



Defining success in rare disease pediatric trials

Introduction

Rare diseases are often chronic conditions that begin to manifest during childhood¹. The effects of disease change everything from direct consequences of having the condition to impact on the child's growth patterns and development, behavior, psychology, self-worth, and self-belief alongside the untold impact on the families who support them. At the current time there are very few treatments available for rare conditions, but even with supportive therapies, the earlier that medical and supportive intervention takes place, the bigger the impact because it not only helps to slow the disease, but also gives the child the opportunity to mature and integrate into diverse friendship groups for longer. This is why pediatric trials in rare disease are so important; they help to develop the treatments of the future and by targeting treatment of pediatric patients, they also provide the chance to live a positive childhood with as much normal development as possible.

As discussed in our previous paper '**Thinking of the Individual**', these trials are not easy. Every individual is affected differently by the condition and therefore mainstream trial design, analysis, and real-world data methods are suboptimal. Collaboration between all stakeholders is essential for studies that are feasible to run and treatments that matter most to those who take them.

In this whitepaper we discuss the complexities of agreeing the definitions and approaches used to measure trial success, that are meaningful for all involved. Experts might imply we are missing out the family/patient voice.



Success means different things to different people

Clinical trial results need to give people enough information to guide treatment decisions. Two key trial terms that are routinely discussed are:

Measure

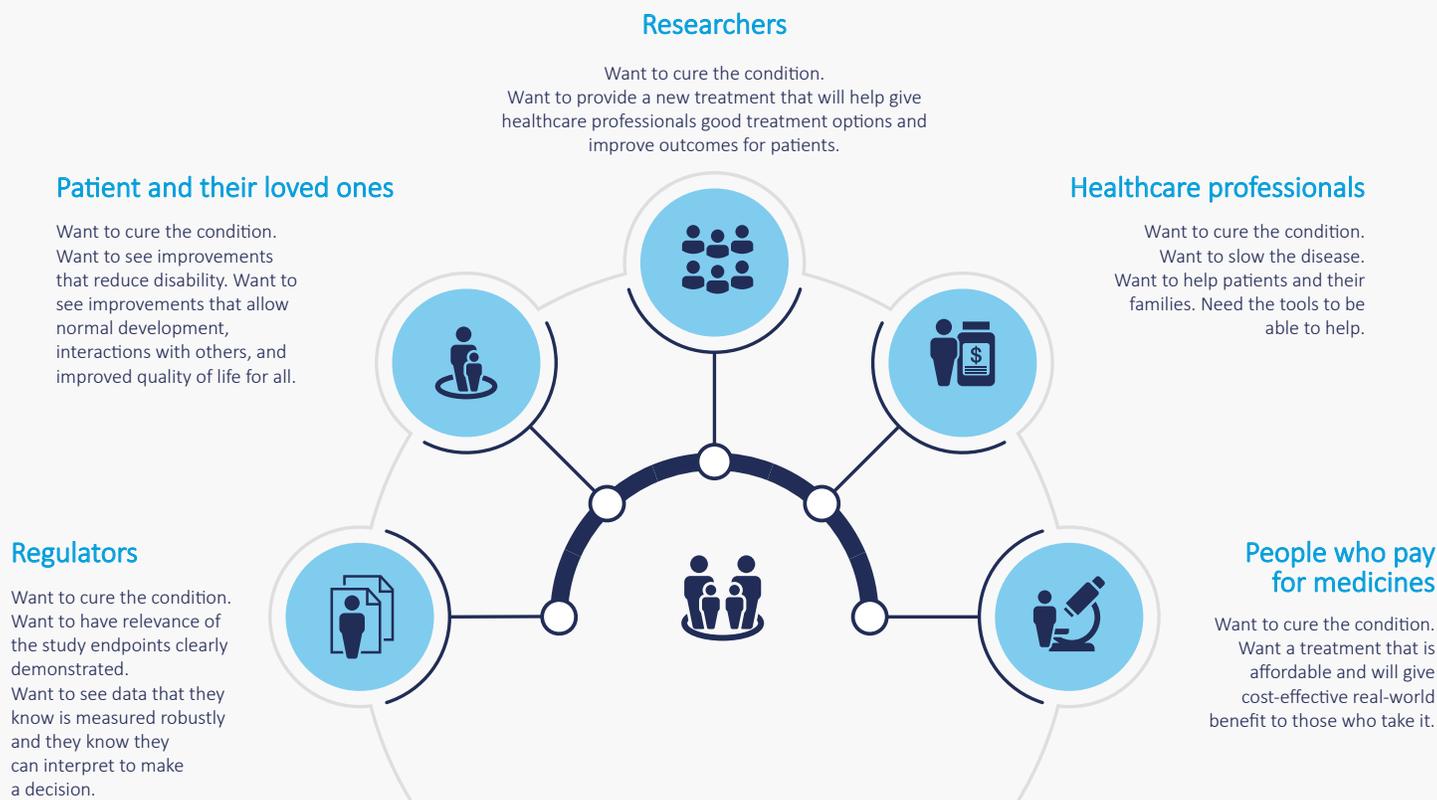
What to look at and the robust method that is going to be used to record how much the drug is impacting this.

Endpoint

The defined amount of change that tells us whether the drug is working well enough or not.

When combined, these terms help to define what to look for and how to record change, as well as the degree of change that is important.

Trials must characterize both the benefits and risks of a new treatment. Working out what potential benefits are possible and then which are most important to measure is a complicated task. There are many people who have opinions on what should be chosen to study, and what level of change in this is meaningful. These include but are not limited to:



Traditionally two main factors have influenced what is chosen. Firstly, giving regulators what they expect to see when they review the drug at the end of development. This is important because if they don't see something that they believe is valid then the drug will not be approved, and people will not be able to access it. Secondly, what clinical experts state is required to best tackle the disease. Again, this is logical, if the drug is not changing the disease, then arguably it's not working.

Both are essential considerations for any medicine – it needs to provide predictable results and the evidence showing this needs to be reliable and understandable. Trials need to go beyond this though. Children and their families live with the condition 24/7 and see the full spectrum of the disease's consequences. They are in the perfect position to offer advice on which disease consequences matter most for improved quality of life, the amount of change that will make a meaningful difference and suggest ways to gather data to measure that change. Their insight goes beyond the clinical mechanism of action and its patients and their families, working with clinicians, that provide the essential linkage with real-world life.

The traditional approach

For years patient and caregiver quality of life was seen as 'extra' data to capture, and the 'core' trial results continued to be gathered unchanged². A comparison of clinical trials for rare disease with those for common diseases in the EU clinical trials register, showed that although many adaptations were made to trial design and delivery to make them more practical, things like primary endpoints and trial durations tended to stay the same³. Information about patient or caregiver experiences and quality of life was instead gathered using add-on questionnaires called either PREMS (Patient Reported Experience Measures) or PROMS (Patient Reported Outcome Measures). These have now become a normal and essential component of nearly all trials and are used to capture patient perspectives and experiences within the trial. The focus of PREMS/PROMS is usually quality of life, daily functioning and symptoms⁴.

Traditional PREMS and PROMS have been created on the patients' behalf by researchers and are very important because they add context and understanding around endpoints and can be used as part of the evidence given to regulators and payers when they make decisions about whether to approve and reimburse the drug⁵.

A few years ago, the International Rare Diseases Research Consortium (IRDiRC) taskforce focused on trying to make these measures more patient-centered. They concluded that multi-stakeholder input is required to develop and validate true Patient-Centered Outcome Measures (PCOMs). Their suggestion was to use mixed methods psychometric research to create PCOMs in rare diseases because it integrates different types of information and is tailored for small numbers of respondents⁶.

However, even after this initiative proposed a method for developing optimal PCOMs, a recent review found that such bespoke assessments tended to be used for understanding the real-world cost of illness for those involved, and quality of life assessments remained traditional⁷. This has created a problem as over reliance on traditional quality of life assessments can overlook aspects of the condition meaningful to patients themselves. In addition, it's trial endpoints that define success and these were not found to be changed or influenced by PREM or PROM approaches.



We need to do more

In 2020 a research group searched for evidence that patients were involved in defining success in primary and secondary clinical trial endpoints and concluded that, at most, there was very limited action⁸.

As described above, the definition of a trial's success rests on whether the primary and secondary endpoints meet pre-defined targets. If this clinical target is not seen as relevant by patients, is unrealistic, or is bigger than that needed to give benefit to patients and families, then a drug can be rejected without patients ever even knowing that there was something with the potential to make their lives better. This has happened in the past for Duchenne Muscular Dystrophy (DMD) where, undertaking a six-minute walk test is an accepted and standard endpoint for trials. This test uses the distance that a person can walk in six minutes as a measure of performance capacity. This is less relevant for young men with Duchenne who have no desire to walk fast. A race for distance-covered is simply not meaningful when compared to loss of independence. For a young man who has lost ambulation and relies on a powerchair, the ability to reach down the side of his chair and place his arm back on the arm rest may equate to self-sufficiency.

Regulatory authorities around the world have started to acknowledge this problem, with the FDA releasing guidance that is leading the charge. A few years ago, the FDA created a group called Patient-Focused Drug Development (PFDD) who have authored four guidance documents to date⁹. These build up into a series and describe how to involve patients better in study design and the creation of more relevant, blended endpoints for trials. The latest guidance that has been released for comment, shows researchers how to begin to analyze results, define thresholds of success, and gather evidence that this change is meaningful to patients themselves^{10,11}. This outlines the expected approach for future trials.

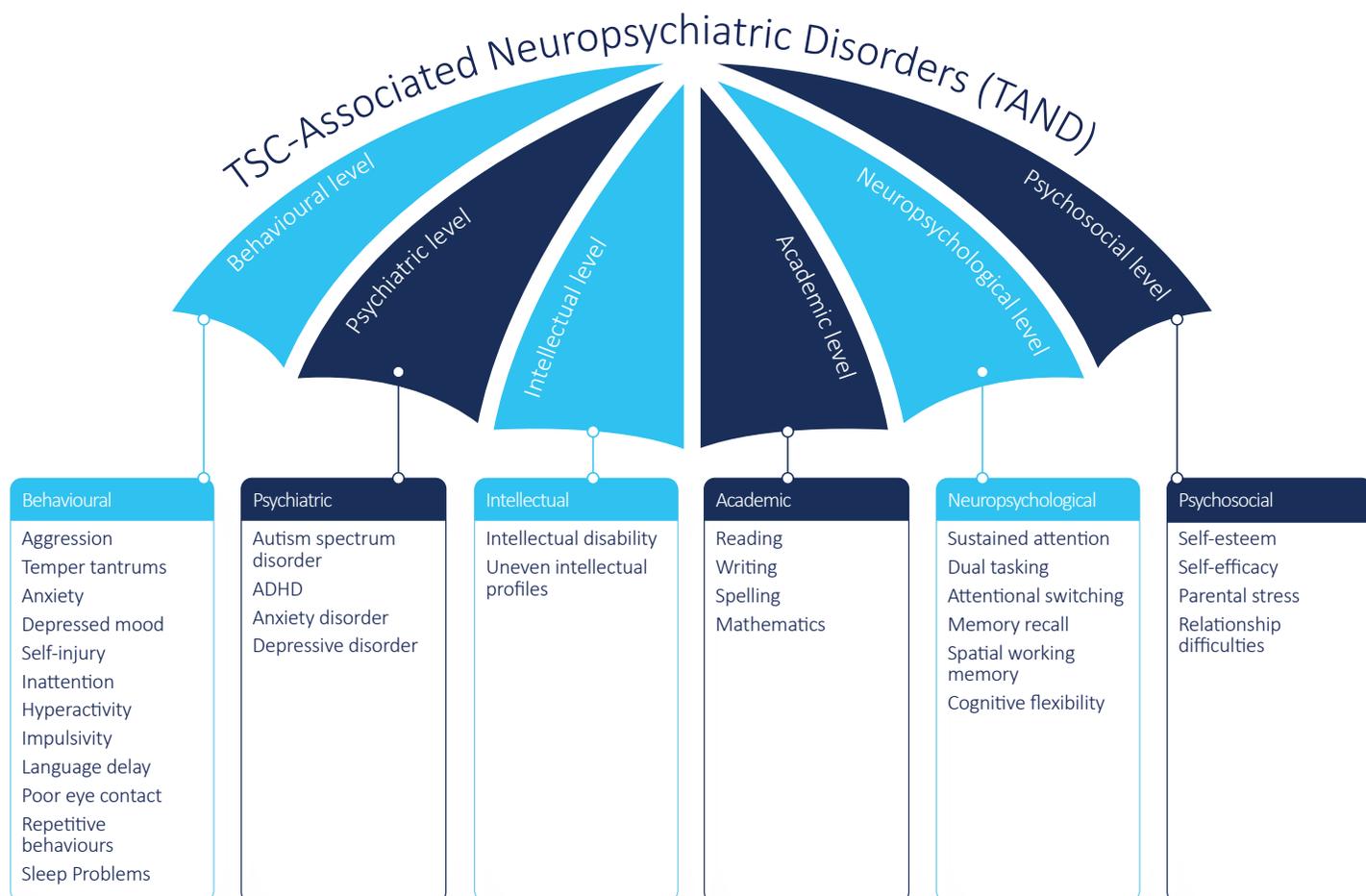
As with every other step of this evolution – there isn't one simple answer that fits perfectly. It's a thought process, and every situation is different requiring a balance of the strengths and limitations of each possible way to measure change¹², but it can be achieved through collaboration between experts and solid research being gathered to underpin decisions and build the evidence base. Reflecting on her attendance at a recent World Orphan Drug Congress (WODC) conference to discuss rare disease endpoint advancement, Managing Director, Strategic Collaborations at Emmes, Christine McSherry stated:

“Research is developing personalized medicine through novel approaches, however we aren't using the same approach in our outcomes and endpoints. For research to evolve we need to reassess this for the good of patients”.

Action, not talk. Early-stage development of new measures

There are several examples of patient and research organizations working together to develop tools that can profile how a rare disease is affecting children as they grow. This is an essential starting point for any future endpoint creation as a robust understanding of the variation in how the disease affects each individual informs how measures can be created. One of these early assessment tools can be found in the rare condition Tuberous Sclerosis Complex (TSC). TSC is a disease in which non-cancerous tumors begin to grow in the brain and elsewhere in the body. It is an incurable condition that is often first recognized in early childhood. An individual's development, functioning, and interaction with others is highly variable and very dependent on the symptoms of the disease that they experience. These symptoms often include seizures, delays in cognitive development, and behavioral issues such as aggression, attention deficit hyperactivity disorder, obsessive-compulsive disorder, and repetitive, destructive, or self-harming actions that can be difficult to manage. There is also a strong link with autism.

Behavioral problems associated with TSC often have a profound impact on both the person exhibiting the behavior and those around them. In some cases, behavior causes more daily concern and has a greater impact on ability for independent daily activities than other aspects of TSC¹³. Yet very few trials of new medicines measure these effects or consider them when defining success.



Recent pilot data supported the discussions that medical and patient communities have been having for a while. The earlier on a child receives the correct treatment the bigger the benefit on the way that young children learn to communicate as they grow¹⁴. Further research is needed, but for those experiencing this, there is no time to wait.

An interesting initiative was started to produce a recognized classification chart, 'TAND' (TSC-Associated Neuropsychiatric Disorders). The inspiration behind the idea came from the HIV community where they produced a similar tool for increasing awareness and consistency in language around a poorly understood aspect of the disease¹⁵.

This TAND checklist is a screening tool represented by an umbrella covering several key domains, each of which lists out the main characteristics of disease impact and has a validated questionnaire associated^{16,17}. The results are used within healthcare by consultants and families to create a mental health treatment plan for those with TSC and integrate this with their overall clinical care.

This is currently not a trial endpoint, but it is an example of one of the many initiatives to give medical communities a way of engaging in a structured conversation for the benefit of the patient, a method of collecting a consistent dataset of individualized profiles, and an agreed scientific wording for publishing and comparing results. This may also be of utility to families who may be able to recognize and understand characteristics of the condition as they arise during developmental milestones.

TAND is now being modified into a validated longitudinal measure for patients that has the potential to be even more useful for future study consideration. If used, this will mean that clinical trials will finally be able to measure the effects of future treatments across the TAND areas that are so important for children's ability to communicate, interact, and be socially accepted as they grow.

Designing endpoints that matter

Emmes Endpoint Solutions (previously Casimir) is an example of a service validating such patient-centered tools to clinical trial standards. The company was founded by parents of children with Duchenne Muscular Dystrophy (DMD). This is a progressive condition caused by changes in some of the genes responsible for the structure and functioning of a person's muscles. As the disease progresses, the muscles' ability to function reduces, causing increasing disability and dependence on others.

The founders of Casimir were parents with children who took part in clinical studies for DMD. These trials were considered to have 'failed' because they didn't meet their primary clinical endpoints. However, parents and children taking part saw life-altering improvements whilst on the trial drug. Something had to change and parents began to work with the FDA's Center for Drug Evaluation Research (CDER) and clinicians to innovate.

They used a video-based approach to characterize outcomes of importance to patients and families, then blended these with activities of daily living (ADLs) and assessments of functional ability to measure and quantify change¹⁸.

Casimir was born, and they started their own trial that subsequently demonstrated real and quantified improvements that transformed the lives of the boys taking part. Even more importantly, these measured changes were focused on areas of greatest relevance to the people affected and the endpoint measures accounted for differences in the way that disease presented during the growth of each child. Eteplirsen, a drug that had previously 'failed' in a trial for DMD, was then approved by the FDA as a supportive care therapy for use in patients with DMD. This is now available in the USA for others living with DMD to help them maintain meaningful activities for independence and socialization.



Conclusion

As an industry we need to do more. In rare disease we can often improve lives most by intervening and developing therapies for children. This brings with it all the added complexities relating to pediatric studies as well as the need to adapt to the highly variable way that rare diseases may present during childhood.

As researchers we need to accept this challenge and change the way we do research to ensure that therapies address the underlying clinical condition and what will make the most meaningful difference for those affected. We are honored to have Emmes Endpoint Solutions as part of our team. Together we are leading the way in patient-centered rare disease trials and embracing the urgent requirement for novel, robust, trial endpoints that measure the success that transforms lives.

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