

Not Just Little Adults

When designing a paediatric protocol, it is vital that the latest ethical, regulatory and practical considerations are taken into account, report Alexander Cvetkovich-Muntañola and Kathryn Bohannon of INC Research

Within the last decade, there has been a significant rise in the number and scope of paediatric clinical trials due to an increased awareness of an unmet need, as well as legislation within the US and EU promoting and requiring paediatric research as a part of drug development.

According to the National Institutes of Health, 70 per cent of the medicines given to children have only been tested in adults (1). As many experts assert, “children are not little adults.” Forcing paediatricians to resort to off-label use and guesstimated dosing may cause harm to children, including toxicity from the active ingredients leading to numerous adverse events and mortality, and paradoxical reactions from additive ingredients and ineffectiveness.

Children are indeed unique in many and various ways. There are obvious anatomical features that differentiate them from adults: they have smaller airways; less protective muscle around their organs; and a greater surface area to body mass ratio. Children also differ from adults physiologically, with a higher metabolic rate, lower blood pressure, faster heart rate and a less mature immune system. There are other important differences between children and adults that affect their medical care beyond the physical, including communication barriers and even emotional considerations.

Fortunately, thanks to relatively new legislation and regulatory policies of the Food and Drug





Administration (FDA) and European Medicines Agency (EMA) for approved and investigational drugs, pharmaceutical companies must address the paediatric population as a more integral part of the drug development process, consider development of more paediatric-friendly formulations, and disclose study results.

As the paediatric population must be addressed within the drug development process, an increasing number of pharmaceutical companies must now conduct paediatric research studies. It is therefore important that companies increase their paediatric competency and understand the unique considerations associated with conducting studies in children.

RECENT LEGISLATION

The US and EU are by far the most advanced with respect to specific legislation and regulations for paediatric clinical trials. The most significant legislation within the US for encouraging and requiring paediatric research is the Pediatric Research Equity Act (PREA) enacted in 2003 and reauthorised in 2007, and the Best Pharmaceuticals for Children Act (BPCA) enacted in 2002 and reauthorised in 2007.

PREA requires that companies include a paediatric assessment with all new drug applications and biologics licensing applications (or supplements) for a new active ingredient, indication, dosage form, dosing regimen or route of administration, unless the sponsor has obtained a waiver or deferral. BPCA includes a provision that allows for a six-month extension of a drug's marketing exclusivity in exchange for a company voluntarily conducting paediatric trials, in compliance with a written request negotiated with the FDA (2).

Within the EU, the Pediatric Regulation came into force in 2007 and established a process for development of a paediatric investigation plan (PIP) that is mandatory for marketing authorisation applications for new products and new indications for authorised products. The European legislation also provides for a six-month extension of the patent or supplementary protection certificate for new products.

The requirements associated with this legislation and regulations factor significantly in the planning and conduct of paediatric research by pharmaceutical companies. If a company intends to market a product in both the US and EU, the company must develop a paediatric plan that will satisfy

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the requirements of the PREA and the Paediatric Regulation, and any voluntary studies that may be necessary if a written request is pursued for additional marketing exclusivity in the US.

Both the FDA and EMA encourage the incorporation of paediatric research early in the drug development process. However, the EU's Pediatric Regulation requires that research be addressed earlier, specifically following the conclusion of pharmacokinetic studies in adults.

UNIQUE PROTOCOLS

It is very important that the design of paediatric trials is customised for children. A common mistake that can be made by a pharmaceutical company is simply 'cutting and pasting' the protocol from an adult trial into a paediatric trial. Inappropriate design will cause delays in obtaining necessary regulatory and institutional review board (IRB)/ethics committee (EC) approvals, poor enrolment, high dropout rates, questionable results and, consequently, an increase in overall study costs.

In designing a paediatric protocol, the company must consider the balance of risks and benefits to the paediatric participants, and design a study that minimises risk and offers the potential for information that will improve the care of children and of the individual study patient whenever possible. The design needs to be appropriate for the stated objectives and take into

account the specific physiology, pharmacology and normal daily activities for each age group.

In designing a paediatric study, each aspect must be thoughtfully considered and adjusted as necessary based on the paediatric participants. Even a clinical trial's basic safety and efficacy endpoints might need to be adjusted. Efficacy endpoints commonly used in adult studies might not translate directly to children and follow-up for safety is routinely more extensive, and for a longer duration, in order to detect any adverse effects that develop as the children grow and mature.

In many cases, a company will need to reformulate the study 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 paediatric 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, and is an issue that companies often underestimate.

The paediatric study's schedule of events and required procedures must be customised in order to minimise risk, discomfort, inconvenience and overall impact on the paediatric patients and families. The frequency and number of procedures should be minimised – especially for infant studies – and, when possible, research procedures should be planned to coincide with standard clinical care procedures.

Table 1: References identified in literature review of blood volume sample safety limits in paediatric clinical research

Source	Total	Relevant references	
		Number	Citation
Medline search (a)	179	3	Madsen <i>et al</i> 2000 Testa <i>et al</i> 2006 Broder-Fingert <i>et al</i> 2009
Medline search (b)	58	2	Cole <i>et al</i> 2006 Broder-Fingert <i>et al</i> 2009
EMBASE search (a)	325	1	Hack <i>et al</i> 2008
EMBASE search (b)	62	0	–
Other (c)	NA	13	US Department of Health and Human Services Pearson <i>et al</i> 2003 Gibson <i>et al</i> 2004 Cable <i>et al</i> 2002 Schwartz <i>et al</i> 2000 USC-LA Children's Hospital Wayne State University Partners Human Research Committee University of California Davis Duke University KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya (d) Gambia Government-MRC Joint Ethics Committee Kauffman 2000

MRC, Medical Research Council; NA, not available

(a) For adverse effects of blood sampling in children

(b) For guidelines and policies for blood sampling in paediatric research

(c) Cochrane Library; Clinical Evidence; American Academy of Paediatrics; Royal College of Paediatrics and Child Health; Google; BloodMed; paediatrics textbooks (Nelson, Rudolph); review of bibliographies; expert consultation

(d) Provided by the KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya, October 2006 with an updated version provided to the author in August 2009

Source: Howie SRC, *Blood sample volumes in child health research: review of safe limits*, *Bulletin of the World Health Organization* 89: pp46-53, 2011. To see the references in full, go to www.who.int/bulletin/volumes/89/1/10-080010.pdf

Efforts must be made to minimise discomfort, pain and fright for the children, and invasive procedures should be used only when clinically necessary. Use of biomarkers may be an appropriate way to minimise invasive procedures. Scheduling of study doctor visits should also be managed carefully in paediatric trials. Visits must accommodate work schedules for parents/legal guardians, patients' school and activity schedules, as well as meal and nap times, particularly for younger children.

One of the most sensitive issues for investigators, parents, patients and IRBs/ECs is the required blood volume and associated number of blood draws. Multiple IRBs/ECs and European regulators place specific limits on the blood volume that may be obtained from children during clinical trials (3).

To minimise the required blood volume and number of draws, companies should consider options such as microvolume blood assays and sparse sampling techniques. To minimise discomfort, studies routinely include the use of IV catheters to reduce the number of needle sticks (particularly for pharmacokinetic sampling), as well as local anaesthesia to reduce the pain associated with needle-based procedures.

A QUESTION OF CONSENT

Embarking on paediatric clinical trials also means navigating legal and regulatory constraints designed to protect this particularly vulnerable population. As paediatric research involves patients with limited legal capacity, there are important considerations with respect to consent for study participation.

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; however, in the UK the standard is under 16 years, in Japan it is under 20 years and even within the US the age may vary by state.

Similarly the requirement with respect to the number of parents that must provide consent varies by country (for example, France requires consent from both parents) and IRB/EC, and may depend upon factors such as clinical setting (for example, emergency medicine), marital status of the parents, and risk/benefit determinations.

While parental consent is a legally binding requirement for participation in paediatric trials, provisions must also be made to include the patients themselves in the discussion and allow them to provide assent for study participation whenever possible and appropriate. Requirements with respect to the age of assent, method and documentation vary by IRB/EC.

Multiple guidance documents and recommendations assert that assent should be obtained from children seven years and older, and that information should be presented to the children in an age appropriate format. The requirements associated with parental consent and paediatric assent for paediatric trials may require the development of multiple consent/assent documents, provision of specialised training and additional oversight/monitoring considerations by the pharmaceutical company.

ONE SIZE DOES NOT FIT ALL

Just as children differ from adults, there are differences within and across the age



groups within the paediatric population. Classification of paediatric patients into age categories is somewhat arbitrary, but commonly used age classification categories include: preterm newborn infants (prior to 36 weeks gestation); term newborn infants (0 to 27 days); infants and toddlers (28 days to 23 months); children (two to 11 years); and adolescents (12 to 16/18 years).

FDA and EMA will require that studies are conducted in each age group in which the drug may provide a meaningful therapeutic benefit and in which the drug may be used in a substantial number of patients for the indications claimed by the manufacturer. Studies are routinely conducted first in adolescents and then in progressively younger age groups after safety and pharmacokinetics are established in older patients. This progression of research across the paediatric age groups may be done via cohorts within an individual study or across multiple studies, depending upon such factors as the indication, pharmacokinetics and formulation.

In designing paediatric studies, consideration must be given to the paediatric age groups included and unique characteristics and considerations associated with the different groups. For example, pre-term newborns present special challenges due to such factors as low birth weight, immature organs and renal and hepatic clearance, respiratory complications, and rapid maturation. Newborns 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 and toddlers continue to present challenges due to their rapid growth, and drug formulation may be an issue since this age group is unable to swallow tablets or capsules. Children require careful monitoring of cognitive and motor development, as well as skeletal growth and weight gain to ensure that the trial is not affecting them adversely. Additionally, younger children often experience needle phobia, anxiety when they are with strangers and other factors that can make obtaining their cooperation a challenge.

Adolescents experience hormonal swings that can affect clinical studies, and must be monitored for any adverse effects on sexual maturation. Privacy is often of great concern to this age group, and care must be used when discussing matters such as the use of birth control during a trial. Compliance may also be challenging with adolescents and can require special incentives and monitoring.

PROACTIVE & STRATEGIC PLANNING

Fortunately, there is increasing awareness of the need for and importance of paediatric clinical trials. As a result of significant legislative efforts within the US and EU, pharmaceutical companies must address the paediatric population during the drug development process; and when applicable, design and conduct paediatric trials in the these appropriate age groups.

Given the many factors that complicate clinical trials in children, sponsors should commit sufficient time and resources to formulating a strategy before beginning paediatric studies. Such a strategy must incorporate the unique considerations with respect to regulatory and legislative requirements, protocol schedule of events and procedures, drug formulation, consent and assent, and age groups.

References

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About the authors



Alexander Cvetkovich-Muntañola, MD, is a paediatrician and provides leadership for INC Research's paediatric clinical trials. He is renowned for his breadth of experience gained over nearly two decades in the medical and clinical research arenas. Alexander has served as a paediatric clinician with an 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, haemato-oncology, CNS, endocrinology, dermatology, infective diseases and vaccines, involving PK studies in subjects from birth until 18 years of age.
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Kathryn Bohannon has 15 years of diverse operational and therapeutic experience within pharmaceutical research and development, including Phase 1-4 clinical research, laboratory R&D, US and global project management, and sales and marketing. Kathy is a paediatric therapeutic leader and strategist with more than eight years of paediatric research experience, including early studies conducted following FDAMA legislation of 1997, and five years of paediatric study and programme management within the Best Pharmaceuticals for Children Act – Coordinating Center (BPCA-CC) under the purview of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Kathy received her BA in Biology from the University of Virginia and has completed graduate coursework in medicine, clinical research and chemistry.
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