



Commentary

The Ultramarathon of Gene Therapy Development for Rare Diseases: How Can We Cross the Finish Line Together?

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ABSTRACT

The promising developments in gene and cell therapy bring an array of hope to the >7000 rare disease patient communities, of which 90% to 95% are still working toward a treatment. However, the pace of gene and cell therapy development pathways often resembles ultramarathon relay races that potentially span decades. It is a pace that is incongruent to the sprint that most individuals with rare diseases and their families are living and working in pursuit of life-saving treatments. It is also challenging for the medical professionals, academic researchers, and pharmaceutical partners working tirelessly to bring a treatment to reality. Gene and cell therapy development programs can have many parallels to an ultramarathon, including extensive training and preparation leading up to clinical trials, selecting inclusion and exclusion criteria, supporting trial participants, and creating support teams. All aspects of the development course carry the greatest hope that as many treatments as possible can cross the finish line. Drawing on this analogy, perspectives and insights from a patient family member and rare disease advocacy leader in a community that has experienced its first clinical trial of gene therapy is shared. Bringing attention to these experiences, challenges, barriers, and potential learnings from a patient family perspective will likely encourage continued improvements in development of patient-driven gene and cell drug and therapy for the rare disease community. (*Clin Ther.* 2022;44:1038–1044.) © 2022 Elsevier Inc.

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INTRODUCTION

When gene therapy returned to the landscape of potential treatments during the past several years, it was met with much excitement, especially by the rare disease community, because of the 90% to 95% of diseases that currently have no medical treatment options. The myotubular myopathy (MTM) community was particularly encouraged because MTM is a rare neuromuscular condition that severely affects individuals across multisystem functions. Individuals with MTM are often affected from birth, and many children who can survive the early days often leave the hospital with some level of mechanical ventilatory assistance, frequently with tracheostomies and full-time ventilatory support. Although prognosis is historically poor, with only approximately 50% of individuals living beyond the age of 2 years, many with this condition are beating those odds with the advancement of medical technology. These individuals are redefining what quality of life is and can be fully active members of society, attending school and pursuing personal aspirations, along with the assistance of their technology and supportive medical care. Although members of the MTM community are often grateful that their children were born at a time when medical technology could support their lives, this community continues to seek gene and cell therapies that may offer these individuals an interventional treatment that would restore the single missing or defective protein, myotubularin, that results in myotubular myopathy.

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The sense of urgency to find a treatment for individuals with a rare condition indeed feels like a sprint of a lifetime. Often it involves venturing into an unknown territory, learning as much as possible, finding anyone who can join you in the race, and getting your running shoes on to hit the pavement. You keep going until you can find or create a treatment that will help. With many rare genetic conditions having a degenerative component or advancing complications over the lifespan, time is of the essence, which inherently creates a sense of urgency. It is no surprise that the driving force behind clinical research and the pursuit of drug and therapy development is often individuals living with rare diseases, their parents, and their family members.

Unfortunately, there is great discordance between the sprinting experience for individuals and families, exerting so much time, energy, resources, and hope—lots of hope—in relation to the reality of the marathon pace or more often resembling an ultramarathon relay race of drug development. Medical professionals, academic researchers, and even pharmaceutical partners are sprinting alongside patients and their support systems. Together, they work tirelessly to bring a treatment from the research bench to the patient through the commercialization process and ultimately enable global access. It is along this ultramarathon relay of gene therapy development that we must take a deeper look. To optimize the number of rare diseases that result in effective treatments and cross the finish line, we must better understand the course challenges and relay handoffs.

PRECLINICAL DEVELOPMENT AND CLINICAL TRIAL READINESS

We can draw a parallel between marathon training and a rare disease community's preclinical work and clinical trial readiness preparations. As the parent of a son who lived 20 years with MTM and as the co-founder and president of MTM-CNM Family Connection, a nonprofit organization dedicated to connecting families affected by MTM and centronuclear myopathy (CNM) to research, resources, and life-enhancing community relationships, it is in this training mode where our family spent many of our days and years. We did everything we possibly could to move the community closer to a clinical trial and hopefully down that path to new therapeutic treatment options. We were committed to helping our son live his best life

possible every day. We openly shared how he was redefining quality of life for those living with this condition, brought families and medical professionals together to learn from each other, and took every opportunity to move toward potential treatments for MTM.

As for so many others in the MTM community, this involved saying yes to every opportunity that came along that had the potential to inch us closer to a clinical trial. Over the years, we were involved in multiple natural history studies, registries, focus groups, medical literature case reports, clinical and home evaluation visits, and historical medical record reviews. We donated to blood banks and tissue repositories, participated in self-reporting data collection surveys, and hosted conferences and patient engagement activities with the community, including with the US Food and Drug Administration (FDA). Although we always hoped our son would be able to benefit from a treatment, as time went on, all of us had a growing sense that it would be unlikely he would personally get an opportunity to participate in a clinical trial. Even with this increasing awareness, we always consented. My son always assented to be a part of the process of moving the research forward with steadfast hope for everyone living with his rare disease. This cooperative attitude is one of the qualities of the rare disease marathon of the drug and therapy development landscape that makes it more aligned to an ultramarathon relay race because the race requires a team to succeed.

CUMULATIVE ADVOCACY

Wherever and whenever individuals enter their disease communities' marathon, it is important to consider both the intrinsic and altruistic opportunities, risks, decisions, and experiences that lay in front of them. Something I like to call "cumulative advocacy" is the evolution of rare disease development that increases through the selfless giving of individuals and families that enter into the community's relay race. It is this culmination of participation, growth, and building on each other's progress that can set rare disease communities up for the greatest likelihood of success. If everyone does what they can, when they can, even if it may be unlikely that they themselves or their loved one may benefit from a treatment, we have the greatest chance of reaching the finish line.

The cumulative knowledge, growth, and experience of a collective rare disease community is what will continue to move forward the ultramarathon relay race of a rare disease. Of course, it is also understandable that everyone must make their own decisions about what participation, if any, is right for them and their family. It is also healthy to recognize that your approach to participation can and likely will change over time, depending on what your course looks like, how many hurdles and pitfalls you experience, and embracing when the vision of your finish line shifts or detours. Overall, it may be helpful for the collective rare disease community to encourage greater acknowledgment of individuals who lay the groundwork and made progress by participating in preclinical trial activities. In addition, whenever possible, circling back to inform past participants and their families of progress can be incredibly important and meaningful.

BALANCING CARING FOR TODAY WITH PURSUING FUTURE CURES

As the opportunities for potential cures widens in the realm of gene and cell therapies, it will be important for the entire medical community to encourage a balance of hoping for curative treatments and managing the cares of today. With the current-day possibilities of gene and cell therapies, there has been a noticeable culture shift regarding medical decision-making among families who have children born at a time when enrollment in a gene therapy trial is possible. In contrast, many families with older children in the community learned to adapt and adjust to a life with medical technology, addressing medical issues in the present. For example, some families may hold off on consenting to medical procedures that potentially could benefit their child in the present day, thinking that a cure will come first. It will be increasingly important for practitioners to help families balance caring for their child's needs in the present, while supporting them in any considerations that need to be given if they would also like to pursue inclusion in ongoing or future trials.

In some respects, the language and culture of cure may also downplay or overshadow the strides that have been made in our community. Many of us live our lives daily trying to convince society that our children are more than their disease or the technology that supports their lives. Although in pursuit of these

exciting, potentially curative interventional treatments, we must also safeguard the inherent value of all children's lives and support decisions that will help keep individuals safe, healthy, and thriving, including safeguarding the progress made in the areas of diverse ability awareness, acceptance, and inclusion.

BUILDING TRAINING PARTNERS AND MARATHON SUPPORT TEAMS

During this training or preparation stage, essential time and energy are put into bringing together a support team of multiple stakeholders: individuals and families, academic researchers, medical practitioners, and early pharmaceutical industry partners. Our organization's efforts focused on gathering all stakeholders through national conferences to enhance stakeholder collaboration and clinical trial readiness. Hosting collaborative conferences, where everyone learns together and from each other, empowered patient engagement as a necessary component of therapy development in our community.

At every juncture of the development process, individuals and family members can add invaluable insight and feedback, often proactively preventing future challenges in clinical trial design. Individuals living with MTM and their families have found optimal ways to manage the disease. We have hung on every word published and shared information passed down from generations. We can string together events that seem like outlier circumstances, unlocking important understandings of the disease that need to be recognized in the context of a potential treatment or intervention. These real-world data are ideal for natural history studies, but if contextualized in isolation without the inclusion of patient and medical community studies, important opportunities will be lost. Generating more written case studies will allow medical issues to become searchable. In turn, medical literature becomes a powerful driver in connecting rare cases and identifying important trends. One tangible example of how individuals with MTM and their families contributed to the pace at which our community could progress toward clinical trials was through significantly accelerating the national history and preclinical data collection process. By allowing research studies to collect data and evaluate patients in person at our national conferences, research teams were able to collect data onsite from many patients in a short period, saving research and resource expenses.

PARTICIPANT SELECTION

So many patients and families were willing to participate in our community's clinical trial readiness activities and research to advance the course of therapy development. Through the building of our multistakeholder conferences, we also provided a shortcut to clinical trial recruitment, a common challenge pharmaceutical partners face in the treatment of rare disease. In bringing the community together and bringing awareness to the trials, there was broad interest in participation. The reality, though, is that the inclusion and exclusion criteria for the selection process can be brutal.

Getting into the Boston Marathon can be brutal, too. You can do everything right—train-train-train, make your required time—and still not get into the highly competitive Boston Marathon. This experience can be much like the experience many patients with rare disease and their families face: the anticipation, the disappointment, the devastation. Of course, unlike the Boston Marathon, which occurs yearly, for families desperate to have access to a clinical trial these feelings are magnified by the reality that participation may be the only opportunity afforded in their lifetime.

It is especially hard for patients and families to experience not getting into a clinical trial that they were instrumental in bringing to reality. Including patient and family stakeholders in the creation of inclusion and exclusion criteria is essential for mitigating risks, optimizing potential for broad inclusion, minimizing barriers to participation, and conveying the importance of codesigning trials with those who will be participating in them. Being transparent about anticipated age limits or other restrictions as soon as possible can also proactively preserve relationships with community members who otherwise might feel misled. Furthermore, it is incredibly important to consistently remind the community that a clinical trial is investigating the safety and efficacy of a gene therapy product that is yet unknown.

INFORMED CONSENT, SHARED DECISION-MAKING, AND WEIGHING RISKS AND BENEFITS

Informed Consent

Signing waivers or, in the case of gene therapy trials, consenting to participate and be dosed with a new gene therapy is a critical process that mandates informed consent. From a patient and family perspective,

consent must be explained in a way that matches the importance and weight of decisions that are being made. Consent cannot just be a form; it must be understood as a process, one that is ongoing and should be evolving as a trial progresses. For participating individuals and their families to make the most informed decisions regarding gene therapy, the entire field needs to be considering how to ensure that consenting individuals and their families are provided with the most up-to-date data in the context of an ongoing trial. Throughout a trial, consent should be an evolving and living process, one that is iterative and is built on in a timely way as results and information from prior participants emerge. The stakes are too high to not be doing this in the most transparent ways possible.

Shared Decision-Making

Once the most up-to-date data are presented, families then must personally weigh for themselves or their loved one the risks and benefits of participation. The weight of these decisions also calls for closer consideration and resources to be given to building effective teams around participants and their families. Patients and families should also be asked to identify key medical practitioners and individuals who are essential in helping them make medical decisions, and they should be integrated into shared decision-making teams with the trial site principal investigators. Resources should also be dedicated to building strong clinical trial teams that have individuals skilled and dedicated to having goals of care, quality of life, and high-stake conversations, including having conversations about the possibility of serious adverse events, developing contingency protocols, and having open, honest conversations of the risk of death. Communication and relational skills are often practitioner skills that must be attended to, developed, and practiced when working with and assisting patients and families in high-stakes medical decision-making. Resources must be committed to this critical piece of shared decision-making and ongoing communication about the clinical trial experience.

Weighing Risks and Benefits

It would be nice if risk-benefit calculations, analyses, and conversations could be neatly packed into a quantitative response or percentages. However, in

reality, each individual and family defines quality of life differently. Families in our communities have often fought for years to redefine what quality of life means to them, their child, and those around them. It is not surprising that when the MTM community held a patient-focused drug development meeting with the FDA, we heard directly from individuals and families that although most live with great hope and a desire to markedly improve the physical lives of their loved ones, they are also looking for treatments that provide even small amounts of improvement. Many of these tangible desires were in the areas of less reliance on ventilators to breathe, small improvements in hand strength with the goal to more easily navigate a computer used to communicate, and less dependence on the number of interventions needed during a day. These patient-oriented goals are often at odds with research study end point goals of gene therapy trials, which might include more significant results, such as walking and running, or existing quantitative measurements, which are validated but not as meaningful to the patients. This incongruence leads to speculation regarding the definition of successful therapy. Because families must weigh the increasing risks associated with dosing levels of the gene therapy vector, discussions regarding patient-perceived benefits that might mitigate these risks at lower doses are worthy of consideration, with direct input from the families. The MTM patient community still lacks access to data and information to review dosing decisions that have been made, calling attention to the importance of integrating the patient voice, perspectives, and priorities in clinical trial design and dosing protocol decision-making.

After 4 tragic deaths in the MTM gene therapy clinical trial, the MTM community must recognize and acknowledge that potential future gene therapy trials will always carry some risk, possibly even the greatest risk of one's life. The focus needs to shift to helping patients and families best understand the possible risks of participation in trials, what is being done to try to identify risk factors, and efforts to mitigate that risk. Increasing energy and resources in ensuring that families have teams of professionals surrounding them to support their decision-making when considering trials is of the utmost importance. Working through the process of weighing risks and potential benefits of a trial is uniquely personal. Developing supportive systems of communication, shared decision-making,

and soliciting personal quality of life and goals of care conversations will be most helpful for our rare disease community in moving forward with future clinical trials.

Trial Participation

It is important to recognize and honor the brave individuals and families who decided to enter the marathon course of a community's clinical trial. Many enter a trial with great hope that their participation will bring them personal progress and improvement in their rare disease clinical course, but because this is a trial there are no guarantees. The entire community, other patients and families, medical practitioners, academic researchers, and pharmaceutical partners are running alongside the trial participant, hoping with great anticipation that the outcomes are successful and that the next phase of the trial will bring larger numbers of slots for participation, broadening of inclusion, and even universal access.

TRIAL COMMUNICATION AND UPDATES

Ongoing, Bidirectional Communication:

Rare disease communities in a clinical trial are often grasping for any information that can be gathered about how the trial is progressing. Unfortunately, many patient communities are finding that their greatest source of information from trial sponsors is being shared through financial updates to investors, not aimed or tailored to the patient community. It is important for pharmaceutical industry partners to initiate communications directly tailored to the patient community throughout a clinical trial, particularly when complications arise. Community conversations with clinical trial sponsors should be ongoing, even if there is nothing new to report. Although recognizing concerns about such communication being seen as promotional of an unapproved drug, there must be ways to continue dialog with the patient community during this critical stage of product development. Creating opportunities for bidirectional communication and exchange of ideas validates the important role of patient engagement, which in turn will develop transparency and trust, both essential values for successful clinical trials.

Aligning Expectations

Trial sponsors and other stakeholders can work with patient organizations to help align expectations.

Instead of managing expectations, which suggests a controlling or superior position by the sponsor, families and pharmaceutical industry expectations about the clinical trial should be aligned. Achievement of this goal requires conversations and opportunities for patient and family stakeholders to share their hopes, needs, and insights along with pharmaceutical industry partners. Aligning expectations involves collaboration and bidirectional communication to establish mutually understood goals. It also establishes the relationship for better chances of success down the road should the course detour from original expectations.

The Relay Race: When the Baton Is Passed, or Dropped

How can we improve the relay hand-offs and ensure that vital information provided by the patient community will remain a part of the institutional memory of a sponsor, even if the sponsor staff working with patient advocacy organizations leaves? Especially in the pharmaceutical field, with a known history of turnovers, difficulties with retention, and intercompany movement, how do we safeguard valuable information shared? Many patient advocacy organizations that partner with trial sponsors work in a voluntary capacity, and although they are more than willing to do whatever they can to convey patient stories, perspectives, and invaluable information, we need to build better infrastructures and engineer systems for preserving and transferring information that is exchanged between the community and a sponsor or other stakeholders, especially when safeguarding community data that will be essential for any clinical trial in the future. Considerations need to be given for how that information can be shared, maintained, transferred, or used by any future community trial. Patients and family members need to be prioritized and valued as irreplaceable assets. Building internal infrastructures that value the insights gathered from the patient community and their time spent providing that insight ensures that we do not lose ground on this ultramarathon relay race for treatments.

Emergency Pit Stops: Serious Adverse Events and Clinical Holds

Many setbacks, detours, emergency stops, and even events that alter the ability of one to complete a marathon at all can happen. We need to expand

opportunities for inclusion of the patient and family when serious adverse events or deaths have occurred. Being in a community with a trial that has had 2 clinical holds by the FDA, it was surprising to learn that there was no formal, preexisting pathway for the patient and family community to provide our insights, comments, concerns, or even potential knowledge the investigative teams should be considering in trying to solve problems and move forward in a safer way. Although I am grateful that the FDA has expanded its opportunities for patient engagement with a variety of general opportunities, such as Patient Listening Sessions and Patient-Focused Drug Development Meetings, which our MTM community had an opportunity to participate in, those sessions are by definition (and counterintuitively) not related to any specific trial or drug product. When trials are on clinical hold, how to better incorporate patient and family knowledge should be considered to pave the way forward.

Committed to the Course and Still Racing to the Finish Line

Even with all the challenges that have been experienced in the MTM community's ultramarathon relay race toward a gene therapy treatment, patients and families are incredibly resilient. Our patient advocacy organization, in collaboration with others, is not waiting on the sidelines but instead convening supportive stakeholders, committed to better understanding the role myotubularin fully plays on multiorgan systems and the potential challenges that have been more prominently exposed in the community's first clinical trial. We will continue to encourage transparency not only for the benefit of this rare disease but also for all those in pursuit of gene and cell therapy development. We remain open and willing to work with and include all stakeholders who desire to be collaborative partners in the therapy development process and help each other get to the finish line.

CONCLUSION

With the personal investment individuals living with rare diseases and their families make in terms of time, energy, and resources, more committed, passionate, motivated, and knowledgeable drug and therapy development partners cannot be found than those living with these conditions. The collective rare disease community also desires stakeholders who will take

real action to place patients and families at the heart of their work and patient-driven missions. The MTM community is grateful for all the medical professionals, academic researchers, and pharmaceutical partners who are living up to that mission and encourage others to join the drug development collective course. Perhaps together we can make the pathway faster than the ultramarathon relay race that we find ourselves on today and remain forever hopeful in this pursuit.

ACKNOWLEDGMENTS

This article is dedicated to those in the MTM community who have said yes to participating in clinical trial readiness activities and clinical trials, especially the 4 children who died in our community's first trial and their families. And for my son, Will, who bravely lived everyday of his 20 years with MTM, was an advocate for the community, and sadly died in November 2021 from complications of MTM. They will always be remembered.

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