WHITE PAPER

Comprehensive Challenges in Global Pediatric Clinical Research

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As per the Indian regulations, there are no particular guidelines for the pediatrics trials and is only specified in the schedule Y. As children are legally unable to give written informed consent, and are dependent on their parent(s)/legal guardian to assume responsibility for their participation in clinical studies. Written informed consent should be obtained from the parent/legal guardian. However, all pediatric participants should be informed to the fullest extent possible about the study in a language and in terms that they are able to understand. Where appropriate, pediatric participants should additionally assent to enroll in the study. Mature minors and adolescents should personally sign and date a separately designed written assent form. Although a participant’s wish to withdraw from a study must be respected, there may be circumstances in therapeutic studies for serious or life-threatening diseases in which, in the opinion of the investigator and parent(s)/legal guardian, the welfare of a pediatric patient would be jeopardized by his or her failing to participate in the study. In this situation, continued parental/legal guardian consent should be sufficient to allow participation in the study. For clinical trials conduct in the pediatric population, the reviewing ethics committee should include members who are knowledgeable about pediatric, ethical, clinical and psychosocial issues.

If novel medicine is anticipated to treat both adults and pediatric patients, the pediatric population must be integrated in the clinical trials beginning onwards. If pediatric data is not incorporated, this wants to be reasonable in detail. When studies in children will be more appropriate when there exists some initial experience on use of products in adults or studies in children might take longer than studies in adults. In addition, pediatric trials may be delayed when development of a pediatric formulation is not complete. Safety data from earlier adult human exposure and should be available, appropriate repeated dose toxicity studies, all reproduction studies and the standard tests should be available prior to the initiation of trials in pediatric populations.

**Age classification of pediatric patients**

**Preterm newborn infants**; unique spectrum of diseases, rapid development and differences in their body functions, unique response to treatment, requirements for forms of medications that can be safely administered given their especially small size.

**Term newborn infants (0 to 27 days)**; volumes of distribution may be different than those in older pediatric patients; blood-brain barrier is not fully mature. Oral absorption may be less predictable, hepatic and renal clearance mechanisms are immature and rapidly changing.

**Infants and toddlers (28 days to 23 months)**; rapid mental, physical and immune development. Elimination of drugs from the body may exceed that in adults. Considerable variability in response to medication, because the development does not occur at the same rate in all children.

**Children (2 to 11 years)**; large variation and variability in development. Onset of puberty is highly variable and heralds a time of accelerated growth and marked changes which may alter response to medications and doses required.

**Adolescents** (12 to 16-18 years which is dependent on region); sexual maturation; medicinal products may intervene with the actions of sex hormones and impede development. Rapid growth and continued neurocognitive development. Increasing independence and responsibility; willingness to take medication may become a problem.

**Global Challenges in conducting clinical trials in children**

1. **Challenges for the sponsor**
   - Relative rarity of specific diseases
   - PK/PD studies
   - Appropriate formulations are important for drug delivery
2. Challenges for ethical issues
   - Pediatric trial design
   - Risk-benefit analysis
   - Consent and assent to participate
   - The use of placebo controls
   - Including healthy children

3. Challenges for the Investigators
   - Recruitment and Retention

4. Challenges for the CRO

Challenges for the sponsor

Relative rarity of specific diseases: The relative rarity of the condition in children, as compared to adults in that extraordinary effort would be needed to include children, although in rare diseases or disorders where the applicant has made a particular effort to assemble an adult population, the same effort would be expected to assemble a similar child population with the rare condition. These studies have been difficult to execute, because of the many barriers in conducting clinical trials in pediatric medicine: the relative rarity of disease, disease heterogeneity, lack of research infrastructure, ethical issues in pediatric research, and difficulty in identifying valid clinical end points.

PK/PD studies: A pharmacokinetic study of a drug showed that its clearance is linearly correlated with body surface area and creatinine clearance, with smaller children having greater drug exposure than larger children. Multiple drug agents that clearly demonstrate a dose-effect in adults have failed to show such a dose-effect in children. The apparent simplicity of the pediatric pharmacokinetic study is deceptive. The material reported in a pediatric pharmacokinetic publication does not include the trials and tribulations endured by investigators during the study; problems and pitfalls that are encountered again by others in further pediatric studies. Study design cannot always be extrapolated from information based on adult experiences. Many differences exist in physiology, pathology, pharmacokinetics, and pharmacodynamics between children and adults. For example, in pharmacokinetics, there are differences in metabolic pathways, in organic functions, and in metabolic rates. In pharmacodynamics, differences exist in receptor functions, effect or systems, and homeostatic mechanisms. Growth and development influence side effects, and the dose of medications is dependent on body weight or surface area. Finally, age influences severity of disease, pathological agents, and natural history. These differences imply that extrapolation of adult data on medicinal products for the child population is inappropriate.

Appropriate formulations are important for drug delivery: Another major problem for children, as well as the aged and infirm, is drug formulation. Large dose pills or capsules do not lend themselves to delivery of smaller doses in accurate and palatable ways. The growing availability of drugs targeted for childhood illnesses is focusing efforts on child-friendly delivery methods. Issues to be considered when developing a pediatric formulation: a) what is minimal dosage frequency? b) One dosage form fits all or a full range, c) Minimal impact on life style (especially for adolescents) d) Minimum, non-toxic excipients, d) Convenient, easy and reliable administration e) Easily produced, elegant and stable f) Cost and commercial viability.

Challenges for ethical issues:

Pediatric trial design: The study is designed to provide drug company decision makers, drug delivery developers, device designers, healthcare marketers, and supply chain participants with a detailed understanding of the economics,
technologies, formulation factors, and commercial opportunities for drugs developed to meet the therapeutic needs and physiological limitations of pediatric patients. Recent recognition and industry acceptance of the unique therapeutic needs of pediatric patients has led to regulatory activity and development programs that are re-defining this market segment. To encourage drug developers to perform clinical testing in pediatric age groups for drugs anticipated to be used for children, the FDA and the European Commission has adopted special rules and guidance. The result has been a push by developers and formulators emphasizing the creation of formulations engineered and packaged specifically for children to meet the needs of pediatric patient populations.

**Risk-benefit analysis:** Doses which are safe and effective in adults normally cannot be simply adjusted to children, as children have a different physiology than adults. Therefore clinical studies are conducted to investigate safe and effective dosing in children. Discovering adverse events that may be specific to children and long-term risk-benefit analyses are of particular interest in pediatric studies. It is important that nonclinical toxicology studies designed to support the safety of clinical trials in pediatric subjects identify hazards specific to the treated population. These studies can provide information useful in limiting the risk of experiencing adverse events and identify appropriate clinical monitoring. When adverse effects are observed in nonclinical toxicology studies, there are a number of possible uses of these findings. Blood level monitoring could then be used in clinical trials to minimize the probability of such an adverse effect occurring. Consideration of the risk-benefit analysis of a given drug therapy is important.

**Types of Research That May Be Conducted in Children:**

- Research involving no greater than minimal risk.
- Research involving greater than minimal risk but offering prospect of direct benefit to the subject – if the risk is justified by the potential benefit to the subject and if the potential benefit is at least equivalent to existing alternatives.
- Research involving greater than minimal risk and no prospect of direct benefit but yielding generalizable knowledge about the subject’s disorder or condition – if the risk is a minor increase over minimal risk and if the risk is similar to those experienced in equivalent medical situations, and if the generalizable knowledge to be gained is vital to better understanding the subject’s disorder or condition.
- Research otherwise not approvable (i.e., offers no direct benefit to subjects and is more than a minor increase over minimal risk) that offers the opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of all children. This type of research must be submitted to the Secretary of Health and Human Services and approved by a special panel.

**Consent and assent to participate:** The consenting process within pediatric clinical trials is more complex than in adult trials. Pediatric patients are legally incapable of providing valid consent on their participation in a pediatric clinical trial and require parental written informed consent. The consent of the parents should express both their own wishes and the will of their child. An assent process that protects the child’s dignity and welfare is crucial, and should be adapted to the developmental, social and psychological variability’s among pediatric patients. Investigators, study sponsors and Ethic Committees must take these variabilities into account. Meanwhile, future efforts should be directed to provide a clearer picture of the ability of children to understand research and provide detailed guidance on the informed consent and assent processes in different developmental ages, while also considering cultural and familiar influences.

**The use of placebo controls:** There are ethical considerations when conducting studies in diseases where a treatment is already available, where placebo control is relevant, and in an emergency setting. All of these affect the willingness
to participate in clinical research. However, these arguments in favor of the continued use of placebo controls have been strongly criticized. Among the most important criticisms of the continued use of placebos is that placebo use may subject the study participant to increased risk from not receiving active therapy. Use of placebo is especially suspect if an accepted treatment exists for a given condition and the potential subject is to be withdrawn from or denied active treatment in order to be enrolled in the study. Although the case could be made that the subjects were protected by the option to withdraw, the stronger argument is that the subjects were subjected to an unnecessary risk of harm, therefore making the study designs unethical. On the other hand, if there were no effective treatments for the condition under study, then placebo use would certainly be ethical, at least for the initial studies of the proposed new treatment. Once a new treatment is shown to have some benefit, however, further use of placebo in subsequent trials would not be acceptable. Placebo use could also be ethical if placebos were used as an “add-on” to current treatment or if currently available treatments were themselves risky to the subject. Additionally, the case could be made that placebo use could be ethical if the potential subjects were untreated before entry into the study. However, this argument is difficult to accept, especially when it is known that the subject would clearly benefit from receiving standard therapy and could be harmed by omitting it.

Including healthy pediatrics: Studies should ideally not be performed in pediatric when they can be performed in adults. In certain situations, studies need to be performed in children who are healthy at the time of the trial. Prevention or vaccine trials contain healthy children but target a population likely to benefit from the result of those trials overall. Whenever possible the elder age groups should be considered for inclusion before the younger ones. Over half felt that healthy children should not take part in research for general pediatric conditions even if this may be relevant to them in the future. The role of the healthy child in research still remains to be clearly defined.

Challenges for the Investigators

Recruitment and Retention: Patient recruitment and retention is one of the major challenges in pediatric research. Investigator must expertise to evaluate the requirements of the clinical trial. Collaborative efforts with the site staff include evaluation of study design and impact upon the parents and patient, education of the parents and patients in order to ensure that they understand their obligation to study procedures, and consideration for the needs of the families, such as scheduling visits after school hours.

Challenges for the CRO

Drug companies face many challenges in pediatric clinical research. Pediatric trials come with a high level of complexity and cost. In order for professionals to carry out a successful pediatric drug development plan, they need the right infrastructure and information to avoid obstacles such as slow recruitment, noncompliance and difficulties in developing the right study criteria and protocol. When conducting research on children, drug companies must ensure that ethical boundaries are observed in both the design and execution of pediatric trials. CRO professionals can evaluate the current issues in pediatric drug development and recruiting, the execution of studies including developing countries, issues with timeliness and requirements. Contract Research Organizations have the experience and expertise to successfully conduct studies in neonates, infants, children, and adolescents. They can manage pediatric trials from study design to submission of pediatric data required by regulatory agencies including compliance with the guidelines and regulations. The best practices for overcoming these challenges, experienced in-house regulatory professionals those provide guidance on pediatric development and regulatory strategy. Special protection must be given to children participating in clinical research. Because their involvement is essential to making improvements in children's healthcare, enrolling a child in a trial is ethically acceptable and necessary. CRO has the experience with pediatric trial design and execution to ensure that while children benefit from medical progress, they are not exposed to unnecessary risks by participating in clinical trials.
CRO understands pediatric research and has insight of working with investigator, sponsors and regulatory agencies in developing novel approaches to successfully manage pediatric clinical trials. Patient recruitment and retention is one of the biggest challenges in pediatric research. CRO has the expertise to evaluate the requirements of the clinical trial and develop recruitment plans in partnership with the sponsor and investigative sites in order to meet project timelines. We work with site staff to achieve recruitment goals. Collaborative efforts with the sponsor and site staff include evaluation of study design and impact upon the parents and patient, education of the parents and patients in order to ensure that they understand their obligation to study procedures. CRO ensures that investigators are fully trained and understand their responsibilities in the parental permission/informed consent and assent process. In order to ensure a successful trial for all involved, it is essential that the investigators provide understandable study information and clearly explain expectations to both the patient and the parents during the parental permission/informed consent and assent process and for the duration of the study.

Conclusion

Pediatric research is increasing in volume and has become a global phenomenon. The special challenges of clinical studies demand careful planning and resourcing if the goals of the initiatives from regulators, governments, and health organizations are to be achieved. Integration of pediatric drug development in the planning process and assessment of the return on investment is important. An understanding of the clinical needs in children and what studies are feasible. Harmonization of regulatory requirements will hopefully lead to a reduced clinical trial burden and an avoidance of the overexposure of children to untested medicines. Clinical study risk assessment and contingency planning and the careful placement of the studies taking into account cultural, regulatory and clinical practice differences between countries will ultimately determine the success of pediatric development. The CRO’s provides a guide to interpreting the level of evidence that a study can provide for a particular research question. Identifying and implementing effective, evidenced-based care is considered best practice in pediatrics. An evidence-based clinician reviews the current literature to understand the evidence before addressing the concerns of parents such as those in the pediatric studies, but it is important to determine what counts as good evidence. Engaging in evidence-based practice requires the clinician to interpret the evidence from research studies. Research study design and type are important considerations when determining if the conclusions of the study are valid and to provide sufficient evidence to guide clinical decisions.