



FEATURED ARTICLE

PEDIATRIC CLINICAL TRIALS: ONE SIZE DOESN'T FIT ALL

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According to the National Institutes of Health, 70 percent of the medicines given to children have only been tested in adults.¹ But “children are not little adults,” as Renee Jenkins, past president of the American Academy of Pediatrics, once said.

Children are unique in many ways. There are obvious anatomical features that differentiate them from adults: they have smaller airways, less protective muscle around their organs, and a greater body to surface area to body mass ratio. Children also differ from adults physiologically, with a higher metabolic rate, lower blood pressure, faster heart rate and less mature immune system.

But the differences between children and adults that affect medical care extend beyond the physical, including communication barriers and even emotional considerations.

Despite these many differences, the majority of drugs are not tested in children, and pediatricians are forced to resort to off-label use and guesstimated dosing. Off-label use may result in toxicity from the active ingredients leading to numerous adverse events and mortality and also paradoxical reactions have been reported from additive ingredients. On the other hand, inappropriate dosing might result in ineffectiveness.

Fortunately, that is changing, thanks to new regulatory policies of the FDA and EMEA for approved and investigational drugs. The new legislation is forcing pharmaceutical companies to conduct pediatric studies as an integral part of the normal development of a medicine and to disclose the results of such studies (main obligation) in exchange for a reward (incentive). The FDA also has had success with its pediatric exclusivity incentive program, which provides six months of marketing exclusivity to sponsors that conduct pediatric clinical trials.²

Since pediatric data must be provided for all indications in which the drug will be used - or is anticipated to be used - in children, and studies must address multiple pharmaceutical forms and routes of administration suited to children, there is an increasing number of sponsors that undertake pediatric studies. That is why it is important that pharmaceutical companies increase their pediatric competency and recognize that children are not little adults when it comes to trial design and conduct either.

Unique Protocols

The most common mistake sponsors of pediatric clinical trials make is “cutting and pasting” the protocol from their adult trial into their pediatric trial. Inappropriate design will result in delay in getting necessary regulatory approvals, poor enrollment, high dropout rate, questionable results and consequently will increase study costs.

The design of pediatric trials must be customized for children. The protocol must be of value to children and in most cases to the individual subject. The design must be appropriate for the stated objectives and should consider specific physiology, pharmacology and physiology and normal daily activities for each age group. The frequency of number of procedures should be minimized, especially for infant studies and if possible research procedures should be conducted to coincide with standard clinical procedures.

The quantity and type of procedures should be related to minimize discomfort, pain and fright and invasive procedures should be used only when clinically necessary. Sponsors might need to consider specifying the use of an IV catheter to minimize needle sticks and local anesthesia prior to needle-based procedures. An increased use of biomarkers is also an appropriate way to minimize invasive procedures.

One of the most sensitive issues is allowable blood volume and frequency of blood sampling that differs across age groups. In particular, European regulators have placed very specific limits on how much blood can be drawn from children during clinical trials, and sponsors of most U.S. trials also follow these guidelines.³ To ensure the limits are not exceeded, sponsors might need to revise their plan for blood-based analyses and incorporate microvolume blood assays and sparse sampling techniques. Use of IV catheters minimizes the number of venipunctures required in PK studies.

Scheduling of doctor visits must also be managed carefully in pediatric trials. Visits must accommodate school schedules, as well as meal and nap times, particularly for younger children, but also the working schedule of their parents/legal guardians.

Even a clinical trial’s basic safety and efficacy endpoints might need to be adjusted for pediatrics. Efficacy endpoints commonly used in adult studies might not translate directly to children, and safety follow-up must almost always be larger and longer to detect any adverse effects on development as the children grow.

Beyond adjusting the protocol for pediatric trials, sponsors might need to reformulate their drug for administration to children. Many drugs for adults are formulated as tablets or capsules, but such a route of administration is not appropriate for younger children. Whether a pediatric version of a drug is best delivered orally in a syrup form, nasally, transdermally, rectally or via injection is a matter that can require considerable preclinical time and effort to sort out, and it’s an issue that sponsors often underestimate.

A Question of Consent

Embarking on pediatric clinical trials also means navigating treacherous legal and regulatory constraints designed to protect this particularly vulnerable population.

The standards for obtaining parental consent for a child to participate in a clinical trial vary geographically. In many countries, the consent of a parent or legal guardian must be obtained for children under 18 years of age, but in the U.K. the standard is 16 years, and in Japan, it is 20 years. In the U.S. it varies from state to state, but is usually 18 years. Although NIH says it is 21 years, state law usually prevails.

Similarly, in many countries only one parent must sign the consent form, but in some countries, like France, both parents must sign. It also depends on the marital status of the parents, evaluation if there is greater than minimal risk with no benefit to the child and if the indication is within the field of emergency medicine.

While parental consent is a legally binding requirement for participation in pediatric trials, it is also necessary to have an assent form to be signed by the child. Assent assures the child understands the potential risks and benefits of the trial, and it must be obtained for children older than 6 or 7 years of age, in most cases, although there are assent forms designed for younger children using pictures and simple words.

One Size Doesn't Fit All

Just as children differ from adults, the various age groups of pediatric patients differ from each other. Pre-term newborns, or those born prior to 36 weeks of gestation, present special challenges due to their potentially low birth weight, very immature organs and renal and hepatic clearance, respiratory complications, rapid maturation and other issues.

Newborns, which generally fall between birth after 36 weeks of gestation and 28 days of age, have an immature blood-brain barrier that must be accounted for, as well as immature organs that change rapidly during the first few weeks of life.

Infants, which are two to 24 months in age, continue to present challenges due to their rapid growth, and they also present administration difficulties due to their inability to ingest capsules. Children, which technically range from two to 11 years of age, require careful monitoring of cognitive and motor development as well as skeletal growth and weight gain to ensure that the trial is not adversely affecting them. Additionally, younger children often experience needle phobia, stranger anxiety and other factors that can make obtaining their cooperation a challenge.

Adolescents, or those age 12 to 18 years, experience hormonal swings that can impact clinical studies, and must be monitored for any adverse effects on sexual maturation. Additionally, privacy is of high concern to this age range, and care must be used when discussing matters such as the use of birth control during a trial. Compliance is also a challenge with adolescents and can require special incentives and monitoring.

Studies must be conducted in each age group in which the product will provide a meaningful therapeutic benefit and in which will be used in a substantial number of patients for the indications claimed by the manufacturer. The best practice is to begin with adolescents and gradually move lower and lower in age as appropriate. This can be done via separate cohorts rather than separate trials, but it usually requires pharmacokinetic works in each subset.

Given the many factors that complicate pediatric clinical trials, sponsors should commit sufficient time and resources to formulating a strategy before beginning pediatric studies. Such a strategy must incorporate protocol design, drug formulation, consent, enrollment and many other factors.

At INC Research, our pediatric team has conducted 135 clinical trials in more than 30,000 pediatric patients at more than 2,000 sites. Our experience spans all pediatric age groups, all geographies, but in particular in North America, Europe, Latin America and Asia, and a diverse set of indications within respiratory/allergy diseases, hemato-oncology, CNS, endocrinology, dermatology, infectious diseases, vaccines and more.

In addition, we have a huge data base of investigational sites and KOLs in all countries where we run pediatric clinical trials. We have experience in evaluation of sites and their appropriateness for pediatric clinical trials and we have established several types of pediatric training that might be required for the site staff. We also have a huge pool of project leaders, medical monitors and CRAs experienced in pediatric research.

We manage pediatric clinical trials from start to finish using our Trusted Process – from protocol design to delivering the particular pediatric data required by regulatory agencies across the globe. We also provide consultancy for full program development, indicating the best regulatory strategy and design of required clinical trials. Our creative enrollment strategies and risk management plans ensure timely recruitment and retention, as do our relationships with thousands of pediatric trial sites.

With our support, many customers have met the demands of FDA Written Requests in the pursuit of marketing exclusivity. We also have extensive experience in writing the Pediatric Investigational Plan (PIP) required by the EMEA in various pediatric indications.

For more information about INC Research's pediatric expertise, contact Alexander Cvetkovich-Muntañola at acvetkovich@incresearch.com.

About the Author

Alexander Cvetkovich-Muntañola, MD, is a pediatrician and provides leadership for INC Research's pediatric clinical trials. He is renowned for his breadth of experience gained over nearly two decades in the medical and clinical research arenas. Dr. Cvetkovich-Muntanola has served as a pediatric clinician with expertise in pulmonology and neonatal intensive care, and as a researcher in the clinical trials arena. He has also served as a medical consultant to UNICEF health based initiatives in Belgrade. He has experience in various indications in pulmonology and allergy, hemato-oncology, CNS, endocrinology, dermatology, infectious diseases and vaccines, involving PK studies in subjects from birth until 18 years of age.

References

¹<http://www.nhlbi.nih.gov/childrenandclinicalstudies/whydo.php>

²<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm077915.htm>

³http://www.who.int/bulletin/online_first/BLT.10.080010.pdf