion.⁵ With a pediatric study it is easy to overlook the child, since the parents/guardians

are usually the decision-makers. When designing a study, feasibility and logistical considerations for obtaining samples are compulsory. Scheduling blood samples around normal blood draws for clinically indicated labs or creating a pharmacokinetic study that reduces the number and volume of blood samples are essential components of a successful trial. It is imperative that the voice of a child, who may be afraid of needles or blood draws, is heard.¹

During pediatric trials it is important to continually reiterate the procedures, schedules, and commitments. Many families may be preoccupied by the clinical issues; consequently, participating in a clinical trial may not be a priority. After enrollment many parents/guardians appreciate a study co-ordinator who continually reminds them of the details of the study, which may include upcoming procedures, visits and expected time commitments. It is important to be proactive with families, anticipate their needs and concerns, and allow them the opportunity to reconsider and/or withdraw at any time, or refuse procedures that may cause discomfort to their child. It is the study team's responsibility to assist the family in determining when enough is enough. It is imperative to support the research subject's family but it is absolutely essential to become the subject's advocate, regardless of age.⁶

Conclusion

In summary, there are many aspects of pediatric trials that make them unique. The IRB's determination of risk sets the stage for the clinical trial. The IRB establishes how many parental/guardian signatures are required as a result of the assigned risk category. They decide whether the knowledge gained outweighs the risks. Once IRB approval is granted, it is up to the study team to uphold the determinations, and to abide by the protocol. Due to the unique nature of pediatric trials, it is essential that all of the aforementioned scenarios be considered when designing a trial. ■

References

1. Calldwell P H, Murphy S B, Butow P N, Craig J C, "Clinical trials in children", *Lancet* (2004);364: pp. 803–811.
2. Green J B, Duncan R E, Barnes G L, Oberklaid F, "Ethic forum putting the 'informed' into 'consent': a matter of plain language", *J Paediatr Child Health* (2003);39: pp. 700–703.
3. Levy M L, Larcher V, Kurz R, "Informed consent/assent in children. Statement of the Ethics Working Group of the Confederation of European Specialists in Pediatrics (CESP)", *Eur J Pediatr* (2003);162: pp. 629–633.
4. Kopelman L M, Murphy T F, "Ethical concerns about federal approval of risky pediatric studies", *Pediatrics* (2004);113: pp. 1783–1789.
5. Gill D, "Ethical principles and operational guidelines for good clinical practice in pediatric research. Recommendations of the Ethics Working Group of the Confederation of European Specialists in Pediatrics (CESP)", *Eur J Pediatrics* (2004);163: pp. 53–57.
6. Tait A R, Voepel-Lewis T, Malviya S, "Factors that influence parents' assessment of the risks and benefits of research involving their children", *Pediatrics* (2004);113: pp. 727–732.