Eight Must-Know Considerations About Rare, Dermatologic Trials for Children

Highlights:

- Approximately half of rare diseases affect children, and in the EU, more than 1,000 rare skin diseases are known – many of which are of genetic origin and manifest in childhood.
- Challenges include standardizing measurements and assessing meaningful outcomes
- Improving quality of life may require new thinking, genetic testing, and a multidisciplinary team approach

Did you know that approximately half of rare diseases affect children, and in the EU, more than 1,000 rare skin diseases are known? Sadly, several of these rare dermatological conditions are of genetic origin and manifest in childhood – making an impact on children who may never live to adulthood without early intervention. In delaying treatment, these pediatric patients cannot always recover the loss of function if the skin cells die. So, not only is it important for drug developers working on new treatments for dermatologic diseases that affect children to include them in the clinical trials for new drugs, it is now mandated by the FDA. However, including children presents its own set of operational challenges.

Dermatology trials are somewhat unique, and even more so with children included in the trial. Let's discuss some of the key considerations that should be taken into account when planning rare, dermatologic trials for children.

1 **Clinically meaningful outcomes must be considered carefully.**
With little, or no, robust longitudinal disease models, there may be a lack of understanding of the natural history of the disease. Efficacy endpoints are qualitative and subjective in many cases, creating a high level of variability in interpretation. Because the results are often observed visually versus quantitatively as in other therapeutic indications, we must count on the trained eyes of the investigators – meaning these individuals must have the experience to recognize the often-subtle disease-state differences.

2 **Standardizing assessment: a challenge, and a necessity.**
Standardizing global assessments of diseases that present with a dermatology indication is challenging. These must be taught to the investigator because they are visual. And since the conditions are rare, there is less room for error because the sample size is so small that detrimental effects are exponential.

3 Dosing must also be standardized.
Calculating and managing the drug supply is impacted by variability in dosing by various investigative sites. Since some of the drugs are topical, calculating the amount to be used, especially for children, can be difficult. When it's a topical drug, the amounts to be used may be based on body-surface area. The CRO should have experience in determining body surface area for children, and ways to standardize amounts to be given.

4 Measurement of outcomes requires rater consistency.
Since the measurement of outcomes may also be variable, it is important to establish ways to account for size reduction of lesions on rating scales that are as precise as possible. Centralized photos with circumference, diameter, height, or other identified criteria can be used to document degrees of change. The challenge is in ensuring that there is rater consistency across participating investigators, particularly in Phase III studies when the drug should be showing distinctive efficacy in narrow result ranges. Investigators' trained eyes must discern differences in improvement through validated rating scales. We also need more composite measures for validation of outcomes – because it is improving quality of life that is important.

5 Quality of life is what is most meaningful to these patients.
It's hard to quantify the impact these diseases have on children. Sometimes it hurts for them to smile or sing or even to talk. They may not be able to play sports or even just play outside. Lesions, blemishes and scars can be embarrassing to teenagers and may lead to shyness, depression, and self-imposed isolation. These are the impacts that are often the most important components to children and their families. Therefore, quality of life needs to be just as important to regulators, academia, and developers as it is to the families. We, who work in the industry, must take a holistic approach to these drugs and the quality of life issues implicated with them.

Patient-centric assessments are critical. We use questionnaires to assess quality of life measures. Investigators need to ask the children and the families themselves what enhancements they perceive, what they can do more actively, or how they feel about themselves as a result of improvement in care.

6 Think about the role technology and innovation can play.
With the advent of new technologies such as gamification for questionnaires, rewards for remote participation in electronic surveys, and the addition of wearables and active measurement devices, there is a lot of opportunity for technology to play a part in trials. We see it really starting to happen in Phases II and III especially. But sometimes, with dermatologic, rare and pediatric clinical trials, the challenge is in developing wearables that are not painful on the skin, so we must take extra measures to make sure they are, in fact, "wear-able" for this patient population. Before designing these types of innovations, it is important to have a conversation with your CRO and investigators to choose the proper wearable solutions.

It's also important to recognize that "innovation" doesn't always mean technology. It may also mean getting involved with key opinion leaders associated with institutional and academic settings, parent groups, or private clinic sites that have close relationships with patients. The more collaborative the relationships developed are, the greater the likelihood for opportunities to improve enrollment and complete studies on the desired timeline.

7 Genetic testing must be a component of rare, genetic disease trials.
Access to, and acceptance of, genetic testing is of critical importance when earlier intervention makes a difference. Numerous investigational treatments show optimal benefit if initiated pre-symptomatically, thus delaying onset of symptoms and preserving function for a longer period for these children. Newborn genetic screening is powering clinical trial participation and, therefore, potentially enabling access to life-altering treatments. Working with physicians, clinics, investigators, and disease groups to help them understand the advantages of genetic testing is something that we can do to help improve trial participation and outcomes that impact quality of life.

8 A multidisciplinary approach is needed, even when the trial name just says dermatologic.
One of the greatest misconceptions for dermatologic disease is that it's "just a skin problem, so what's the big deal?" Sometimes these diseases manifest in more than just one clinical presentation – they can impact the eyes, eyelids, hair, nails, and/or mouth, in addition to the skin. Some patients, due to skin issues, may not be able to sweat, or may be at risk for dehydration. For some, infections can be fatal. In other words, dermatologic diseases, especially in children, may be much more serious than the general public may think.

These disease trials will often require a large care team at the investigative site level and a plan for multidisciplinary solutions for diverse clinical presentations or side effects. Therefore, it is important to involve other subject matter experts when the sponsor is planning the trials. In some cases, the Principal Investigator may be a dermatologist but the rest of the care team may include an ophthalmologist, respiratory specialists and general practitioners. If an auto-immune disease is an underlying factor an immunologist will be required. If there are feeding implications, a dentist or ENT may be needed. Pediatricians are often the experts in cases where young children are involved.

The good news is that with advances in medical care and new treatments, we are now seeing some rare diseases that have historically been fatal for children, no longer terminal. As the next generation of patients grows older, they will need to transition from a specialty pediatrician to adult care. And that will require access to multidisciplinary care centers that are not as common in adult settings. As researchers, we need to support this transition of care.

Need assistance in thinking all of this through with a team that cares?
Please email ContactUsGroup@synteract.com if you would like to learn how we can help bring your rare, pediatric dermatology trials to life. With six Centers of Development – staffed by specialists not only in dermatology but also in general medicine, neuroscience, oncology, pediatrics, and rare and orphan diseases – we can put together cross-functional teams that meet the specific needs of your study, across multiple areas of therapeutic demand.