Key considerations when conducting rare disease paediatric trials

Introduction

Medicines for children

The development of medicines for children has changed beyond all recognition over the last century. If you go back to the early 1900's, children were simply not considered – a classic example being James Soothing Syrup that was approved and sold for infant diarrhoea. The active ingredient? Heroin[1]. As the years progressed, the decades have become littered with examples of children and adults being impacted by well-meaning carers who had little means to know better. This was until a shocking number of children died after taking a syrup where the active ingredient was mixed with a constituent which attacked childrens' kidneys. The outrage that followed brought about the first regulations for medicines and the need for a demonstrated safety level deemed okay.

Unfortunately, this was not the end of such tragedies. We instinctively protect and nurture our young – the idea of studying drugs in paediatrics was so far beyond people's culture that it simply was not required. Doctors on the front-line were left to adapt adult medicines for children in practice based upon experience and guesswork - with no data to support the metabolic impact of that drug in children. The well-publicised Thalidomide disaster as well as the chloramphenicol 'grey-baby' tragedy (where the antibiotic was insufficiently eliminated thus causing a build- up of toxins), resulted in further improvements in regulations, ethical guidelines, and standards for studies[2].

Regardless of these step changes, there were several practical – and seemingly insurmountable challenges associated with conducting clinical studies in children. Faced with strict regulations, along with immense practical difficulty, paediatric trials were simply deemed too hard and, in many cases, avoided. Labels on bottles and in medicine boxes stated that the drug should not be used in children and doctors on the front-line were left in a difficult position.

This continued well into the early 2000's when, after decades of campaigning by health care professionals, the regulations changed again. All manufacturers of new drugs needed to also conduct studies to assess their suitability for children unless there was a legitimate reason why this should not occur[3,4].

The age of routine paediatric trials was born.

Paediatric trials in rare disease

Although the need for paediatric studies was fully accepted, many companies struggled to cope with these new requirements. The impact cost to the pharmaceutical industry of paediatric regulations was estimated to be €2,106 million per year and, although smaller than before, there remains today a substantial difference between the proportion of children burdened with a condition and the corresponding child-adult proportion of studies aiming to address it[7, 8]. When coupled with the fact that roughly 25 to 30% of paediatric trials fail for various practical reasons, the topic of delivering optimised paediatric trials remains highly relevant today[5,6].

Within this debate, understanding and integrating the multitude of varied regulations and ethical considerations into the design of the study continues to be essential. However, the experience and protection of children within trials, as well as the quality of data gathered to facilitate approval is dependent upon the operational delivery of the study itself. This responsibility rests largely on the shoulders of the study delivery team in the research organisation who are running the trial. This is the case for all studies but is complicated still further within the speciality of rare disease, where difficulties such as geography, sparse knowledge of the condition, and emerging treatments such as gene therapy all converge.

Within this report we would like to share with you some of the learning, considerations, and insights that we have gained through many years of experience delivering paediatric trials in rare disease with the hope that this sparks healthy debate and further roll-out of optimised trials.

Delivery of rare disease paediatric trials

Overview of key considerations

The rights of, and respect for, every individual child is paramount within paediatric research – whether they are volunteering to take part, or whether they are someone who may take the medicine in the future. This is why, as shown in Figure 1, ethical considerations need to run through every single activity and decision that is taken[9]. This ethical and scientific integrity is reinforced by strict regulations that trial designers must integrate to ensure that sufficient standards are upheld throughout[10]. This informs and supports the front edge of the study – the operational and considerate delivery of the trial for each child.

Figure 1: Overview of key considerations for paediatric research in rare disease.

The Protocol

Many sponsors will first conduct a trial in an adult population to learn and then try to adapt the protocol for children. Although this may initially appear to be the most efficient route, it often turns out to be false economy; unforeseen patient, clinical and especially legal requirements add time and resource-burden as many protocol amendments are then needed[11].

The more efficient approach is for the clinical team to work with experienced study operations specialists merging the key scientific requirements and learning from the adult trial with the delivery methodologies that are known to be acceptable and regulatory-compliant for paediatrics. This ensures the trial meets its key objectives whilst being designed around the needs of the children involved whilst anticipating the predicted effects of the drug on their bodies.

Recruitment and Retention

Recent research has highlighted that nearly 30% of paediatric clinical trials are discontinued due to low rates of recruitment6. In each of these studies, although children took part, there were insufficient people wanting to take on the burdens of the study for researchers to accumulate sufficient data and no conclusions were reached. Children and their guardians volunteered their time and were rewarded with no advance in treatments for future generations in their position. Although this can happen, teams should learn from all relevant stakeholders to plan a trial that is deliverable, suitable, and achievable for all involved. There are many reasons why trials fail, and why this is even more tricky to navigate for rare diseases. A couple of the major ones are outlined below

Cost

Designing and delivering a paediatric trial is expensive and involves many child-specific differences from the adult-norm. New formulations may need to be developed, monitoring approaches may differ, and study-requirements must often be modified and delivered within the child's family support bubble. Such adaptations often lead to a higher cost-per procedure than adult trials, and traditional adult costing models set as initial budgets do not work optimally in the paediatric arena[12]. In addition, many companies and clinical sites have under-developed infrastructures to deal with these realities of paediatric studies, which again adds operational complexity and increased cost. It's therefore important to select a partner who already has good relationships with specialist paediatric sites since it may address many of these considerations quickly if the right experience is available at the outset.

Geography

It is widely understood that rare disease trials need to cover a greater geographical scope so that sufficient participants with the condition can be recruited. However, an often-forgotten consequence of this is the influence of socio-cultural features of the geographic areas involved[13, 14]. Different cultures have different opinions about clinical study design and feasibility[15]. Good communication with patients and their families by the study operations team during set-up, and continued by health care professionals during study delivery is needed to ensure that potential volunteers are informed and prepared for what is going to happen. This reaps reward in the person's ongoing participation in the trial and, if engagement is delivered well, patient organisation and expert partners may actively be able to promote the recruitment approach[16].

An example of this is our own concierge service that breaks down the geographical barriers to study entry for children and their families. When used in a study it opened the option of a UK based trial up to families from across the globe. Translations of documents were rapidly approved by the same ethics committee reviewing the trial, the accessibility of the study was increased for the community, and the potential recruitment population was increased for trial sponsors.

Informed Consent Processes

Many trial naive patients and families may be unfamiliar with the formal process of 'Informed consent'. For this process, the individual needs all the information to be shared with them, along with any support they need to understand it well, so that a documented decision about whether to take part in the trial can be made. This informed decision should happen at the start and continue throughout their ongoing participation. As such, participants should continue to have relevant and updated information explained as researchers learn so that they can continue making optimal decisions about their participation.

For children, it is their parents or guardians who make the decision to join a trial on their behalf. This means that, not only does the study team need to produce information for guardians, but they also should produce information that is interesting and clear for children to enable them to engage in the process. The choice of format (e.g., booklet, short movie, game) and the content should be age appropriate as well as considerate of the conditions the children live with. There are many additional regulations and legislation that must be complied with in this area and, unless working with experts who deliver relevant paediatric studies, it is unlikely that sponsors will be able to seamlessly integrate these into the study development process[17,18].

Many children with rare conditions have had to live with burdens that have large and long-term consequences for their daily lives. In some respects, they can be mature beyond their years, in others, the condition itself may have caused them to lose skills they had as a much younger child. The concept of assent should always be considered, and an active decision taken as to whether it's relevant for each population and trial. Assent is the act of formally discussing the trial with the child and asking for their agreement to take part so that it is not just the adult making the decision on their behalf. Although the adult still completes the formal consent process, the child is actively engaged and there is a documented trail of them having their opinions respected[19,20,21].

Monitoring Safety

The safety monitoring required for a study is shaped by a complex blend of the burdens of the rare condition (plus any risks this brings), age of the participants, potential side-effects of the drug, regulatory compliance, and standard study parameters. It is tempting therefore to ensure that as many samples as possible are taken in hospital so that healthcare workers have the best chance of protecting children. However, this can add burden to the patient and their family with an increased risk of drop out and discontinuation or at best, low adherence to the trial. Both outcomes are a challenge for the trial and do not deliver the level protection for our young that people were aiming for. Paediatric trial delivery must therefore be optimised for families, study operations experts and healthcare professions so that a balance can be reached that maximises learning and patient protection alongside the daily practical impact of the study itself on volunteers.

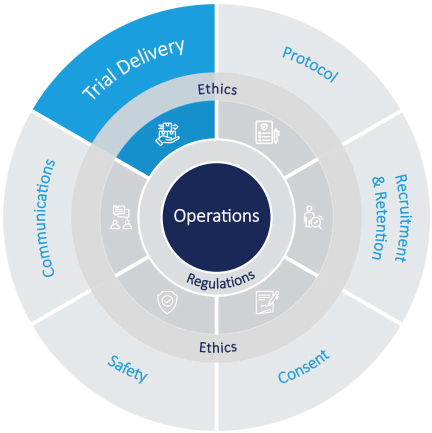
Predicting what's likely to happen and early detection of side-effects is particularly complicated in children with rare conditions. Simply because these conditions are rarely seen, there is normally less research available that characterise the natural course of the disease itself. In addition, children can sometimes show effects that are unexpected and not observed in adults. The team of families, healthcare professionals, and scientists need to be able to tease these elements apart and try to decide what the drug is causing so that we can protect the child involved. Wrong decisions can lead to side-effects being missed, or – as often happens – the symptoms being over-interpretated and patients being prematurely withdrawn. This results in poor patient retention and the risk that an effective, new treatment is made available simply because the trial could not gather the information needed. This is a fine line and having an operations team who can deliver accurate data at the right time, as well as support good communication amongst the study community can make a difference.

Trial Communications

As outlined above, good communication within a trial is essential for building a community of people who can come together to optimise the study design, delivery, recruitment, retention and ultimate patient experience. Clinical operations teams provide the essential infrastructure and communication routes to support this timely and clear information sharing. Examples of this have been included in the table below.

Group	Example Communication Activities
Patient Organisations, Networks and Experts	Gathering input into study delivery methods, approaches and support for trial recruitment, and sharing of trial progress and results amongst the relevant patient community.
Participants and their Families (before, during, and after the trial)	Children need to know what is going on and this information must be delivered in an age- and situation-appropriate way by the most relevant person for that child. Usually, the child's family provide 24/7 care. Families can often be wary of the risks associated with their child taking part in a trial and accurate 'lay person' communication tools provided to them for the clinical teams to use is essential when trying to dispel unfounded fears. If not done well, this is a very frequent cause of poor study recruitment and retention (information source: learning gained by from patient organisations) . The study team must ensure that mechanisms are put in place for the relevant support and information to be provided to the family and that they themselves have open communication routes for sharing data and getting help[22].
Clinicians and Study Sites (e.g., hospitals)	Study sites need accurate and up-to-date information. They need to be able to inform and support the patients and families in their care, as well as take part in the decision-making process about the drug.
Study Sponsors	Study sponsors need to see accurate and timely information from all sites so that they have an overview of what's happening in the trial, can spot early signs of problems and discuss these openly with the rest of the study and clinical team so that rapid and appropriate action can be taken.

Trial Delivery



Children are vulnerable and trials must be delivered using a child-first approach. Every action must be ethically considered and the potential for discomfort and/or distress considered during trial-design. For example, the length of assessments and interviews, the number of visits to hospital the family must make, the duration of the study and the frequency of drug intake.

Even simple procedures such as bloodletting are not that straight forward. Children can sometimes find blood sampling painful; the overall volume of the sample is smaller than for adults, and the hospital environment with unfamiliar health care staff such as phlebotomists can be highly stressful. In this example, alternative approaches such as engaging the parents to take a blood microsample in the child's home environment should be considered if possible[23,24]. Although these may seem to be infrequent, such practices are making it into hospital standard of care routines and have met with resounding positive feedback[25].

In addition to child centered delivery design, signs of impact on the child such as anxiety, discomfort and pain must always be measured throughout the study and compared with validated age-appropriate scales. This is to ensure that undue distress is prevented, and experienced study delivery teams should be able to recommend successful methods to achieve this for relevant paediatric populations.

Summary

The history of paediatric medicines is both long and traumatic, as people navigated the tension between protecting the young and needing to study medicines in order to treat their illnesses and develop therapies. Modern day ethics and regulations are starting to right the wrongs of the past and list the requirements for high-quality paediatric trials. However, especially in rare disease, many challenges remain when creating well designed, budgeted, child- cantered trials that maximise learning whilst optimally protect those involved.

Through our many years' experience of delivering such studies for the rare disease community we have come to realise the benefits of partnership between study sponsors and specialist study delivery teams within a clinical research organisation. Their joint expertise, as well as networks and infrastructure, ensure that they can reach out into communities with a willingness to engage and co-create. This leads to the building of good relationships between researchers and the communities they serve, as well as the routine successful delivery of paediatric clinical trials that give the hope of treatments for patients in the future.

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