Conducting clinical trials in rare neurological disorders

Introduction

Delivering trials alongside people who live with, and work on, rare diseases is a rewarding experience where everyone is driven by the common need to make a difference. We have written previously about the extra expertise and thought that underpins many aspects of trials into treatments for rare conditions, including trial design and delivery considerations, the involvement of children, and the novel statistical approaches needed. Impact of the conditions themselves, however, on trial design and delivery considerations can also be significant.

It is widely known that approximately 300 million people around the world are living with rare conditions[1]. Approximately one third of rare conditions are acknowledged to include neurological components and symptoms due to the condition affecting the number and/or function of nerves[2]. So, even if they are not categorized as a neurological rare condition, patients' may still cause a wide range of nervous-system derived experiences, including (but not limited to) pain, headaches, seizure-risk, mobility issues, and/or reduced mental capacity.

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Whitepaper

Rare disease experts with experience in clinical trial design and delivery use their knowledge to build with these conditions in mind. Every child's experience of their condition is likely to be different, and the breadth of symptoms that rare disease trial participants may experience needs to be acknowledged from the start.

In this white paper we will be exploring some of the modifications and approaches needed to ensure that trial participants who experience neuronal effects of their condition have positive experiences in research.

Trial Practicalities

1. Consent vs assent

The topic of consent and assent in pediatric trials has been discussed previously[3]. However, this information-sharing and agreement process needs to be considered even more carefully when a neurological aspect to a condition is involved. Figure 1 represents the situation for most rare disease pediatric trials.

Figure 1. *Roles for consent and assent in standard pediatric trials*

For all trials, children (as defined by their local legal systems) are not able to sign a consent form to take part in a trial and their parents or legal guardians take on this responsibility. At all times participants and their representatives should be fully informed of what is expected in the trial. Topics including the benefits and risks of taking part, and their rights (e.g. the right to withdraw at any time), should be presented and thoroughly discussed, with all questions answered.

This information-sharing begins before a family decide whether to join a trial, and continues throughout their entire trial participation, with information updated as more is understood by researchers.

Trials involving participants who may have additional learning needs, or reduced capacity to express themselves, need to be designed to ensure that extra attention is routinely made throughout this process to spot signs of undue distress or confusion in patients[4].

As a minimum, this means that the roles for each member in the discussion should be clarified. This is the responsibility of the investigator and, in most situations, occurs subliminally and naturally. However, in some circumstances, such as the involvement of complex family dynamics, or in a culture of strong medical hierarchy in the doctor-patient relationship, extra clarity may help. The protocol can be used to encourage investigators to recognize these situations and provide either provide this clarity themselves, or involve a third party who is trained to support people with these additional needs.

1.1 Legal representative

As described above, a legal representative often has to sign the information consent form on behalf of the pediatric patient. Who this actually is in practice, is driven by legal requirements and is therefore dictated by the geographical location of the treatment center. For example, in some regions only one parent needs to sign, in others it's both.

For rare diseases where the trial drug is potentially the only lifesaving option, the decision whether to start or continue a trial can take on additional significance for the families involved. When unique family dynamics come under this pressure there is the potential for emotionally charged discussions to occur.

For example, if grandparents have legal custody of the patient, but parents are also attending clinic visits and their opinions differ.

> **Shared Learning**
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> Emmes have multiple examples of resolving legal representation issues. In most cases this has arisen when someone other than the child's parents are legally approved (by court order) to represent the individual. In all situations, documenting guardianship at the start of the trial, with evidence stored in the medical records, has provided a solid foundation for discussion and support for the investigator and research nurses involved.

1.2 Consent/assent over time

Some rare disease trials last for many months, if not years. During this time the child grows both physically and mentally. It may be appropriate to begin written assent processes part way through a study, or swap from the patient giving assent to consent. In many situations it is the trial investigator who has the responsibility of deciding whether the patient has sufficient mental capacity to understand the true impact of their choices and consent on their own behalf.

However, the parents/legal representatives know the patient better and witness the patient in their home environment where they may be able to communicate their thought processes more comfortably and effectively than in the clinic environment or on a virtual call.

It is again the investigator who needs to take all of this into consideration and make the final decision as to who is legally appropriate for consent and how assent should be documented. However, a well-written protocol can provide the investigator and families with support by communicating a clear framework for checking when such changes may need to occur (e.g. age categories, or linking with specific study eligibility criteria assessments/study results).

1.3 Who makes the decision?

Normally it is completely clear who is making each decision in the consent/assent process. However, when the patient is incapacitated, a legal representative and investigator can effectively override the patient's own assent choice. In the words of the International Conference on Harmonization, Good Clinical Practice Guideline:

> *"Although a participant's wish to withdraw from a study must be respected, there may be circumstances in therapeutic studies for serious or life-threatening diseases in which, in the opinion of the investigator and parent(s)/legal guardian, the welfare of a pediatric patient would be jeopardized by his or her failing to participate in the study. In this situation, continued parental (legal guardian) consent should be sufficient to allow participation in the study."*
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> Good Clinical Practice, International Conference on Harmonization (ICH)

Genetic treatments are being studied in rare disease trials more frequently than ever before and bring with them the potential to cure people of life-limiting conditions. In this light, the term 'life-threatening' in the GCP guidance takes on far more frequently observed role in the study. This can put extra pressure on parents, who understand that this may be their child's only current hope for a long-life, even when their child has had enough of the day-to-day requirements of trial participation. How do they respect their child's wishes and individual needs, whilst also effectively overriding their decisions?

In the future, especially if the trial is not successful, the child is more likely to remember this overriding of their wishes than the context of the long-term risk they were unable to comprehend at the time.

Shared Learning

Experts at Emmes have found that budgeting appropriately to provide funds for travel assistance, flights, hotels, meals etc for both the patient and primary caregiver is a simple but critical step to take at the start.

It gives the study sites the ability to work with participants and their families to ensure that their individual needs are met. Partnering with patient advocacy groups and linking families with their additional support systems is also proven to be beneficial for all involved.

2. Remote versus in-clinic visits

The widespread acceptance of Telehealth that COVID-19 prompted is one of the few positive aspects for rare disease patients coming out of the pandemic[5]. Orphan drug trials were already embracing virtual visits and home-based measurement, but the ease at which studies can routinely include these elements has increased.

This is hugely beneficial for patients who may have difficulties traveling — either due to the practicalities of traveling itself, or the impact of the long day on fatigue and other symptoms they may routinely manage.

For patients with neurological concerns, considerations for travel may need to be specifically clarified and addressed in study budgets and designs. If there are mobility issues, providing suitable transport options, or alternative closer clinics may be needed for in-person assessments.

For patients with additional learning or communication needs, a video or telephone call may be insufficient for interacting well with the individual. In all of these scenarios the guidance and input from legal guardians will help their care team tailor options to fit their needs best. However, the care team need to know from the trial protocol what options are, and are not, within scope of budget and study requirements.

Trial design activities, such as measurement tool selection, need to be balanced by the team to ensure they're achievable for those taking part. The information collected must be useful and informative for future treatment decisions. It must therefore be collected via a trusted (proven and 'validated') measurement tools (or approaches such as survey, or medical-grade activity tracker).

Many of the accepted measures for neurological conditions are surveys, observations, or physical challenges and require large time investment from patients and their caregivers. The total number of assessments, as well as who conducts the assessment should be debated. Telehealth requires measures undertaken at home — this does reduce travel burden, but it also increases the 'to-do' list for caregivers, who are quite possibly providing full-time care, working, and looking after family all at the same time.

Balancing the scientific requirements of the trial with these practical considerations of clinic vs home measurement as well as time and emotional impact for those involved is a trial design consideration that should be routinely applied within rare disease clinical research organizations.

3. Delivering a trial that lasts

Working in partnership with patients from the start of trial design is fundamentally important in order to balance the approach used, clarify the wording in the protocol to support shared decisions, and ensure that the trial is achievable for those taking part.

In the words of Liz Curtis, CEO and Founder of The Lily Foundation when she was talking to Emmes:

> *"We think here at the Lilly Foundation that Orphan drug developers are becoming increasingly aware of the importance of patient involvement in trial design. Badly designed trials won't retain the numbers that are needed to gain useful results...We're more and more frequently being asked to look and to give feedback in the early process of trial designs to make sure that these trials are realistic for patients... this means that it's much easier for patients to take part..."*
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> Liz Curtis, CEO Lilly Foundation

In addition to working with trial experts to make changes to the study before it starts, patient organizations can also help to communicate the trial well: Ensuring that the language used is understandable; that the implications of taking part over the entire duration are fully understood from the beginning; and that the best format is used for communication the information.

Patient groups see so many examples of trial information and interact with so many families that working with them allows pre-competitive best practice to be circulated and the experience for all improved.

Conclusion

This standard of blending requirements of patients with the requirements of other experts into a multi-disciplinary trial design and delivery is a skill that orphan drug focused clinical research organizations have honed to optimize both research and patient/caregiver experience.

When combined with a study design that clarifies predictable condition-related requirements to support trial delivery from sponsor through to decision-making in clinic and at home, this can transform the practical delivery and impact of a study for those involved.

These considerations, alongside optimized communication with patients, can prevent trials from struggling to retain participants, and avoid unnecessary protocol amendments. Most of all, it ensures that the trial experience can be tailored with individuals in mind. We are tackling the challenge of conducting research into treatments for rare disease together as a community and, together, we can make sure that every single person's experience matters.

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