Pediatric Clinical Trials: Is Collaboration Between Sites and Sponsors the Answer?

Dr. William Treem
Dr. Maria Jose Redondo
Dr. Claire Sears

PEDIATRIC CLINICAL RESEARCH IS CHALLENGING – BUT THE CASE IS COMPELLING

The statistics around pediatric clinical research do not make for comforting reading: More than 50% of the drugs prescribed to infants and children have never been studied in adequately powered clinical trials for safety and efficacy in the populations in which they are prescribed. In the US, there is a relatively consistent nine-year gap between approval of medicines for adults and the labelling of those medications for children with the same disease indication.

When it comes to medicines, children cannot be considered "mini adults," and so there is a compelling need for pediatric clinical research that supports expansion of clinical treatments available for childhood diseases. Indeed, many of the conditions in question are specific to children; even where the pathology is similar, adult studies cannot adequately inform use of medicines in children due to differences in physiology, drug metabolism, and dosing requirements – and, at times, even natural history of the disease and response to treatment.

We have made progress in legislation requiring pediatric clinical research to be carried out, and in providing incentives to pharmaceutical companies to do the studies. However, 60% of studies mandated by law through the Pediatric Research Equity Act have not initiated enrolment, and only 17 products have received approval for new pediatric formulations for children and infants under US law since 2007. Similarly, in Europe, 30% of pediatric investigational plans submitted to the EMA have not been completed with adequate justification, and a further third have been delayed, with sponsors requesting more time.

There is no denying that pediatric clinical research is challenging. Disease pathology, pharmacokinetics, and response to treatment often differ with age, patient size and/or maturation, meaning that multiple age groups must be studied, which leads to more complex, and expensive, clinical trials.

Add to this the extremely important ethical, legislative and regulatory factors, as children are a vulnerable population research group that garners special Institutional Review Board (IRB) attention. This can lead to variability in IRB approval times. Early phase studies that would be done in healthy adult volunteers are more commonly carried out as short duration studies in children with the same disease. As these studies are of little clinical benefit, IRBs often have a high threshold for approving such trials.

But the case to conduct clinical research in the pediatric population remains compelling. So how can we improve the way we do these studies? We'll delve into five specific areas: (1) Feasibility, (2) Collaboration, (3) Compensation, (4) Patient-centricity, and (5) Pediatric Networks.

REDEFINE FEASIBILITY

Let's look at how we determine the design of pediatric clinical trials, and ask whether we can broaden our definition of "feasibility" to ensure the protocols will enroll patients in the real world. A really robust feasibility process would consider a number of different factors:

- Prevalence of unique subjects that satisfy study inclusion/

exclusion criteria in the population (using big, real world data)

- Clinical site infrastructure
  - Site organization
  - Adequacy of research personnel
  - Training and experience of site personnel
  - Data collection and IT systems
  - Culture of collaboration (centralized IRB, master contracts, etc.)
  - Participation in networks
- Assessment of trial burden (on patient, family, and site)
- Patient/parent participation in trial design.

Some pharmaceutical companies are starting to use big, real-world data to pressure test their protocols, utilizing multiple databases of de-identified patient-level data that include >20 million children. This methodology uses a web-based standardized analytics application to convert observational data sources into a Common Data Model. Clinicians can query the data according to the specific parameters of the study, their particular patient population, and enter particular inclusion/exclusion criteria to choose patients who would qualify for the study.

Using this interactive platform to look at a real-world population meeting study protocol criteria, clinical teams can explore:

- Disease natural history: patient demographics, comorbidities, concomitant medications, and treatment utilization
- Background rates for events, for assessment of safety or efficacy
- Generalizability of clinical trial subjects to a real-world population.

In the future, through agreements with participating institutions, anonymized data could be transferred back to institutions and actual patients identified to the treating physicians. This would allow the treating physician to determine which patients under their care qualify for the trial.

CREATE A CULTURE OF COLLABORATION

From an investigator's point of view, participating in industry-sponsored pediatric clinical research can often seem unattractive. There is often a lower level of input by investigators on study design; as such, lower academic value is often placed on such studies, both by investigators and their institutions, when compared to investigator-initiated research. Add the concurrent challenges of insufficient training and expertise in conducting pediatric trials for drug approval, inadequate clinical trial infrastructure and site resources, and scarce funding sources, and it is not hard to see why sponsors can find it difficult to recruit sites and investigators for pediatric studies.

However, if we can more clearly identify what sites and sponsors are looking for, collaboration is more likely to flourish.

Trial sponsors seek a culture of cooperation and collaboration in working with sites. In addition, sites with technological readiness offer a significant advantage over those without appropriate technological capabilities. An important way for sponsors to cultivate ongoing site relationships covering trials in multiple therapeutic areas is to collaborate and consult during the early stages on areas like feasibility evaluation, study design, and protocol writing. A site that is invested in a study from the outset is more likely to recruit well.

In turn, sites are also eager for early consultation in program development and feasibility. There is no substitute for the sponsor having a relationship with the principal investigator (PI) at the site or with the clinical research office at the site. Even when a CRO is running the trial, the sponsor must be involved, particularly on a physician-to-physician level. Including PIs in data analysis, and reporting and publication, is very important. PIs can provide a lot of good input. They deserve to be included in that process and help ensure reporting of unbiased results. This level of inclusiveness goes a long way towards developing an engaged relationship.

In pediatric studies, sponsors know each PI will only enroll a few patients, so the idea is to develop a relationship with a site that goes beyond any individual trial and will be sustainable through multiple pediatric trials of drugs for multiple indications at that same site. As such, there is less focus on the specific investigator and more focus on a center-wide partnership encompassing multiple sub-specialty areas, and engaging the site's clinical trial infrastructure.

PAY SITES FOR THEIR WORK

Pediatric studies can carry a higher administrative burden that is often not adequately reimbursed. Pre-study, investigators and sites have start-up fees through activities such as IRB applications, contracting and budget negotiations, investigator meetings and site research personnel training – which are often not reimbursed. During the study, sites spend a lot of non-reimbursed time for invoicing, implementing protocol amendments, and dealing with monitoring visits. Sponsors should offer fair compensation not only for the number of patients enrolled, but also for the time and effort required to get that first patient in.

BECOME TRULY PATIENT-CENTRIC

Several sponsor companies are implementing innovative pilot projects to support the move from the site-centric to the patient-centric operating model. In classic pediatric studies, recruitment, consent, monitoring and assessments, data capture, and quality monitoring, all happen at the site. This is a big burden for parents and patients, as well as for sites and investigators. With the use of technology, some data monitoring visits can be done in the patient's home or in the local doctor's office, relieving some of the burden of travel to the research site.

In pediatric clinical research, the time that patients spend away from school and parents spend away from work can deter participation. Sponsors and sites can collaborate on better estimating patient availability, and invest in schemes to facilitate enrolment and retention (including weekend, summer, and vacation participation).

The role of the patient and parent advocacy groups in pediatric trial planning and execution is vital. Including them as part of the feasibility assessment, and having parents and patients define what for them are meaningful clinical benefits and endpoints, and what they see as affecting their quality of life and their disease, can bring great benefits to study conduct. Especially in the case of rare diseases, or for morbid and even fatal diseases, the patient/parent perspective on benefit-risk analysis can differ from the regulatory agencies' and sponsor's assessment.

Other areas to foster include a broader support of pediatric clinical research and fundraising, and publicizing the unmet medical need for new therapies. Patient/parent advocacy groups are extremely motivated, and, as such, support for the formation of patient registries to collect natural history data can be hugely beneficial.

BUILD NETWORKS TO FACILITATE RESEARCH

We ask industry colleagues, "What if you instantaneously had 100 multi-specialty capable pediatric sites at your fingertips for the vast majority of your pediatric studies?" Most jump at the idea of having direct access to willing, capable, trained sites experienced in multiple trials, therapeutic areas and age groups, and a source for early, rapid, robust expert clinical trial advice. Networks of sites like this can provide enormous efficiency gains through shared procedures and processes, and standardized regulatory grade data collection. Experienced networks can also be a resource for advancing the science of pediatric drug development, and advocating for sound regulatory policy.

Many of the challenges we have discussed thus far can be addressed by developing multispecialty-capable, phase 1-4, neonatal to adolescent, global, pediatric, clinical trials networks.

There is ongoing work in the US through the Critical Path Institute and in the EU through the Innovative Medicines Initiative (IMI), sponsored by the European Union Commission, to build this kind of network. We've already learned quite a lot about what makes networks successful and sustainable from landscape questionnaires carried out by nascent networks.

A sustainable business model for a network is based on efficient delivery of trials, breadth of expertise and participation, and collaboration of multiple sponsors. Initial funding is needed from a public-private partnership with multiple stakeholders (industry, academia, hospitals, patient organizations, SMEs, etc.).

Supplemental resources are necessary to overcome enrollment challenges so the sites can focus on identifying appropriate trial patients. Reducing administrative site burden supports routine, consistent enrollment through uniform processes and procedures across the network. The network must also look after its members, with investigator "ownership" of planning and execution key to success, as are opportunities for academic career development.

Over the last few years, PCORI (the Patient-Centered Outcomes Research Institute) has funded a US network called PEDSnet, a consortium of some of the largest children's medical centers collaborating to efficiently conduct clinical research in routine care settings and to engage families, clinicians, and health system leaders in generating pediatric knowledge. Over the last ten years, the Children's Research Network in the UK, sponsored by the National Health Service, has developed a nationwide pediatric clinical trials network with a large portfolio of both industry and non-industry sponsored trials that it routinely delivers on time, achieving targeted enrolment and completion.

There are also examples of therapeutic area-specific networks that are working together to improve pediatric clinical trials. For example, the T1D Exchange is a clinical network of more than 70 clinics across the US, with access to a registry of more than 26,000 people with T1D, and a Biobank housing a vast collection of bio-samples. It also incorporates an online patient/caregiver community termed "Glu."

TrialNet is a network of Diabetes research centres of sponsors and investigators collaborating to prevent Type 1 diabetes. There are about 20 centers in the network, throughout the US and internationally, conducting clinical trials; an additional 150 centers collaborate with this network.

About the Authors

Dr. William Treem *is Senior Director, Pediatric Drug Development, Janssen Pharmaceutical Research and Development.*

Maria Jose Redondo*, MD, PhD, MPH, is Associate Professor of Pediatrics, Pediatric Diabetes and Endocrinology, Texas Children's Hospital, Baylor College of Medicine.*

Claire Sears, *PhD, is Director of Data Solutions at DrugDev.*

WE CAN DO BETTER

We know that the landscape of pediatric drug development is inefficient. But we also know that we can do better, and collaboration is the key. Collaboration is vital on three different levels:

1. Encourage engagement between sponsors and investigators/sites
2. Involve patients/parents in trial design to improve feasibility and relevance of studies
3. Build and use sustainable pediatric clinical trial networks to harness the expertise, organization, efficiency, and energy to solve the specific challenges of pediatric research.

References available upon request.