Emmes

Recruiting and Retaining Patients in Sickle Cell Disease Trials

Sickle Cell Disease (SCD) is a rare disease, affecting about 100k people in the US and 20 million worldwide.[1] Although anyone might inherit SCD, it is most prevalent in people of African descent, as they make up ⁹⁰ percent of the SCD population in the US. It also strikes people with Hispanic, South Asian, Southern European, and Middle Eastern roots.[2]

CURE SICKLE CELL.

BMT CTN
Blood & Marrow Transplant Clinical Trials Network

Overcoming the Barriers to Success

For people living with SCD, new, curative therapies in development offer hope for eliminating SCD's painful and debilitating symptoms, halting disease progression, and prolonging life.

Yet, such advances present significant challenges. Both gene therapy and hematopoietic stem cell transplantation (HSCT) are complex and costly to deliver and can provide some burdensome for patients. It follows that conducting clinical trials in these therapy areas is fraught with both design and operational hurdles for Sponsors – particularly with respect to patient recruitment and retention. Arguably, these activities are even more difficult in SCD than in other rare diseases given the characteristics of the patient population and the unique properties of the disease itself.

Patient Recruitment and Retention: A Long-term Commitment and Heavy Lift

In the US, recipients of gene therapy must be followed for 15 years post procedure to monitor for any "delayed adverse events due to the unique genome modifying activity of such products."[3] Patient motivation to continue seeing a specialist can wane if the procedure was not successful, or equal.

Patients whose disease was arrested move on with their lives and are not always invested in participating in continued research. This is especially true for young adults who are a very mobile segment of the population and are, therefore, harder to track and may have moved further away from the clinic.

Patients living with SCD who responded to a survey fielded by Emmes in partnership with the Cure Sickle Cell Initiative (CureSCi), have mixed reactions about participating in clinical trials, ranging from enthusiastic to hesitant. However, a majority states they would consider participating if approached. SCD patients enrolled in an observational study of patient experiences expressed even more favorable attitudes toward clinical trials, with 77 percent to 92 percent agreeing with a series of positive statements about clinical trials.[4]

Additionally, CureSCi found barriers hindering patient recruitment and retention in trials of advanced therapies for SCD include, severity of their disease, logistical burden of multiple clinic visits, and long-term follow up, an understanding of the expected side effects/risks, and the likelihood of the new treatment being better than their current treatment. Participants would, of course, hope to experience a noticeable improvement in their health.[5]

Nonetheless, it is critical for patient safety and regulatory compliance, as well as for the value of the research for Sponsors to continue collecting data on participants whether or not the treatment was considered successful.

Sponsors developing these advanced therapies for SCD will need to take active measures to avoid delays in the study development timeline. They should begin by acquiring an understanding of the factors that influence patient recruitment, socioeconomic challenges, ways to minimize potential patient burdens related to assessments and long term follow up. Getting early input on the protocol design from lead investigators from participating institutions is crucial to understanding the barriers in that region. e.g. Insurance, language, trust of healthcare, referrals/travel, standard of care at the center.

Then, they will need to employ the strategies and best practices recommended by advocacy groups and research professionals with specific experience in conducting SCD trials.

Best Practices: Strategies to Bolster Success

The recommendations offered here are drawn from Emmes' 45+ years of experience in clinical trials, including decades of cell and gene research and the qualitative research we've done with the SCD community. We rely on our close association with key opinion leaders in SCD research (including at the National Institutes of Health (NIH)) and our relationship with the leading patient advocacy groups, CureSci and BMT CNT, for SCD.

Recruitment

Simplify data reporting for clinicians.

As patients complete and submit their sickle cell clinical trial application, the FDA requires that three external clinicians review each application in real-time due to the sensitive laboratory results. However, in most cases, the patient and clinicians are not physically present together. To overcome this challenge, Emmes leverages Advantage eClinical platform that enables remote access to real-time patient data for review. With our Advantage eClinical platform, the patient recruitment process can be successfully completed, ensuring the enrollment of patients.

Study protocol design.

Emmes has incorporated the involvement of all site principal investigators in the protocol team calls as part of the protocol design. Several factors need to be considered, such as the number of treatment options presented and the approach to timing. As the patient's care team involves the hematologist, the SCD doctors and the translation doctor, it is essential to include them in the protocol planning and budgeting. For numerous individuals with SCD, their hematologist plays a crucial role in connecting them to SCD clinical trials. Based on our experience, when the hematologist initiates discussions about a new clinical trial early in the patient's journey, particularly when their condition is stable, the chances of the patient meeting the criteria for innovative therapies or transplantations increase significantly

Emmes can facilitate the establishment of relationships and the protocol team calls with the principal investigators of the broader care team. This enables us to assess the patient pipeline and address any issues faced by study sites in recruiting participants and for the hematologists and SCD doctors to collaborate and expand eligibility criteria once safety has been demonstrated.

It is crucial to work closely with hematologists and their team to maintain ongoing engagement with the patients.

All of these factors have a direct impact on the attractiveness of a trial to potential participants.

Patient visit schedule.

Our experience has shown, when developing the study protocol design and patient visit schedule, Sponsors should seek patient input on different aspect of the protocol at the design stage prior to submitting the IRB. We collaborate with patient advocacy groups like CureSCi and BMT CTN that in turn work with Community Input Panels and the Patient Care Giver Community to weigh in on everything from the consent form and informational materials to recruitment plans and campaigns to the protocol itself.

When developing the visit schedule, patient considerations include assessing travel needs (patient reimbursement, allowance of assessments to be done locally or at home) and frequency of trial related assessments (reducing surveys or biospecimen collection). This allows for better clarity of consent forms & visit schedules that can a line with the patient's current standard of care visits to decreases the number of unnecessary visits for the patient.

Additionally, by considering patient feedback, Sponsors have been able to reduce the patient burden during a gene therapy trial by:

- Reducing out of pocket cost
- Tailor the consenting process to be more individualized
- Increase the focus on mental health and families

Develop a comprehensive, thoughtful, unrushed approach to informed consent.

In 1932, US Public Health Services (PHS) launched a study in Macon County, Alabama to study, where the researchers in charge of the study deliberately withheld treatment in order to monitor the progression of the disease as it advanced unchecked." Due to mistrust of clinical trials within the Black Community, patients wrestle with the decision to participate.[6]

In Emmes' experience, informed consent process is most productive and beneficial to patients when:

- The consenting process is an on ongoing conversation with the patient
- Individuals know and understand what they are signing up for
- Sufficient time is built in for the consent development process
- Delivers information in digestible "chunks" over time and includes FAQs
- Serving up information via different media and video to accommodate different learning styles
- Offering supporting documents in layman's terms
- Provides review sessions

Arm clinicians with educational materials.

Many patients do not want to enroll in a sickle cell clinical trial where they consider the standard of care sub-par. To help clinicians, SC patients and nonmalignant diseased patients understand the importance of enrolling and staying in the sickle cell trials, Emmes works with patient advocacy groups, such as BMT CTN and CureSci to generate personalized IRB letters.

The personalized IRB letters can be targeted towards clinicians, allowing them to enhance their knowledge and effectively communicate the study details to their patients. Additionally, these letters can be created as informative handouts for clinicians to distribute to their patients. This approach aligns with the discovery that the majority of patients consider their healthcare provider as their preferred source of information regarding clinical trials.[7]

Assess and support patient readiness for gene therapy.

The CureSCi Patient Readiness and Resilience Working Group has published a report on its recommendations for assessing and underpinning patients' readiness for such a major treatment initiative.[8]

Recommendations include:

- Performing an institutional self-assessment of available psychological supports and resources
- Providing tailored, comprehensive education about gene therapy, starting 6-12 months prior to treatment
- Conducting a readiness and resilience assessment with patients in the form of a clinical interview (and possibly cognitive testing and validated questionnaires)

Retention

Make data reporting easy for patients.

Finding appropriate short-term endpoints in SCD still poses a challenge, and effectively documenting episodes of sickle pain can be complex.9 However, Emmes has the expertise to tackle this obstacle by simplifying patient reporting through the utilization of responsive user design in our reporting tool, Advantage eClinical ePRO. In addition, Emmes maintains robust partnerships with transplantation centers to thoroughly review patient reporting documents. By scheduling regular meetings with study coordinators, we are able to effectively monitor and ensure high patient retention throughout the duration of the study.

Furthermore, patients can report via modern web browsers from any tablet or smartphone, including their own devices. We partner with the CIBMTR Survey Research Group to develop an intuitive design that requires fewer clicks, combined with reminders and notifications can patient data reporting quick and straightforward.

Monitor sites closely.

SCD trials necessitate in-person visits, which can pose challenges for patients in terms of ongoing assessments due to travel logistics to the study site. However, Emmes has extensive experience incorporating a study protocol that enables non-local patients to conveniently utilize their local healthcare centers for routine visits, while also providing reimbursement for patients who must travel to the study site for infusions. This comprehensive approach may involve providing transportation to and from the clinic, offering childcare services at the clinic, minimizing travel requirements through meticulous study design, and even substituting scheduled visits with televisits. By leveraging the right technology platform, patients can conveniently attend visits remotely via a secure portal that also facilitates seamless documentation of the visit.

Moreover, Emmes incorporates a cutting-edge Global trace tracking system for patient specimens. This advanced technology empowers us to proactively identify patients who may be at risk of dropping out from the trial. In the event of a missed reporting milestone by a site, we swiftly reach out to the dedicated study coordinators to guarantee continuous patient involvement and dedication.

Consult with sites on their contact methods and their tracking system.

Sites may, for instance, need to gather more information from patients in their intake forms to make it easier to track them down in the future. Sites may also welcome help from your contract research partner in reaching participants who've completed the active portion of the study. Emmes had created tailored Patient Site Access questionnaires that specifically address the needs of sickle cell patients when determining the appropriate site. These questionnaires consider various factors such as the patient's identity, geographic location, and urban diversity.

Use technology to strengthen compliance, proactively identify potential issues and enhance engagement.

Patients may sometimes miss visits for various reasons. Emmes utilizes Advantage eClinical, which has the capability to flag any missed milestones, enabling investigators to quickly reach out to their patients and to effectively identify potential problems and risks at an early stage. Advantage eClinical, has the capabilities to easily send out personalized and automated email reminders to participants via cite investigators regarding their medication, visits, and study milestones. These reminders are essential for maintaining patient involvement and dedication to the study, leading to improved participant retention, and enabling seamless communication with both internal and external stakeholders.

Importance of Patient Advocacy Groups

Establishing strong relationships with advocacy groups is crucial. These groups offer invaluable insights throughout the clinical development process, addressing logistical challenges and ensuring smooth protocol implementation. For SCD studies, connecting with diverse patient support organizations is essential to gather feedback on study design and patient populations. These groups play a pivotal role in engaging patients and assisting in investigator identification. Advocacy groups also host forums that shed light on patients' primary challenges and concerns, serving as a crucial resource for patient engagement and investigator identification

Activities that have been are effective in establishing connections with patients through advocacy groups include:

Stress the importance of continued data collection with patients.

Patients can only begin to appreciate this when they understand the objective of the trial, how the data will be collected and used and ultimately the benefit and impact that it will have on their community.

Share study results when appropriate.

Study participants often express an interest in seeing study results beyond their own trial experience. Many research institutes share de-identified information (via a website or email blast) with these study results to the patients as both a courtesy to participants and a way to keep them engaged.

Support clinicians in building a personal relationship with the patient.

CureSCi research revealed that this is the most effective way to retain patients in a long-term study.

Where appropriate, involve the patient's family.

Given the need for family support over the course of gene therapy and HSCT trials, it is important to ensure that family members and care givers understand the process and are ready, willing, and able to help the patient cope.

Offer support from mental health professionals.

The decision to participate in an advanced therapy trial is a major life decision for prospective participants, with ramifications for their health, their fertility, their personal and professional lives, and even their identity. Patients may need help working through their concerns, and having mental health professionals available either on site or via telehealth can help them make a decision they'll be comfortable with.

Devise a strategic communication plan for reaching patients where they are.

A multi-pronged approach will include outreach via the appropriate social media, patient groups, and clinicians. For one trial, Emmes used a combination of approaches that included promoting details of the study via CureSCi's account, sending an email from CureSCi through the Sickle Cell Disease Association of America (SDCAA) and Sickle Cell Community Consortium (SCCC), and devoting a trial-specific webpage to the study on the CureSCi website.

Conclusion

Recruiting and retaining patients in advanced therapy trials in any indication requires a well-developed strategy and the support of an experienced partner. As the challenges are magnified in SCD research studies, Sponsors are well advised to explore the mindset and situation of patients so that they can successfully apply a patient-centered approach. Reaching, educating, and engaging SCD patients over the long term will require an investment, ingenuity, and persistence.

The research community must remember that for SCD patients, while this is a hopeful time, the decision to receive an experimental therapy is an extraordinarily difficult decision. And, in some cases, it is made against a background of disappointment or even distrust. As one patient input panel member noted recently, "I am excited about science and progress, but am frustrated that it is a dangling carrot to people who cannot get decent care. If people can't get the best care today, how can we hope to convince them they can be cured?"

The situation calls for understanding, applying a patient-centered approach, and adopting best practices-including technology that integrates seamlessly into the everyday life of patients.

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