Optimising Trial Design Across the Ages

The nuances of conducting clinical trials for paediatric and adult patients are important to consider, especially with the growing challenges in recruitment and regulatory/ethical compliance

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Global regulatory authorities continue to have an increasing interest in allowing both paediatric and adult patients in clinical trials. Additionally, rapidly expanding numbers of clinical development programmes in rare diseases have led to key challenges in recruitment. Global outreach is often necessary to achieve targeted enrolment across a patient population of varying ages. Therefore, it is important to discuss the regulatory, start-up, operational, and medical challenges and considerations of clinical trials that include both paediatric and adult patients.

Regulatory

There are numerous regulatory considerations for trials involving paediatric patients. Global drug development strategies need to incorporate an understanding of logistical, scientific, and regulatory components for inclusion of paediatric patients. Regulators such as the FDA and EMA both require paediatric plans to ensure appropriate development of drugs and biologics in the paediatric population. However, in some scenarios, particularly involving rare or orphan diseases that target younger populations, discussions regarding the inclusion of paediatric patients may occur outside of standard procedures or earlier in the clinical development programme. Therefore, if a trial intends to include paediatric patients, clinical development must be proactively aligned with and support future labelling prior to implementation of the trial.

Regulators are typically open to discussions regarding the inclusion of paediatric patients in adult trials if there is a possibility for direct benefit. When considering the inclusion of paediatric patients, regulators will expect that additional safeguards as required by regulation are in place. This includes the possibility for direct benefit to the patient, or to provide a greater understanding of the disease. This higher standard is to ensure that children are not placed at unnecessary risk and have the potential to benefit from the investigational therapy.

In preparation for discussions with regulators, it is critical to consider not just the clinical trial design, but to also review chemistry, manufacturing, controls, and nonclinical components of the programme. For example, if very young patients are to be enrolled, a paediatric formulation of the product may need to be developed as these patients may not be able to swallow certain oral products. Furthermore, existing nonclinical and clinical data in conjunction with the known mechanism of action of the product should be reviewed to determine if nonclinical juvenile toxicity studies to support dosing in younger patients are necessary prior to enrolling paediatric patients in clinical trials.

In the US, if the product can be demonstrated to be targeted for the prevention or treatment of a rare paediatric disease that is serious or life-threatening and manifests in youth, a rare paediatric voucher that grants priority review of a subsequent marketing authorisation application may be granted (1). Review and receipt of the rare paediatric voucher will occur during review of the marketing application, but a request for rare paediatric designation can occur at the same time as the request for orphan drug designation and/or fast-track designation.

Start-Up

Clear and upfront communication regarding enrolment with investigative sites is one of many factors that play a part in ensuring a successful study start-up/activation process for clinical trials involving paediatric patients. While

a successful or timely study start-up is key to all clinical trials, this is especially true in paediatric trials and, in many instances, may be considered 'make it or break it' with this patient population. In addition to focusing on the regulatory and ethical requirements, focusing on the site and investigator's engagement is imperative. Targeted start-up discussions early on can provide key insight into site-specific requirements, levels of interest, and potential roadblocks that would perhaps not be identified until a more critical time point.

Apart from competing priorities at the site, one of the biggest impediments during study start-up is the number and type of queries received from institutional review boards/ethical committees (IRB/EC). Additionally, it is becoming increasingly common to see a higher number of queries with paediatric and/or rare disease trials, as well as a higher number of sub-committee reviews at the site. There can even be a need to have two centres in one area to cover the age range of paediatrics at one centre and adults at another. In many situations, the standard IRB/EC approval is no longer the only committee approval needed by the site. During the IRB/EC process, a clinical trial may also necessitate review and approval from a site's radiation/biosafety committee, data security committee (i.e., for clinical trials involving electronic diaries/questionnaires), paediatric research committee, and gene therapy committee, among others. Therefore, proactive collaboration across study team functions to develop supplemental documents and/or cover letter language (i.e., justification for use of placebo) that can be incorporated into initial submissions can be instrumental during the IRB/EC process. This proactiveness on the part of the study team by demonstrating an 'above-and-beyond' approach and easing site burden in having to provide this type of information internally can also increase the motivation of the sites and investigators.

Operational

Consenting presents a unique challenge to trials that have multiple age groups participating. Working with sites and closely collaborating with regulatory groups to establish appropriate assent and consent documents is the first step. Beyond the complexity of differing age of majority guidance by country, implementing the correct administration of the consent/assent process is the next challenge. It is imperative to ensure that the patient (and the patient's parent/guardian(s), when applicable) is properly provided with all available information prior to agreeing to participate. With paediatric trials, or trials involving cognitively impaired patients, this is not straightforward. Successful tactics have included age-appropriate assent and consent tools to support the consenting process, such as illustrations or videos to understand the study requirements and implications. Additionally, reminders to the sites/investigators to address consenting/assenting requirements as the patients become older within the trial is critical to ensure compliance from both a regulatory and ethical perspective.

In rare diseases, it is common for sites to frontload their recruitment with pre-identified patients, whether the trial is expected to be difficult to enrol or if managing a long waitlist will be challenging. In all clinical trials involving cohorts and/or competitive enrolment, cohort management and the site's understanding of the trial's enrolment management plan is a key part of carrying out an efficacious study. This is especially the case when dealing with predefined enrolment numbers by age, or protocol-specified processes for opening certain cohorts sequentially. It is imperative that these types of plans are discussed upfront with sites/investigators to not only ensure that sites prioritise/expedite their start-up process, but also to avoid having negative statistical impacts on the trial by having only one site contributing most of the patients for the entire trial. Great communication is instrumental to avoid any frustrations and damage to site relationships.

While every trial design should take into account the patient population and avoid being overly burdensome, this is especially true for trials involving children or patients who require a caregiver. Parents or guardians will need to take time off work and potentially travel great distances in order to support the patient's participation. Parents and guardians of individuals with certain diseases, especially rare diseases, can often experience frustration due to the lack of any specific treatments for their disorder and, as a result, recruitment into a trial is rarely problematic. Nonetheless, even in the setting of noticeable clinical benefit, patients and their families may experience fluctuations in attention to trial requirements, such as due to fatigue with travel for trial-related visits, making patient retention a high priority.

One way to facilitate patient retention is careful consideration of the trial design to ensure it is appropriate for the ages of patients participating. Protocol endpoints may not be appropriate for patients of all age groups. Within the protocol design, it is common to identify endpoints that will apply to certain ages in addition to endpoints that can be applied to all ages. For example, while an adult may be able to remain still for a long MRI scan without sedation, this is unlikely and should not be expected to occur for a toddler.

Questionnaires and patient-reported outcomes need to be age appropriate, and parent/guardian participation may be required to complete assessments for the younger age groups. Another important consideration is whether patients are to complete the same questionnaire/patient-reported outcome they started at the beginning of the trial regardless of their current age, or if they should switch from paediatric to adult versions as they age within the trial. Similar to the consenting/assenting process, this should be discussed regularly with sites and investigators to ensure both consistency and accuracy across the trial.

Medical

Drug formulation will also need to be appropriate for all ages of participating patients. The disease state or age of a

patient may make some modalities of investigational product administration challenging or impossible. Partnering with child life specialists to help with learning how to swallow oral capsules has been a useful strategy to improve compliance and expand the eligibility of participants.

One of the mantras of medical care is that children are not small adults. Similarly, in the conduct of clinical trials, it is important to avoid ascribing adult parameters to paediatric patients enrolled that may be inappropriate. Triggers for alerts of electrocardiogram findings (such as QTc) and certain laboratory values, for example, should be based on age-specific ranges. This avoids receipt by the site of inaccurate results or queries, and subsequent interventions that may not be necessary or even harmful. Furthermore, patients will not be erroneously screen-failed. It may also be helpful to sites and investigators, as well as the CRO staff, to evaluate possible disease-specific lab values that do not require an alert. For example, patients with a muscular dystrophy will almost always have an 'abnormal' level of certain measures of muscle enzymes, which are not clinically significant and typically do not necessitate an intervention regardless of patient age.

Phlebotomy can be difficult with any patient, but may be particularly complicated in children given their small veins, as well as their potential for becoming distressed and upset, or adult patients with cognitive impairment. Therefore, it is critical for sites to have detailed instructions on the collection and handling of these samples. Sites should be made aware of which labs to prioritise in the event it is not possible to obtain adequate volumes of blood. Additionally, there are specific guidelines, which may be site- or country-specific, concerning the maximum allowable volume based on percentage of body weight that can be collected in a single blood draw or over a specified period of time (e.g., over a 30-day period). Adherence to these blood volume considerations can be aided by providing sites with tables or charts with specifications and limits by age and size.

Paediatric patients and adults with cognitive impairment are vulnerable populations, and attention must be given to ensure the overall safety of any trial participant, but particularly those deemed vulnerable. As mentioned, many of these patients may suffer from rare diseases, and new potential therapies generate substantial excitement. Nonetheless, especially in early phase, first-in-human, and/or dose-finding studies, safety is frequently the primary endpoint. Despite the costs, time, and logistics, the creation of a data safety monitoring board in some form is a valuable component of a clinical trial, and, in some cases, even mandated by certain regulatory authorities. Depending on the particular therapeutic indication, it may be useful to have a range of experts participate in safety monitoring in order to ensure appropriate knowledge about age variability in disease.

Designing, conducting, and completing clinical trials with both paediatric and adult patients is filled with many nuances. Careful planning across multiple functional areas, including regulatory, start-up, operations, and medical monitoring, can prevent certain pitfalls and assist with proactively managing those inevitable obstacles. Despite the complexities, these trials offer incredible potential for benefit for all involved, not least of which are the patients themselves.

References

1. *Visit: www.fda.gov/drugs/development-resources/rare-pediatric-disease-priority-review-voucher-program-section-529*

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