Improving Paediatric R&D Success: Integrating the Younger Patient and Caregiver's Perspective into Trial Design

Given the multitude of nuances to consider when conducting a paediatric trial, it is vital that sponsors form a comprehensive strategy early in trial design. Here, we discuss several noteworthy nuances that sponsors should consider when aiming to advance drug development with the needs and perspectives of younger patients and their families in mind

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Disease presentation and related outcomes for children compared to adults can be noticeably different due to developmental and physiological differences. As there are increasing incidences of chronic diseases in younger patients, we are seeing a stronger industry-wide focus on paediatric clinical research and development to improve tailored paediatric care.

According to ClinicalTrials.gov, there are currently more than 4,100 paediatric clinical trials in active or recruiting stages, which indicates that the pharmaceutical industry understands the need to meet the unique requirements of younger patient populations.[1] But now trial sponsors, their clinical research organisation (CROs) partners and study teams must focus on the many components that can play a role in successful paediatric clinical trials, such as treatment formulations and dosages, ethical and legal considerations, juvenile mindsets and the roles of parents and caregivers.

From a bird's-eye view, these considerations may seem straightforward and easy to assume, but according to a *Clinical and Translational Science* journal article, approximately 20% of paediatric trials fail due to suboptimal design and planning, or lack of sufficient enrolment.[2] The spectrum of paediatric trial participants can vary from infants to toddlers and teenagers. Depending on the trial and target patient population, sponsors need to account for and address diverse needs and levels of behavioural independence, while keeping in mind that all aspects of trial design must consider caregiver perspectives too.

Compassionate Protocol Design and At-Home Trial Participation

The COVID-19 pandemic showed the tremendous burdens caregivers faced when working to keep their children involved in critical research while also juggling responsibilities for work and home and their own physical and mental health. As sponsors, CROs and study teams adopted decentralised options to ensure continued trial participation, awareness grew about digital solutions, including telehealth, that helped maintain trials during shutdowns. However, it is still crucial to consider how the human element in decentralised approaches plays an integral role in successful patient engagement and trial outcomes. Deploying high-quality, credentialed health professionals, including nurses and phlebotomists, to care for patients in the comfort of their homes offers children and their families the flexibility and support they need to participate in research, and is an example of why compassionate trial design can be critical.

Children with autism, for example, may have a hard time staying engaged in clinical trials. Trial participation can mean a new provider, site team and

location to get acquainted with, on top of their ongoing care specialists and related activities. It can also mean the potential for additional blood draws and other necessary trial procedures. Having the familiar aspects of home, including their toys, preferred television programmes and/or pets, can ease fears or hesitations during necessary trial visits and procedures. Additionally, ensuring mobile health professionals are experienced in comforting paediatric patients and addressing unique needs while collecting blood samples or taking basic vital signs can be key to how well a child with autism stays engaged with the process. When possible, consistency in the staff who come to the home will help the child and loved ones develop relationships and create a more relaxing environment.

As we experienced during the pandemic, it is vital to protect children with cancer or other conditions that cause them to be neutropenic from the risk of infection. At-home trial participation can reduce exposure to infection due to site visits or travel to and from site visits.

For caregivers, juggling their child's healthcare with work responsibilities, other family obligations, packed daily schedules and more can be challenging and emotionally burdensome, and sponsors are working to integrate their perspectives into paediatric trial design. For example, parents interested in enrolling their child for a trial that provides access to a needed treatment may hesitate due to necessary site visits and related logistical burdens. Coordinating travel to and from visits and taking their child out of school, especially if the child is immobile or very sick, can be difficult both physically and emotionally for the child and caregiver. What happens in cases of rare disease paediatric trials where participating principal investigators and site teams are limited in number, and site visits require caregivers and patients to travel beyond their local sites, potentially across the country? Required travel, time away from work and home and burdens on their children can limit enrolment despite the child and/or parent's desire to participate. For paediatric patients and their loved ones, as well as site teams having a tough time with trial enrolment, mobile research services can help ensure important research continues for those in need.

Though there are benefits to the human touch in decentralised solutions, sponsors and CROs have a lot to consider when integrating these services into paediatric trial programmes. Having experienced project management teams who proactively plan the intricate administrative oversight and training of remote clinicians and related activities, while prioritising patient safety and trial quality, is necessary for success when in the field.

Safety Testing via Blood Collection

Whether studies are paediatric- or adult-focused, the number one priority for sponsors, CROs and study teams is to ensure the studied treatment does not harm trial participants. From a clinical laboratory perspective, safety testing typically involves securing the participant's complete blood count and a biochemistry panel, which may include more than 20 varying serum chemistry markers that detect the drug toxicity impact on vital organs. Though large labs may run more than 1,000 panels daily via automated solutions, small-volume samples from paediatric participants require special handling and sampling techniques.

Insufficient Blood Volume

At trial design, it is critical to account for, and integrate, solutions to address the potential for panel testing cancellations that occur in paediatric trials due to small volume samples. It happens more often with younger patients due to smaller, delicate veins to draw from and fear or nervousness about the collection process.

If low volume samples logged and inputted into an automated analyser have insufficient amounts to run the needed panels, the outcome can be a 'quantity not sufficient' measure or test cancellation. For children who may already fear, or get upset when, having blood drawn, cancelled testing can add emotional and physical burdens for them, their parents and site teams who must work through another collection.

As an example, younger patients (eg, six years old or younger) with spinal muscular atrophy may be suffering from cancer or a rare genetic disorder, which

Patient Age Group	Chemistry Panel (20 analytes) WHOLE BLOOD	Chemistry Panel (20 analytes) SERUM	Hematology (CBC)	TOTAL Whole Blood Volume
<2 years old	1.1 mL	0.4 mL	0.6 mL	1.7 mL
2 to 6 years old	2.6 mL	1.0 mL	1.2 mL	3.8 mL
>6 years old	3.5 mL	1.4 mL	2.0 mL	5.5 mL

Figure 1: Recommended blood volume by age

can be debilitating and stressful for them and their caregivers. Study teams need to consider how to make blood collection as painless as possible for these patients while also minimising how much is necessary to draw and test. When the patient's needs are well known and not likely to change, sponsors and lab services can adjust on their ends, providing an alternative approach to panel testing tailored to the needs of younger patients. Along with the option to effectively test a larger chemistry panel when receiving insufficient sample volume, lab experts can customise 'short sample' panels to prioritise analytes most needed for medical monitors, such as those for kidney or liver damage. For example, for children two years old and younger, it is possible to accurately analyse a chemistry panel of 20 analytes with only 0.4ml of serum using these microsampling capabilities **(Figure 1)**.

In leveraging these alternative short-sample panels for paediatric participants, it is key for sponsors and their lab partners to ensure:

- Decisions to run these types of panels are made by licensed medical technologists
- Lab experts have appropriate training on how to identify and handle such paediatric samples upon receipt.

Unlike adult participants, younger patient populations, especially those seven and younger, have smaller and more delicate veins, and as such, sponsors need to ensure phlebotomists drawing samples use a smaller gauge needle (a 23-gauge butterfly needle instead of a 21-gauge needle used in adults). These smaller devices are designed to combine the control provided by a syringe with clot activators and/or anti-coagulants that are commonly available in evacuated blood tubes, allowing for a gentler collection process. Furthermore, in studies involving intravenous medications and repeated blood draws, consideration of indwelling catheters, such as peripherally inserted central catheters (PICCs) and central lines into the child's arm, neck or leg, can greatly decrease the burden on them and their families and improve the quality of blood sampling.

Multi-stakeholder Collaboration to Advance Paediatric Cancer Care

The US Food and Drug Administration's RACE for Children Act is changing the treatment paradigm for children with cancer.[3] Since August 2020, this regulation has required all new investigational adult oncology therapies being reviewed by the FDA for use to also be evaluated for safety and efficacy in paediatric cancers if the treatment is relevant at a molecular target. Most oncology treatments for adults approved in 2019 and 2020 would have been impacted by the RACE Act **(Figure 2)**. This opens doors to precision oncology for children, but a 2021 IQVIA Institute analysis found that despite more than 70% of all ongoing oncology trials involving RACE-defined molecular target drugs, only 6.9% include paediatric participants.[4] Some of this disparity arises from concerns around testing new molecules in children, while others

2019 APPROVALS

FDA CLASSIFICATION	MOLECULAR TARGET	MOLECULE
Gene abnormality	PI3Kα	Erdafitinib
	NTRK fusion	Fedratinib
	FGFR	Pexidartinib
	JAK	Zanubrutinib
	KIT; CSF1R; FLT3	Trastuzumab deruxtecan
Cell lineage	BTK	Enfortumab vedotin
Cell lineage; Other	HER2; Topoisomerase	Polatuzumab vedotin
Other	Tubulin	Selinexor
	Tubulin	Darolutamide
	XPO1	Selinexor
Automatic waiver	AR	Darolutamide

2020 APPROVALS

FDA CLASSIFICATION	MOLECULAR TARGET	MOLECULE
Gene abnormality	KIT; PDGFR fusion	Avapritinib
	KIT; PDGFR	Ripretinib
	MET fusions	Capmatinib
	RET fusions	Pralsetinib
	RET fusions	Selpercatinib
	FGFR	Pemigatinib
	NOTCH	Tazemostat
Cell lineage	CD19	Brexucabtagene autoleucel
	CD19	Tafasitamab
	CD38	Isatuximab
	GD2	Naxitamab
	HER2	Margetuximab
	HER2	Tucatinib
Other	DNMT	Cedazuridine/ decitabine
	DNA Alkylator	Lurbinectedin
	Topoisomerase	Sacituzumab govitecan
	MEK	Selumetinib
	Tubulin	Belantamab mafodotin
Automatic waiver	GnRH	Relugolix

Source: IQVIA Institute, Dec 2020; FDA, Drug Approval Databases, accessed Dec 2020, https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases; FDA, Relevant Molecular Targets for Cancer Drug Development for Children, accessed Dec 2020, https://www.fda.gov/media/128614/download

Figure 2: Recently approved therapies with molecular targets

struggle with the challenges of enrolling younger patients with these rare tumours. There are several key challenges for pharmaceutical and biotech companies to better fulfil the requirements of the RACE for Children Act and drive potential of their own paediatric oncology trial programmes:

- Paediatric cancers are rare diseases with very small patient populations, requiring a good understanding of the tumour biology for childhood cancers
- As previously noted, children and adolescents have specific vulnerabilities and developmental issues that require added safeguards compared to those typically provided for adult patients
- As seen in paediatric trials overall, paediatric cancer trials may experience study delays or incompletion – this is often due to poor design and failure to get adequate enrolment
- Understanding which molecular targets are subject to paediatric trials as per the FDA's list and prioritising those with the most potential to benefit paediatric oncology patients
- Identifying which molecular targets the FDA may waive requirements for in paediatric studies due to limited applicability in paediatric tumours.

From the FDA to patients, caregivers, advocacy groups and drug developers, all stakeholders play an important role in achieving the goals of the Act, especially through early engagement (pre-phase 1 studies) with one another and by leveraging each's area of expertise to ultimately improve available treatments for children with cancer. In aiming to shift expectations for paediatric oncology drug development, there is a need to strengthen stakeholder collaboration, for which the industry is already seeing tangible progress.
For paediatric cancer trial sponsors, smarter and more efficient trial design approaches that better coordinate trials worldwide can help reach more patients. Through large-scale sequencing efforts among newly diagnosed patients and those with relapsed or refractory cancer, sponsors can break down silos to better identify specific biomarkers that drive target patient selection in trials.

There is also interest among sponsors to work alongside academia and cooperative cancer research groups to establish master protocols and platform-type studies. To avoid duplication of effort when working on individual programmes, there is also a bigger push to share and harmonise paediatric oncology clinical trial data and combine insights, especially since patient populations are extremely small. This will require appropriate and secure data aggregation and sharing platforms and systems to share critical genomic, clinical outcome, toxicity data and more.

Enhancing Paediatric Trial Design

It is obvious that sponsors, CROs and study teams need to ensure that safeguards are in place to protect children participating in critical research that impacts their health. There will be deviations from protocols during these trials, especially as children age and change, and additional patient-specific nuances are uncovered. This is where experience in paediatric-focused trials counts. Carrying through successes and key learnings from previous trials, while also understanding the unique vulnerabilities of the patient population at hand to ensure trial design incorporates patients' perspectives and related needs, can be tremendously beneficial. A strategic, proactive approach integrating younger patient and caregiver perspectives into paediatric trials can improve health outcomes for children living with various conditions.

References

1. *Visit: clinicaltrials.gov/search?term=pediatric&aggFilters=status:rec%20act*
2. *Visit: www.ncbi.nlm.nih.gov/pmc/articles/PMC6510379/*
3. *Visit: www.fda.gov/media/122696/download*
4. *Visit: www.iqvia.com/insights/the-iqvia-institute/reports/advancing-pediatric-cancer-research*

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