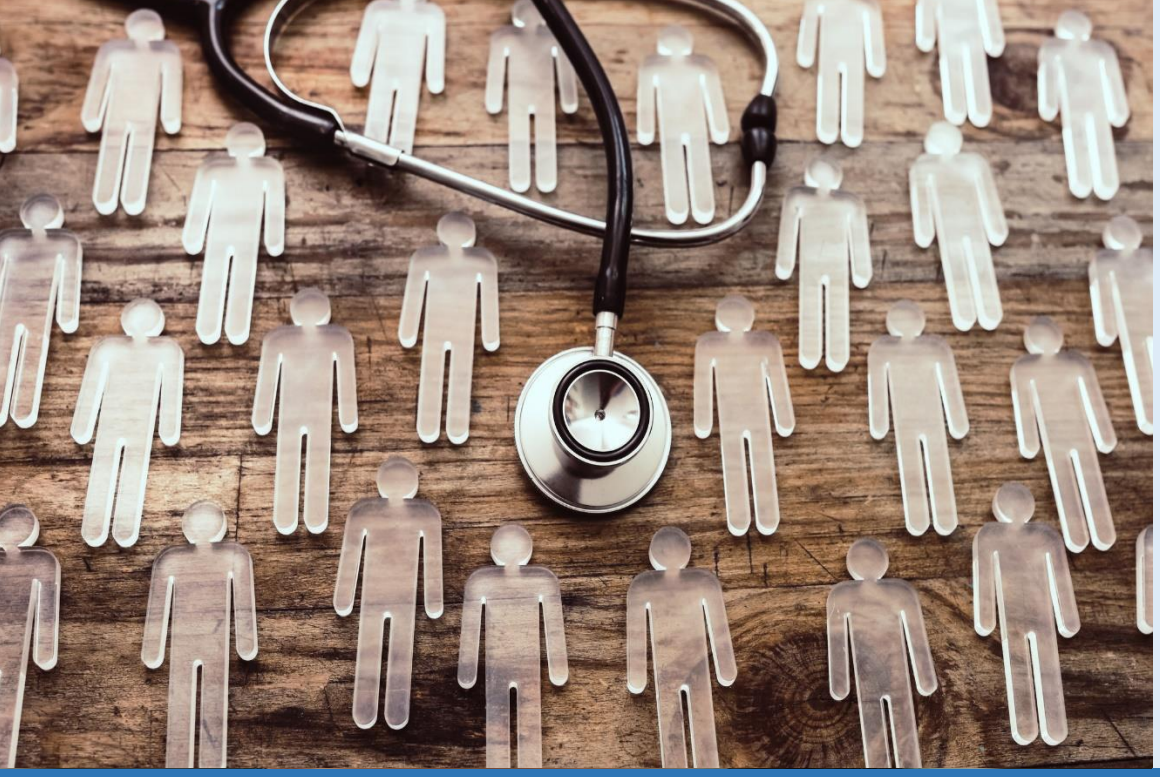


REGULATORY FOCUS

Strategies for pediatric clinical trials and drug development

Susanne Schmidt, MD, PhD

This article discusses the considerations for designing and conducting pediatric clinical trials from a pediatrician's perspective. The author covers pediatric subpopulations, issues related to age, endpoints, and pharmacokinetic considerations, while presenting practical solutions and ethical considerations. Patient and family–centric approach to studies and engagement with patient advocacy groups are also discussed. The author concludes with some recommendations about pediatric clinical trials involving cell and gene therapies, which are expected to increase significantly in coming years.

Introduction

Regulatory professionals often talk about how clinical trials for demonstrating pediatric effectiveness are difficult to design, get approved, and to conduct. The US Food and Drug Administration (FDA) has said that up to 50% of these trials are "not interpretable" because sample sizes are too small, endpoints are poorly defined, pharmacokinetic (PK) and pharmacodynamic (PD) correlations are not well enough established, and that many trials have used an incorrectly identified dosage.

Given these difficulties, there are several considerations from a pediatrician's perspective which, if considered, may help clarify, simplify, and solve some of the problems in designing and conducting pediatric effectiveness trials. These considerations have to do with the nature of the pediatric population and subpopulations, designing studies around standards of care, addressing ethical considerations, and beginning trial development with the end in mind.

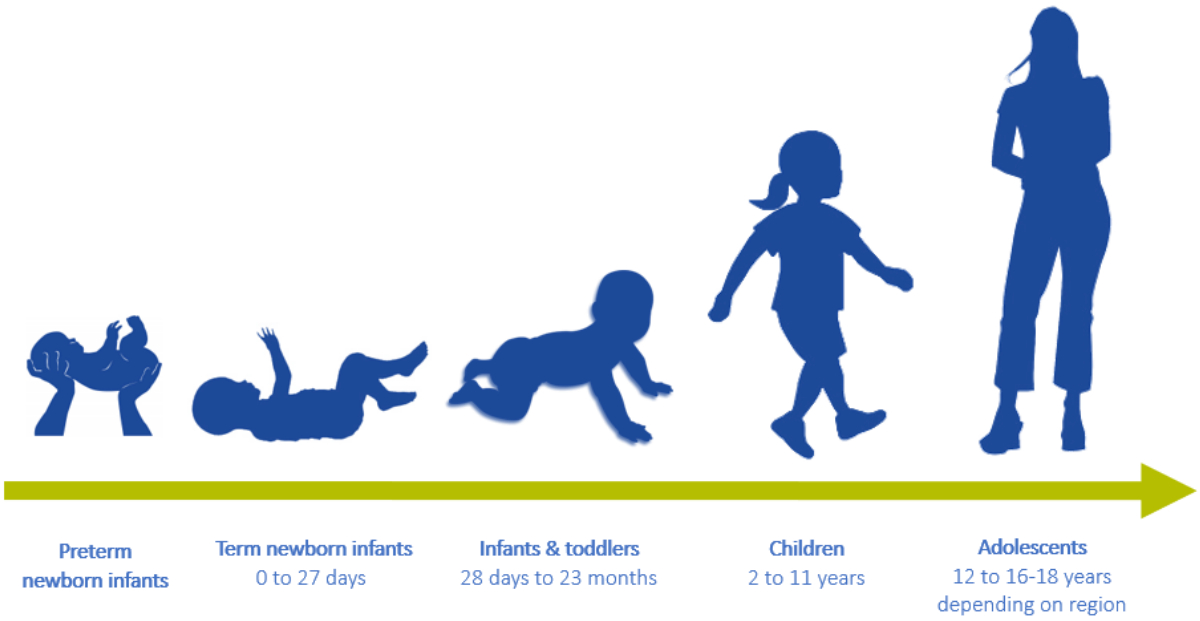
The pediatric patient population: Differences from adults

Exactly how children are unlike adults from a biomedical perspective bears some explanation and, most importantly, consideration in successful clinical trials design and conduct.

First, it is necessary to define the pediatric subpopulations because they cover a range of ages – from newborns to the age of 18 years, depending on the regions (**Figure 1**). For all pediatric subpopulations, drugs may behave differently in their bodies than in adult bodies. Bioavailability, especially, may vary because of differences between the two populations in drug absorption, distribution, metabolism, and excretion.

Such variation is related to children having proportionately larger body surface than adults, thinner skin, higher respiratory rates, and smaller airways, and faster heart rates. In addition, children have lower blood pressure than adults, higher metabolic rates, immature blood-brain-barriers, and enhanced central nervous system receptivity. Children also have less protective muscle around their organs than do adults, and their immune systems are less mature.

Figure 1. Pediatric subpopulations[a]



[a]ICH harmonised guideline. Addendum to ICH E11: Clinical investigation of medicinal products in the pediatric population. 2017.

It is also important to remember that, generally, children are more vulnerable than adults, and not just in biomedical terms. They are more vulnerable because of their inability to give consent and in their understanding and decision-making capacities. They are also vulnerable because they lack autonomy and are dependent on their caregivers.

This vulnerability has necessitated protections, such as those mandated by the International Council for Harmonisation.[1] Protective measures for pediatric patients are aimed at:

- Minimizing risk while providing the prospect of direct benefit to the patients,
- Assent and parental permission process,
- Staggered enrollment approach (from the oldest to the youngest pediatric age group)
- Providing treatment continuity after clinical study,
- Limiting placebo use, and
- Involvement of data safety monitoring boards.

Considerations on pediatric clinical trial design

For a variety of reasons, clinical trial protocols need to be designed and customized for the specific pediatric population, and not just re-worked from adult protocols. The primary endpoints used for adults may be different than – or even inappropriate for – pediatric trial participants. In addition, developmental variability should be considered and the study design must be realistic and "family friendly." Unsuitable designs are those that impose unreasonable burdens on children and their families, and an unsuitably designed trial will impede enrollment, affect retention, and probably lead to higher costs and approval delays.

The specific type of pediatric study will affect trial design. It is crucial to consider whether the study is interventional or observational, first in human, or first in pediatric patients. In addition, the type of drug – whether it represents a new class of drug, is repurposed, or a new formulation of an existing drug – must be considered, especially for safety issues.

To be successful, a protocol must include a clear definition of the targeted pediatric patient population and offer an understanding of the standard of care involved. Endpoint selection is critical; two or more primary endpoints, or composite endpoints, might be selected because of disease complexity or lack of consensus. Endpoints that matter to patients should be included, not just those that satisfy regulators, and so too, should patient or proxy-reported outcomes be included, complete with scales or questionnaires that are valid for the specific pediatric population. Extrapolation from adult data should be considered when possible.

Designing for success

The available patient pool for pediatric trials is often limited, so an adaptive study design could be considered. This means making sure the study can be modified even as data are being gathered and possibly incorporating traditional phase 2 and 3 study designs into a single trial.

Standard clinical trial elements that should be carefully considered are control groups and placebos, remembering that placebo use should be limited. Also, because children are involved, local guidelines may limit invasive procedures, for example, the volume of blood sampling.

The incidence and prevalence of the disease and its geographical distribution must be considered, along with an assessment of the impact participation may have on the family, including distance to the study site, frequency of visits and, if hospital stays are required, how long will they be.

The age of prospective pediatric participants must also be considered because each age group may have differing issues. For example, newborns have the potential for long-term developmental effects, whereas confidentiality issues may be involved with older children and adolescents. Age-appropriate formulations should be used in pediatric trials, taking into consideration a patient's age as well as development status; the disease under study; dosing and its frequency; treatment duration; route of administration appropriateness; and the flexibility to use different formulations in the same study based on the age ranges of the participants.

Pharmacokinetic considerations

Because of differences in absorption, distribution, metabolism, and elimination, the PK and PD of a drug used in children may differ significantly from the same data from adult usage. PK studies in children should allow the calculation of a dosing regimen that will achieve safe and effective therapeutic levels similar to those approved for adults. However, because of physiological differences, each pediatric age group might need to be evaluated separately because newborns and teens obviously may differ greatly. After a therapeutic dose has been determined by PK parameters, follow-up studies can be initiated to collect the necessary data for establishing safety and efficacy

Endpoints, assessments, statistics, and follow-up

Specific endpoints for pediatric clinical trials might include physiological measures and benchmarks, such as weight and height, thyroid hormone, insulin-like growth factor, skeletal growth, and pubertal development. Endpoints for cognitive development, both short and long term, can be evaluations of attention, memory, learning and language skills, and/or assessments of developmental age/IQ. Endpoints for the assessment of behavioral and psychological maturation and developmental milestones may encompass quality of life and school performance and, for infants and young children, mental, motor, and behavioral developmental milestones. For premature infants, look for known complications and effects of prematurity.

Every assessment needs to be evaluated on whether it is necessary – and safe – to collect whatever data add to the overall study, bearing in mind the obligation to prevent unnecessary exposure, risk, or burden to the children in the study or to their families. It is important to be aware that some assessment procedures carried out with children, such as CT and MRI scans, may require some sedation. Attaining ECGs and blood and urine samples may be problematic, especially urine sampling over a 24-hour period or from diapers. Frequent blood samples may require indwelling catheters rather than subject children to frequent venipunctures.

For a meaningful statistical analysis, it is important to consider the appropriate sample size and potential stratification for age groups.

Future considerations

Patient and family–centric trials and rare disease research

Future efforts to develop pediatric clinical trials should always include a patient and family–centric approach. This approach seeks to involve patients and their families at all stages of drug development, to incorporate their feedback into trial design, and to design a truly patient and family–friendly trial that matters to both parties and can have a positive impact on patient recruitment and retention. This becomes particularly important when developing drugs for a rare disease, which might just recently have been described in a handful of patients, are quite unknown in the medical community, and for which there are no established outcomes. The effort to enhance the incorporation of the patient's voice in medical product development and regulatory decision making has become an initiative for both the FDA[2] and the European Medicines Agency.[3] The initiative includes, for example, using patient-reported outcomes and conducting qualitative patient interviews and natural history studies.

The patient and family–centric approach also requires clinical trial developers to engage early with regulators and patient advocacy groups and to stay engaged from the study design phase through recruitment. Useful groups include, for example, Conect4Children[4] and the International Neonatal Consortium.[5]

In summary, studies using the patient and family–centric approach in studies in rare diseases should identify, early on, the relevant endpoints, symptoms, standards of care and therapy, and the targeted patient population. Protocol design should, from the beginning, try to streamline visits, minimize invasive procedures, and support and "map" the patient and family journey. After the study's completion, do not forget to share the results with the participants and their families and thank them for their participation.

Cell and gene therapies

The FDA is preparing for substantial growth in clinical trials for cell and gene therapies. Specifically, the agency is expecting 10-20 new products to be approved by 2025 and, accordingly, is hiring 50 new clinical reviewers.

For several reasons, cell and gene therapy studies may be designed, implemented, and carried out somewhat differently than traditional drug effectiveness studies. Some of these studies may have the potential to be truly curative and reverse the underlying pathology. They may also involve very young patients who should be diagnosed within a certain timeframe before treatment initiation (**Figure 2**).

The delivery of a product and an appropriate dose remains important, but there may be a period of pretreatment, such as carrying out immunosuppressant regimens. Hospitalization and postoperative stays may be long because these are generally very complex trials and are restricted to a few specialized centers, with high impact on patient and family and long-term patient follow-up.

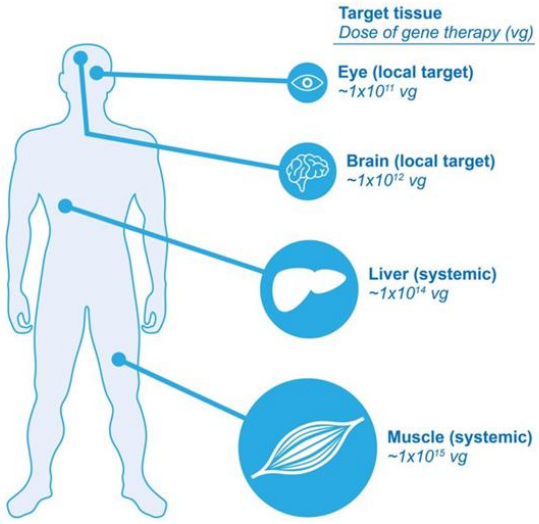
Summary and conclusion

To summarize, designing and implementing clinical trials with pediatric patient participants has unique challenges over and above those usually faced in clinical trials with adult participants. Pediatric patients are different physiologically than adults, and those differences likely mean that there are different PK and PD effects between the two groups because the drugs may work differently in the pediatric subpopulations in terms of absorption, distribution, metabolism, and elimination. Once more, obtaining samples, especially invasively, and scans, such as CT and MRI, may be more difficult with pediatric patients and need to be carefully considered whether they are truly needed for the trial.

The considerations reviewed here cover study protocol design and emphasize that, from the beginning, at the protocol development stage, it should be recognized that children are more vulnerable than adults and that vulnerability must be addressed. It is also important to remember that the pediatric population is defined using an age range between newborns up to age 18, depending on regions, and demands respecting the great differences in development through that range.

Figure 2. Implementation of cell and gene therapy studies

- **Potential to be Curative**
- Often involve very young patients
- Diagnosis of patient within treatment timeframe
- Delivery of product and appropriate dose
- Viral shedding
- Pre therapy – e.g. immunosuppressant regimens
- Hospitalization and post-operative stays can be long
- Restricted to a few specialized centers
- Highly complex trials
- DMC actively involved
- Patient and family impact
- Long-term follow-up of patients



It is also important to choose endpoints for the specific ages of pediatric study participants and not just to re-work protocols and their endpoints from adult trials. In addition, pediatric clinical trials may need to be designed in a more adaptive way, allowing for changes in the course of the study.

A patient and family–centric study design might be more practical and valuable for pediatric studies because the approach can better respect the vulnerability of pediatric patients and their families and make the study less burdensome for the patients and families.

Finally, with the growth of cell and gene therapies, which may often be designed for very young children, at that – the patient and family–centric approach may be not only appropriate, but a necessity, given that these studies are highly complex and are apt to have great impact on the patient and family as they may require hospitalizations and immunosuppressant regimens.

About the author

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