Motivations and decision-making of adult sickle cell patients in high-risk clinical research

Hae Lin Cho, BA1, Scott YH Kim, MD PhD1, Courtney Fitzhugh, MD2, Matthew Hsieh, MD3, John Tisdale, MD3, Christine Grady, RN PhD1

1Department of Bioethics, Clinical Center, National Institutes of Health
2Laboratory of Early Sickle Mortality Prevention, National Heart Lung Blood Institute, National Institutes of Health
3Cellular and Molecular Therapeutics Laboratory, National Heart Lung Blood Institute, National Institutes of Health

Abstract

Background—Potentially curative but high-risk trials of gene therapy or stem cell transplantation (PBSCT) for Sickle Cell Disease (SCD) pose new opportunities for adults with SCD, many of whom experience significant disease burden and complications with few treatment options, as well as stigma and disparities in care. We explored motivations and decision-making processes of enrollees and decliners of such trials.

Methods—Semi-structured interviews with a purposive sample of 20 enrollees and 6 decliners. Interviews explored participants’ SCD experiences, motivations and decision-making about trial participation, understanding of research-related information, and retrospective reflections. Interviews were analyzed with content analysis.

Results—Most identified the purpose of research, risks, and uncertainties of participation. Both enrollees and decliners described deliberative weighing of study risks and potential benefits (especially the prospect of a cure), with heavy factoring of their SCD status, experiences, and

Corresponding author: Christine Grady, Department of Bioethics, NIH Clinical Center, Building 10/IC118, Bethesda, MD 20892, 301-496-2429, cgrady@nih.gov.

Author contributions:
Hae Lin Cho, Scott Kim, and Christine Grady made substantial contributions to the conception or design of the study;
All authors (HC, SK, CF, MH, JT, CG) made substantial contributions to the acquisition, analysis, or interpretation of data;
Hae Lin Cho initially drafted the manuscript, all authors (HC, SK, CF, MH, JT, CG) made critical revisions
All authors (HC, SK, CF, MH, JT, CG) approved the final version;
All authors (HC, SK, CF, MH, JT, CG) agree to be accountable for the accuracy and integrity of the work.

Author disclosures:
All authors are employees of the National Institutes of Health (NIH)
All authors Hae Lin Cho, Scott YH Kim, Courtney Fitzhugh, Matthew Hsieh, John Tisdale, and Christine Grady have no other conflicts to disclose

Disclaimer
The views expressed are those of the authors and do not necessarily reflect those of the NIH or the U.S. Department of Health and Human Services.

Publisher’s Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
desire for a better life. Despite the influence of spirituality/religion and support of family and friends, all described the decision about participation as their own. In some patients, the primary outcome status defined by the trial did not match the patients’ perceived outcomes. Patients with negative experiences expressed a desire for greater emphasis on risks and possible outcomes during informed consent.

Conclusions—This cohort of adults with SCD were thoughtfully deliberative in their decisions about gene therapy or PBSCT trials. Future participants’ decision-making may be enhanced by emphasizing that ‘successful’ scientific outcomes can still involve complications or symptoms and be facilitated by referrals to former research participants and anticipatory discussions.

Keywords
motivations; understanding; informed consent; gene therapy; stem cell transplantation; sickle cell disease

Introduction

Clinical trials testing potentially curative but high-risk interventions for sickle cell disease (SCD), such as gene therapy or stem cell transplantation, pose novel and promising opportunities for adults with SCD, for whom existing standard therapies suboptimally manage their disease. While high-risk trials are familiar in clinical research, the potentially curative nature of these trials, as well as public fear and excitement around gene therapy and transplantation, might affect patient understanding and motivations in ethically concerning ways, even influencing their informed consent.

Previous studies investigated perspectives about transplantation for pediatric patients, for whom transplantation is not considered research.¹,² Other studies examining informed consent or attitudes related to SCD clinical trials have investigated healthcare providers’ perspectives³ or barriers to pediatric trial access faced by patients with SCD.⁴ Very few studies have explored the perspectives of adults patients with SCD receiving transplantation,⁵ and fewer still the perspectives of adult research participants. Adults with SCD constitute a unique patient population: They face enormous illness burdens over many years, experience severe complications, lack curative treatments, and face considerable stigma.⁶ Moreover, SCD disproportionately affects persons who are black, who in the U.S. face significant barriers to accessing adequate healthcare and participating in clinical research.⁷–⁹ Religion and spirituality also play a significant role in the lives of many patients with SCD.¹⁰–¹² Knowledge of how these factors influence patients with SCD might help researchers be sensitive to patient’s concerns and experiences and facilitate informed consent.

Given scarce previous research regarding adult SCD patients’ perspectives about research and significant ethical questions associated with enrollment and participation in potentially curative but high risk clinical trials, we conducted semi-structured interviews with patients with SCD who had already made a decision about participation in autologous gene therapy or allogeneic peripheral blood stem cell transplant (PBSCT) trials. Herein, we describe
their reported motivations, decision-making processes, understanding of research, and retrospective reflections.

Methods

Design

This was a qualitative descriptive in-depth interview study of the motivations, decision-making processes and understanding of adults with SCD who had already decided to participate or not to participate in a PBSCT or gene therapy clinical trial.

Participants

We interviewed English-speaking adults (18 years or older) with SCD enrolled in research at the National Heart, Lung, and Blood Disease Institute (NHLBI), who already had made a decision about participation in a NHLBI autologous gene therapy and/or an allogeneic PBSCT trial. Participants were at multiple stages in the trial, ranging from soon after giving informed consent or deciding against participation, to several years after these decisions.

At least one interviewer (HC, SK, or CG) attended weekly NHLBI research team meetings to review patients scheduled to visit the National Institutes of Health (NIH) Clinical Center. The NHLBI team identified patients who had agreed to participate in either the gene therapy or PBSCT trials and had successful outcomes; patients who had agreed to participate in the trials but did not have successful gene therapy or PBSCT; and patients who had declined participation in these intervention trials. During patients’ visits to the NIH Clinical Center, interviewers explained the interview study’s purpose and invited eligible patients to participate; participants not at the Clinical Center were invited to participate via email and/or phone. Of a total of 33 patients approached for this interview study, 26 agreed and completed an interview (21 in person; 5 by telephone); two agreed to be interviewed but were lost to follow-up; one patient declined; four patients did not respond to recruitment emails or calls.

Procedure

Semi-structured interviews followed an interview guide modeled after the Conditional Probe Interview designed by Kim et al. 2009. Patients were asked broad open-ended ‘stem questions’ about: (1) their SCD experiences, (2) motivations and decision-making about participation in gene therapy or PBSCT trials, (3) understanding of research-related information, and (4) retrospective reflections if they had already either received the experimental treatment or had declined participation. Interviewers further explored patients’ responses with specific probes. For example, if a patient responded that her family had a major role in her decision-making, the interviewer further probed with questions about different roles played by individual family members. Questions were used during interviews to probe patient’s responses and capture unanticipated and spontaneous themes that emerged.

Interviews were conducted either in person at the NIH Clinical Center or by phone for patient convenience. Interviews lasted an average of 40 minutes (range 20 to 76 minutes).
Two interviewers conducted most interviews, with a primary interviewer (HC, CG, SK) asking questions and a second interviewer asking follow-up questions as appropriate. With participants’ permission, all interviews were audio recorded and transcribed.

**Data Analysis**

Interviews were transcribed verbatim and analyzed using conventional content analysis. Each transcript was independently reviewed by two of three interviewers (HC, SK, CG) who identified themes under each of the interview domains (e.g. experience with SCD, understanding of the research, decision-making processes etc.). Using the identified themes and the interview guide, one interviewer (HC) developed a coding framework based on initial review of all transcripts. The research team then reviewed, discussed, and revised the coding framework. Two researchers independently coded each transcript; disagreements (7.0% of all possible codes) were resolved via discussion among three interviewers. We established the trustworthiness and credibility of our data through source triangulation (participants who decided for and those who decided against participation in the clinical trial) and analyst triangulation (three independent coders). Independent coding and discussion of findings with all co-authors helped reduce potential bias.

**Human research participant protection**

The institutional review board (IRB) of the NIH Intramural Program approved the study. Patients provided written informed consent. Patients received a $50 gift card for participation.

**Results**

**Sample characteristics**

Twenty-six adults with SCD completed interviews. Of these, 62% were female, 88% African or African-American, and 54% born in the U.S. (table 2). Nearly all had at least a high school education (88%), and about half (54%) reported inadequate income.

Three-fourths of this cohort (n=20) had agreed to participate in either a PBSCT or gene therapy trial; 13 of whom had already received PBSCT or gene therapy, and were several months to several years post-treatment; and seven who had agreed to participate in either a PBSCT or gene therapy trial but had not yet received experimental treatment. Six participants who agreed to an interview had declined participation in PBSCT or gene therapy trials.

Of the 13 patients who were interviewed after they had received their intervention (PBSCT or gene therapy), nine had complete responses to the experimental treatment, defined as normalization of hemoglobin (Hb) level and type. Two of the 13 patients had partial responses, two others did not respond to the experimental treatment, in that their SCD returned. Five patients, including four of the five who had complete responses to the experimental treatment, experienced significant complications, such as development of leukemia, brain hemorrhage, and medication reactions that resulted in near-death experiences.
MOTIVATIONS AND DECISION-MAKING

Experiences with sickle cell disease

Nearly all those interviewed described significant ongoing challenges due to SCD, including severe pain resulting in frequent hospitalizations and transfusions, near death experiences, and other SCD health complications, such as osteonecrosis, pulmonary hypertension, leg ulcers, and organ damage (table 3). Patients also described functional limitations due to SCD restricting their ability to develop and maintain relationships, work, go to school, and/or travel, summarized by one patient as “being imprisoned in your own body” (Participant #5, pre half matched transplant).

The majority reported having experienced negative interactions with healthcare providers, so much so that some described trying to avoid hospitals even during significant pain crises. During hospitalizations, patients encountered healthcare providers with poor understanding of SCD, stigmatization as ‘drug seekers,’ inadequate pain medication, and long waits in Emergency Rooms that resulted in delays in getting care (table 3). Several described perceived discrimination due to their race. Around half described progressive worsening of their SCD symptoms prior to seeking out NIH.

Decision-making process

Most patients described performing a personal risk-benefit calculus when deciding about participation, factoring their satisfaction or dissatisfaction with their current quality of life in relation to the perceived risks and uncertainties of the trial. Most considered themselves optimistic but largely careful and cautious in decision-making or “cautious risk-takers” (Decliner #5), even almost all of the decliners described themselves as somewhat risk-taking.

All patients who decided to enroll cited the intolerability of their current SCD symptoms and/or hope for a better future without SCD, conveying some version of comparing “what [they] wanted out of life and where [they] presently [were] in life” (Participant #10, post half matched transplant) (table 4). While visions varied of what a better life without SCD might be like, many described escaping SCD pain and overcoming its functional limitations. Patients reported wanting to feel less of a burden on family members, be alive and more present for their children, finish school, and maintain a job. Some ruminated on specific life goals, including going to medical school or having a child. Several explicitly cited lack of other treatment options, or being inadequately managed on, or unable to gain access to, hydroxyurea or blood transfusions. A few patients said that living with SCD was as risky as experimental treatment, as articulated by one gene therapy patient, “I would say, [research is] no more risk than living with sickle cell. I feel like living with sickle cell is more of a risk” (#4, post gene therapy).

For the six patients who declined enrollment in a PBSCT or gene therapy trial, the calculus tilted in favor of not participating because they described their current status as not bad enough to justify the trial risks (table 4). Some cited fear of additional risks due to their age or in a couple of cases the lack of a fully matched donor. All but one who declined emphasized that they did not think their SCD was bad enough to merit the risks of the trial.
Regardless of the enrollment decision, several patients described the strong allure of a possible cure or living without SCD. For one patient whose SCD had resulted in several near-death experiences, the mere possibility of a cure was sufficient motivation to enroll:

   Interviewer: …did you feel like you were taking a big risk?

   Patient: I didn’t care. I didn’t think about none of the risks, and I just, just thought, this might help me. I need to do this, and I didn’t think twice about it cause when I seen that possible cure, I was like, oh Lord, please. (Participant #2, post full matched PBSCT)

Although equally tempted by the possibility of cure, several patients who declined participation stated that they ultimately felt that a successful transplant would not address all of their SCD complications.

Although more than half of the patients referred to altruistic motivations during the interview, none reported altruism as their primary motivation. Five who declined due to the risks also explicitly recognized the benefits of research for future patients. Contributing to science and/or benefiting future patients with SCD was noted by many as an important but secondary motivation, with the primary goal of possible therapeutic benefit.

The roles of families and other patients

In analyzing personal risks and benefits, patients often relied on families and other patients for support and/or information. Patients reported that families usually provided moral support and reassurance, volunteered to be tested as potential donors and said “they would support me in whatever I decided to do (Decliner #2).” Approximately a third of patients reported that some family members, although supportive, worried about the trial or pleaded caution, fearing research-related risks or general mistrust of research and the government.

Over half of those interviewed reported that before deciding about participation, they spoke with someone who had already received PBSCT or gene therapy, including some who had not done well or had experienced complications during the trial. In addition, some patients described how personal experiences with friends who had done well or poorly on research studies affected their views on participation. Four of the six decliners either knew personally, or had spoken to, someone who had not done well on the study.

All but one of those who reported that family or other patients raised concerns about the trial, followed their own risk-benefit calculus over family or other patients’ influence or concerns.

Religious and spiritual faith

Nearly all self-identified as religious and/or spiritual. Most described their faith as a personal belief in God, a few described their relationship with a church community and/or religious leader. (table 5).

About one third said their faith played no role in their decision-making. Those whose religion and/or spirituality played a role most often stated that their beliefs and prayers to God had a general supportive role. For some, this belief took the form of “God’s not going
to give me anything that I can’t handle” (Participant #9, post gene therapy). Others saw the study as a God-given opportunity:

“… The one thing I knew was that God was going to make this something positive, and it might not be for me per say, but on the long-term, it was going to be something great … it’s going to teach them how to do it [gene therapy].”

( Participant #1, post gene therapy)

A few patients said praying to God would help them through the trial in various ways. One patient awaiting transplant, for example, stated, “I believe that He will answer my prayer, that none of those side effects or that none of that bad things will happen to me” and explained how her religion helped her cope with the uncertainties of the trial:

I know that there are risks with this operation. I know there will be things that will happen, and my way of dealing with it is, I know if it comes and when it comes my God will get me through it and my faith will get me through it. He will um – the only way I can be strong is to believe that He is gonna not – it’s not going to be as bad as it could be. (Participant #16, pre half matched transplant)

Another explained that her religious language reflected her confidence in the science: “I am hoping for a miracle, and while I use those words, I feel as if from a scientific standpoint, it still comes from Christ because he was able to provide that knowledge to man, to help man come up with this science, and help man manipulate this science for good benefit for people. So even though I may use the word miracle, it’s really I’m saying: sickle cell is cured by gene therapy transplant” (Participant #6, pre gene therapy).

UNDERSTANDING

The majority clearly described the purpose of research as scientific knowledge and/or benefiting future patients. A small number described a dual purpose of research: scientific knowledge/future benefits and direct benefit to participants. The remaining responses were less clear but did not indicate misunderstanding of research.

All patients expressed awareness that PBSCT and gene therapy studies carried side effects and risks, nearly all named at least one risk of the experimental treatment (e.g., death, cancer, graft versus host disease, etc.). Almost all acknowledged that the treatment might not work. Patients named a variety of concerns when asked to describe their main worries, including unsuccessful response to experimental treatment; death; pain, complications, other research procedure burdens; and potential long-term side effects like cancer.

Three of those who had enrolled but not yet received the experimental treatment, said they were not worried. One explained that he believed in the power of positivity, the others explained that a relatively good health status and faith in science gave them confidence in their treatment outcome.

RETROSPECTIVE REFLECTIONS

The majority of those who had completed the clinical trial or who had declined said that they had no regrets and would make the same decision again. Of note, in over half of
the 13 who had already completed the experimental treatment, patients’ own assessment of whether the trial’s outcome was a success differed from the “objective” response (i.e., protocol defined ‘complete response’). Similarly, whether or not they felt they had made a good decision did not always correlate with trial outcome (table 6). For example, one patient whose donor transplant did not engraft said she had made a good decision and would do PBSCT again because she perceived no harm to her health and had learned more about herself. Conversely, a small number of patients, even some with a complete response to the experimental treatment, felt conflicted or even angry about participation. Mixed or negative emotions almost always stemmed from unanticipated negative experiences, regardless of objective outcome. These unanticipated experiences ranged from serious adverse events to ongoing SCD symptoms, and in one interesting case, a sense of loss of SCD identity.

Two patients who had experienced serious complications stated unambiguously that they would not participate if they could decide again. Interestingly, both still said their decision was good because it allowed them to contribute to science (table 6). These patients wanted more information from researchers, as did one who expressed anger about experiencing serious complications she felt unprepared for, and another who was still experiencing pain despite a complete response to PBSCT. All four stressed that researchers should do more to emphasize potential negative outcomes of the experimental treatments; for example, informing patients that they might experience ongoing SCD symptoms such as pain or serious side effects even after a successful transplant:

… [the researchers] need to be more transparent with what they’re getting these patients involved with. It’s not just about giving people hope and yeah we can give you transplant. Yeah, it’s a great thing. It’s a great option, but be truthful with all the cons. Don’t just make it all rosy and, you know? There’s a downside to everything. Paint all the downsides. Don’t just give people hope and let it seem like, oh once your transplant’s in, and it’s successful, that’s it... the transplant can be successful, but the side effects … can be serious. They can, they can kill you! (Participant #18, post half matched transplant)

However, one of these patients noted researchers “tried their best” (Participant #17, post half matched transplant) to inform her, and the others all acknowledged that researchers may have informed them about the risks, but that risks needed more emphasis:

I just feel like maybe they need to let people know that it’s not – maybe they did. Like I said, maybe they did say it, and I wasn’t listening, but I think they have to emphasize on it... (Participant #7, post half matched transplant)

The majority of those who had received the experimental treatment said they felt the researchers prepared them adequately, although one emphasized the importance of also talking to patients who had been through the study and could share their experiences. All but one of the six patients who declined to participate in a trial felt that they had made a good decision.
Discussion

The advent of potentially curative but high-risk research interventions for adults with SCD presents decision-making challenges with implications for research participants’ informed consent and research experiences.

Our data provide insight into the decision-making processes, motivations, and understanding of adults with SCD considering gene therapy and PBSCT trials that may help research teams support patients making these decisions.

Personal and thoughtful risk-benefit assessment

Patients in our cohort each described thoughtful, personal risk-benefit analyses when deciding about enrollment, consisting of two major factors: (1) how severe or life-disruptive they perceived their SCD to be, and (2) their comfort level with the risks and uncertainty. Although variation in risk/uncertainty thresholds likely affected their analyses, most patients identified themselves as careful, cautious decision-makers, could name possible risks, and weighed them carefully when deciding about enrollment. Despite myriad influences from family, friends, religion and faith, and other patients, our patients were clear that these supported their decision but that they made their own enrollment decision. Patients who decided to enroll said the risks were worth the chance of a better life, often referring to a turning point in which their SCD symptoms and functional limitations worsened to the point they felt they had no other option. Gallo et al.’s cohort of 7 adult transplant patients expressed similar hope for the possibility of a second chance in light of a downward spiral from SCD (JAN, 2019, p 3). In contrast, decliners in our cohort did not perceive their SCD to have reached a severity sufficient enough to take on the significant risks of the experimental treatments, and often cited factors (such as age and lack of fully matched donors) that increased the perceived riskiness of the trial.

Patients spoke about their SCD symptoms but also how SCD interfered with their life plans and social roles like participating in family activities; maintaining relationships with friends; and pursuing educational, career, or other life goals. Others cited avoiding transfusions and hospitalizations as motivating factors, citing their widely negative experiences with hospitals and with healthcare providers who seemed to not understand SCD.

Understanding factors that patients take into account when making decisions about high risk/high reward clinical research could help researchers to better assist potential participants during the informed consent process, for example, exploring patient perspectives about trade-offs and risks, and framing research-related information accordingly. While many studies have explored how adults with cancer make decisions about enrolling in early phase research, patients with SCD face unique and significant challenges related to the chronicity of their condition, relatively few available trials and treatments, and associated stigma, to name a few. Despite these differences, research decisions by the adults with SCD in this cohort were motivated by similar factors as cancer patients making research decisions, namely hope for therapeutic benefit, availability of other options, and lived experiences with disease. Although SCD is a non-malignant and chronic disease, these adults expressed a desire to be rid of it and were willing to accept risks to achieve that goal. Data suggest that cancer patients make relatively quick or immediate decisions about research participation and do not always carefully assess the risks and benefits of the
In contrast, our patients with SCD focused on risks and benefits and generally spent significant time, frequently months and sometimes years, thinking about research participation in a way that is similar to patients with other chronic disorders, although data are quite limited. Perhaps because patients with SCD generally are not facing imminent death, finding the “right time” to participate in research based on their disease severity and quality of life is important. Moreover, rather than weighing the risk of research against death, patients with SCD deciding about PBSCT or gene therapy consider the life they could live with SCD (for better or worse) and the life they could live without it.

Complicating the risk-benefit assessment is that transplantation or gene therapy technically offer the hope of a cure for SCD unlike many clinical trials, including most cancer trials. Although the consent forms for these clinical trials stress that these are research interventions aiming to make transplantation and gene therapy safer and more effective, they also recognize that the participants’ sickle cell disease could be cured, while explicitly cautioning “this cannot be guaranteed and your disease may return.” Patients’ understanding and expectations of a “cure” may differ from how researchers define a successful outcome. Informing patients about the meaning and limitations of a successful response to experimental treatment – or “cure” – could prevent potential misunderstanding and help patients make informed risk-benefit assessments.

**Motivation and Understanding of research**

Desire for therapeutic benefit was the primary motivation of our patients who chose to enroll in clinical research, consistent with prior studies on patients’ decision-making for clinical research. Altruism explicitly played a secondary role for around half of our participants, but by itself was an insufficient motivation. Although desire for benefit can raise concerns about therapeutic misconceptions – when patients misunderstand the purpose of research as individualized treatment – the majority of this cohort, while hoping for therapeutic benefit, clearly described the purpose of research as benefit for future patients, several others said the purpose is to benefit both current and future patients.

**Retrospective reflections**

The majority of this cohort said that they had made a good decision. This finding is similar to those of Gallo and colleagues who reported that the seven transplant patients they interviewed were satisfied with their decision, even though two of them had unsuccessful transplants. Most in our cohort said they were adequately informed by researchers, but the few who experienced serious complications, even those with successful engraftment or reduction in SCD symptoms, said they would have liked additional warnings with emphasis on the possibility of significant adverse events and ongoing SCD symptoms, even when treatment is “successful.” Interestingly, these patients acknowledged that they might have forgotten, selectively heard, or misremembered information provided by researchers. A couple of patients recognized that they had incorrectly believed that responding to the experimental treatment would mean not having to experience any SCD symptoms or complications.
Our data suggest that patients’ motivations and expectations influence retrospective reflections almost as much as the actual outcome of experimental treatment. Informing patients about what a successful response to experimental treatment – or “cure” – means in terms of symptoms and quality of life might help mitigate potential misunderstandings and help patients make informed risk-benefit assessments.

It can be challenging for both patients and researchers to maintain hope in the face of knowledge about research-related risks and potentially unsuccessful outcomes. Similar findings in other patient populations have prompted researchers to propose incorporating anticipatory guidance in informed consent, giving patients time to process “what-if” scenarios with their research team and loved ones. Speaking with other patients who have completed experimental treatments, both with good outcomes and poor outcomes, could also help patients understand various possible outcomes of such research, including uncommon risks.

Limitations

Our study has limitations. First, we interviewed research participants from one research institution who may not be representative of all SCD adults considering participation in high stakes research. Second, our cohort was small and we interviewed patients at various stages of their research participation. Retrospective biases might affect the recollection and/or perspective of patients who had already received experimental treatment. Our data, however, did not suggest that post-treatment patients have an appreciably different perspective on research participation decisions than patients who had not yet received experimental treatments.

Conclusion

The curative potential of PBSCT and gene therapy, even in the context of a clinical trial, and participants’ hope for therapeutic benefit likely influence their decision-making and retrospective reflections about participating in a clinical trial. Yet, despite this, our cohort of adults with SCD described awareness of the purpose of research involving PBSCT or gene therapy, and the associated risks and the uncertainties of the outcome. All described making an enrollment decision (for or against participation) through a careful and thoughtful individualized risk-benefit analysis based on their assessment of life with SCD and their understanding of the research. Some patients, mainly those who experienced complications, asked for researchers to give more emphasis to possible side effects and complications even when experimental treatment itself is successful. Referring patients to talk with former research participants, including those who experienced unanticipated outcomes, clarifying what patients can realistically expect from successful response to experimental interventions, and engaging in anticipatory discussions during the consent process could help address these concerns.

Acknowledgements

This work was funded by the National Institutes of Health (NIH) Clinical Center, Department of Bioethics. We greatly appreciate the patients who volunteered to be interviewed as part of this study.
Funding

Funding for this project was provided by the Department of Bioethics in the NIH Intramural Research program

References

1. Khemani K, Ross D, Sinha C, Haigh A, Bakshi N, Krishnamurti L. Experiences and Decision Making in Hematopoietic Stem Cell Transplant in Sickle Cell Disease: Patients’ and Caregivers’ Perspectives. Biol Blood Marrow Transplant. 2018;24(5):1041–1048. doi:10.1016/j.bbmt.2017.11.018 [PubMed: 29196076]

2. Sullivan KM, Horwitz M, Osunkwo I, Shah N, Strouse JJ. Shared Decision-Making in Hematopoietic Stem Cell Transplantation for Sickle Cell Disease. Biol Blood Marrow Transplant. 2018;24(5):883–884. doi:10.1016/j.bbmt.2018.04.001 [PubMed: 29649619]

3. Raj M, Choi SW, Platt J. A qualitative exploration of the informed consent process in hematopoietic cell transplantation clinical research and opportunities for improvement. Bone Marrow Transplant. 2017;52(2):292–298. doi:10.1038/bmt.2016.252 [PubMed: 27748736]

4. Stevens EM, Patterson CA, Li YB, Smith-Whitley K, Barakat LP. Mistrust of Pediatric Sickle Cell Disease Clinical Trials Research. Am J Prev Med. 2016;51(1 Suppl 1):S78–S86. doi:10.1016/j.amepre.2016.01.024 [PubMed: 27320470]

5. Gallo AM, Patil CL, Knafli KA, Angst DA, Rondelli D, Saraf SL. The experience of adults with sickle cell disease and their HLA-matched adult sibling donors after allogeneic hematopoietic stem cell transplantation. J Adv Nurs. 2019. doi:10.1111/jan.14152

6. Jenerette CM, Brewer C. Health-Related Stigma in Young Adults With Sickle Cell Disease. J Natl Med Assoc. 2010;102(11):1050–1055. [PubMed: 21141294]

7. Luebbert R, Perez A. Barriers to Clinical Research Participation Among African Americans. J Transcult Nurs. 2016;27(5):456–463. doi:10.1177/1043659615575578 [PubMed: 25754929]

8. Chen J, Vargas-Bustamante A, Mortensen K, Ortega AN. Racial and Ethnic Disparities in Health Care Access and Utilization Under the Affordable Care Act. Med Care. 2016;54(2):140–146. doi:10.1097/MLR.0000000000000467 [PubMed: 26595227]

9. CDC. Data and Statistics | Sickle Cell Disease | NCBDDD | CDC. Centers for Disease Control and Prevention. https://www.cdc.gov/ncbddd/sicklecell/data.html. Published August 31, 2016. Accessed May 2, 2018.

10. Cooper-Effa M, Blount W, Kaslow N, Rothenberg R, Eckman J. Role of spirituality in patients with sickle cell disease. J Am Board Fam Pract. 2001;14(2):116–122. [PubMed: 11314918]

11. Harrison MO, Edwards CL, Koenig HG, Bosworth HB, Decastro L, Wood M. Spirituality/spirituality and pain in patients with sickle cell disease. J Nerv Ment Dis. 2005;193(4):250–257. [PubMed: 15805821]

12. Adegbola M. Spirituality, Self-Efficacy, and Quality of Life among Adults with Sickle Cell Disease. South Online J Nurs Res. 2011;11(1). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3137798/. Accessed July 23, 2018.

13. Kim SYH, Schrock L, Wilson RM, et al. An approach to evaluating the therapeutic misconception. IRB. 2009;31(5):7–14.

14. Hsieh H, Shannon SE. Three Approaches to Qualitative Content Analysis. Qualitative Health Research, 2005; 15 (9): 1277–1288 [PubMed: 16204405]

15. Patton MQ Enhancing the Quality and Credibility of Qualitative Analysis. HSR: Health Services Research 1999; 34(5): 1189–1208. [PubMed: 10591279]

16. Hsieh MM, Fitzhugh CD, Weitzel RP, et al. Nonmyeloablative HLA-matched sibling allogeneic hematopoietic stem cell transplantation for severe sickle cell phenotype. JAMA. 2014;312(1):48–56. doi:10.1001/jama.2014.7192 [PubMed: 25058217]

17. Nielsen ZE, Berthelsen CB. Cancer patients’ perceptions of factors influencing their decisions on participation in clinical drug trials: A qualitative meta-synthesis. J Clin Nurs. 2019;28(13–14):2443–2461. doi:10.1111/jocn.14785 [PubMed: 30673153]

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2022 January 04.
18. Weinfurt KP, Sulmasy DP, Schulman KA, Meropol NJ. Patient Expectations of Benefit from Phase I Clinical Trials: Linguistic Considerations in Diagnosing a Therapeutic Misconception. Theor Med Bioeth. 2003;24(4):329–344. doi:10.1023/A:1026072409595 [PubMed: 14620488]

19. Jansen LA, Mahadevan D, Appelbaum PS, et al. Perceptions of control and unrealistic optimism in early-phase cancer trials. J Med Ethics. 8 2017:medethics-2016–103724. doi:10.1136/medethics-2016-103724

20. Dellson P, Nilsson K, Jernström H, Carlsson C. Patients’ reasoning regarding the decision to participate in clinical cancer trials: An interview study. Trials. 2018; 19. doi:10.1186/s13063-018-2916-9.

21. Ulrich CM, Ratcliffe SJ, Wallen GR, Zhou QP, Knafli K, Grady C. Cancer clinical trial participants' assessment of risk and benefit. AJOB Empir Bioeth. 2016;7(1):8–16 [PubMed: 26709381]

22. Lowton K Trials and tribulations: Understanding motivations for clinical research participation amongst adults with cystic fibrosis. Social Science and Medicine.2005; 61: 1854–1865 [PubMed: 15913858]

23. Peay HL, Scharff H, Tibben A, et al. “Watching time tick by…”: Decision making for Duchenne muscular dystrophy trials. Contemp Clin Trials. 2016; 46:1–6. doi:10.1016/j.cct.2015.11.006 [PubMed: 26546066]

24. Turriff A, Blain D, Similuk M, et al. Motivations and Decision-Making Processes of Men with X-linked Retinoschisis Considering Participation in an Ocular Gene Therapy Trial. Am J Ophthalmol. 3 2019. doi:10.1016/j.ajo.2019.03.009

25. Benz EJ, Mondoro TH, Gibbons GH. accelerating The Science of SCD Therapies-Is a Cure Possible? JAMA. 8 2019. doi:10.1001/jama.2019.11419

26. Lapook J Could gene therapy cure sickle cell anemia? CBS News. https://www.cbsnews.com/news/could-gene-therapy-cure-sickle-cell-anemia-60-minutes/. Published March 10, 2019. Accessed June 14, 2019.

27. Rennie S, Siedner M, Tucker JD, Moodley K. The ethics of talking about ‘HIV cure.’ BMC Med Ethics. 2015;16. doi:10.1186/s12910-015-0013-0

28. Appelbaum PS, Roth LH, Lidz C. The therapeutic misconception: Informed consent in psychiatric research. Int J Law Psychiatry. 1982;5(3–4):319–329. doi:10.1016/0160-2527(82)90026-7 [PubMed: 6135666]
Box 1.

Description of gene therapy and peripheral blood stem cell transplant trials

The National Heart, Lung and Blood Institute (NHLBI) conducts various clinical trials on sickle cell disease (SCD). Adult patients in our interview study made decisions about participation in an NHLBI gene therapy and/or peripheral blood stem cell transplantation (PBSCT) study.

- **Gene therapy**: SCD is caused by a mutation in the *HBB* gene, which is responsible for the production of hemoglobin beta. This phase 1 study ([http://clinicaltrials.gov: NCT02140554](http://clinicaltrials.gov: NCT02140554)) aims to use an experimental procedure called gene transfer, in which a corrected copy of the *HBB* gene is transferred via modified HIV vector into a participant’s own stem cells. After conditioning with chemotherapy, participants receive their own gene-modified stem cells through autologous transplantation. Since the study started recruiting patients in 2014, it has received national media attention for its success.27

- **PBSCT**: Bone marrow (BMT) or peripheral blood stem cell transplantation (PBSCT) has generally been performed in children younger than 16 years with SCD because the procedure carries higher risk for adults. Several NHLBI studies are trying to expand transplantation to adults (18 years or older) by using experimental non-myeloblastic conditioning regimens. Instead of high-dose chemotherapy, this regimen involves low-dose radiation and immunosuppressive drugs. Participants in these studies can have a full-match donor ([http://clinicaltrials.gov: NCT02105766, NCT00061568](http://clinicaltrials.gov: NCT02105766,NCT00061568)) or a partial/half-match donor ([http://clinicaltrials.gov: NCT03077542, NCT00977691](http://clinicaltrials.gov: NCT03077542,NCT00977691)), the latter of which is thought to have a higher risk of complications.
Highlights

- Adults with SCD correctly identified research purpose, risks, and uncertainties of gene therapy or stem cell transplantation (PBSCT) trials
- Patients engaged in deliberative, individualized weighing of study risks and potential benefits in light of their SCD experiences
- Family, friends, and religion played a supportive but not decisive role.
- Patients’ subjective experiences did not always coincide with objective trial outcomes
Table 1

Interview Guide: Open-ended Stem Questions

| Experience with SCD                                                                 |
|-------------------------------------------------------------------------------------|
| Could you tell me about what your experience with SCD has been like?                |
| When you went to the hospital, what was that experience like?                       |
| How did you first learn about the NIH?                                              |

| Decision-making process                                                             |
|-------------------------------------------------------------------------------------|
| Could you tell me about how you decided to (not) participate in the trial?           |
| What was your thought process?                                                       |
| Would you say that the decision was a hard or an easy one, and why?                  |
| What role, if any, did your family have in your decision-making?                     |
| Did you speak with any other patients who had gone through the gene therapy/transplant? |
| Would you consider yourself religious and/or spiritual? If so, what role did your faith, if any, have in your decision-making? |

| Hopes/Fears                                                                           |
|-------------------------------------------------------------------------------------|
| What are/were you hoping will happen from being in the study?                        |
| What are/were you most worried about happening to you?                                |

| Knowledge/Understanding                                                               |
|-------------------------------------------------------------------------------------|
| What is your understanding of why the researchers are doing this study?             |
| What is your understanding of the information in the informed consent form?         |

| Retrospective reflections                                                             |
|-------------------------------------------------------------------------------------|
| What happened since you received the transplant/gene therapy?                       |
| How was your experience compared to what you thought or hoped might happen?         |
| Do you think it was a good or bad decision to join the trial?                        |
| What, if anything, do you think researchers could be doing better to prepare patients? |

*BioBlood Marrow Transplant. Author manuscript; available in PMC 2022 January 04.*
| Table 2                                                                 |
|------------------------------------------------------------------------|
| **Participant characteristics (N=26)**                                |
| **Mean age (SD)**                                                     | 39.7 (11.3) |
| **Gender**                                                            |
| Male                                                                  | 10          |
| Female                                                                | 16          |
| **Race**                                                              |
| Black/African American                                                | 23          |
| White/Caucasian                                                       | 1           |
| Asian/Asian American                                                  | 1           |
| Mixed/Other                                                           | 1           |
| **Birthplace**                                                        |
| U.S.                                                                  | 14          |
| Outside the U.S.                                                      | 11          |
| **Education**                                                         |
| Less than high school                                                 | 2           |
| High school                                                           | 19          |
| College or some college                                               | 3           |
| Graduate school                                                       | 1           |
| **Religious Preference**                                              |
| Protestant/other Christian                                           | 18          |
| Catholic                                                              | 5           |
| None/not religious                                                    | 3           |
| **Health Insurance**                                                  |
| Medicare/Medicaid                                                     | 13          |
| Current or former employer                                           | 4           |
| Plan fully paid for by you or family                                 | 1           |
| No insurance                                                          | 1           |
| Multiple/Other                                                        | 6           |
| **Income**                                                            |
| Some money left over                                                  | 4           |
| Just enough money                                                     | 7           |
| Not enough money                                                      | 14          |
| **Phase of trial**                                                    |
| Pre-transplant                                                        | 7           |
| Half-matched transplant                                               | 4           |
| Gene therapy                                                          | 3           |
| Post-transplant                                                       | 13          |
| Full-matched transplant                                               | 4           |
| Half-matched transplant                                               | 5           |
| Gene therapy                                                          | 4           |
| Decline | 6 |

* This patient was the only patient to identify as Hispanic our sample.

† Total does not add to up 26 because one patient did not fully respond to demographic information.
Table 3.

Experience with Sickle Cell Disease (SCD) N = 26

| Experience with SCD has been like?                          | Count |
|-------------------------------------------------------------|-------|
| Severe pain, frequent hospitalizations and transfusions     | 13    |
| Functional limitations                                      | 13    |
| Other SCD complications (e.g., osteoporosis, clots)         | 8     |
| Near death experiences                                     | 4     |

| When you went to the hospital, what was that experience like? | Count |
|--------------------------------------------------------------|-------|
| Healthcare providers with poor understanding of SCD           | 14    |
| Stigmatization as “drug seeking”                             | 9     |
| Long waits/delays in the hospital                            | 6     |
| Understanding the attitudes of healthcare providers          | 4     |
| Discrimination due to minority status                        | 4     |

| How did you first learn about the NIH?                       | Count |
|--------------------------------------------------------------|-------|
| Referral from an outside physician                           | 12    |
| Friend/family member                                         | 5     |
| Circumstance (e.g., happening on an advertisement)           | 5     |
| Self-research                                                | 4     |
### Table 4.
Representative quotes of patients’ motivations and enrollment decision-making

| Participants | Hope for a better future | No other option |
|--------------|--------------------------|-----------------|
|              | ...I had to like put, you know, a lot of stuff on hold in my life, and I feel like this, this protocol um, this opportunity just, you know, will give me a chance for a better life. (Participant #15, post half matched transplant) | I realized if I was to become somebody that I wanted to be, I would have to get rid of this crutch. Everybody would tell me, 'Oh you know, we thought you were going to be the doctor because you're so smart and so bright' … I wanted to be that person … (Participant #12, post gene therapy) |

|                     | Altruism                                |
|                     | ... I lost the younger one [brother] to sickle cell so if they can get something that can get the cure for sickle cell, why don’t [I] do it … (Participant #17, post half matched transplant) |

| Decliners | Relatively mild SCD | Risks not worth potential benefit |
|-----------|---------------------|----------------------------------|
|           | Obviously if you risk something, it’s because you’re expecting a good result, and in case it doesn’t get a good result, you’re prepared to the outcome… but my current health situation wasn’t as bad [as others] because even though I have the liver problem and the pain that I am living with, I still considered that I’m not one of the patients that are really between life and death that they have to go with that [research] because that’s the only, the last resort that they have. (Decliner #4) |
|           | And yes, of course the Holy Grail, which is to live sickle cell free, was kind of at the end, but… it’s not sickle cell free. You’re not – you don’t just become a normal person. You become – you have to live like a person with sickle cell trait that has had a transplant, so you are on antirejection meds for the rest of your life… you still have sickle cell trait, and sickle cell trait comes with its own level of complications … so I was not really satisfied with that end result um in light of all the risks of all the risks I would need to go through to get there. (Decliner #6) |
| What role, if any, did your family have in your decision-making? | N = 26 |
|---------------------------------------------------------------|--------|
| Providing moral support and reassurance                      | 21     |
| Worrying about risk and/or discouraging participation        | 8      |
| Pushing participation                                        | 4      |
| Not involved                                                  | 2      |

| Did you speak with any other patients who had gone through the gene therapy or transplant? |
|------------------------------------------------------------------------------------------|
| No, talked to no one                                                                      | 7      |
| Yes, talked to patient(s) who did well                                                   | 11     |
| Yes, talked to both patients who did well and who did not do well                        | 5      |

| Would you consider yourself religious and/or spiritual? If so, what role did your faith, if any, have in your decision-making? |
|--------------------------------------------------------------------------------------------------------------------------------|
| General support from God and/or faith                                                   | 11     |
| Religious, but no role or influence                                                    | 9      |
| Outcome-related faith in God (e.g., God will protect me from risk)                     | 5      |
| Support from church leaders and/or community                                           | 2      |
| Not religious                                                                            | 2      |

* Total may not add up to 26 because some patients provided multiple responses or did not respond.
Representative quotes of patients’ retrospective reflections

| Successful response, mixed feelings about decision | When I had sickle cell, I knew what was going on with my body… having sickle cell, whenever I got a cold or an infection or something sickle cell, it reacted. But now that I don’t have it, I have no way of knowing like if I’m sick, really sick, or I just don’t know… it’s just like I don’t know my body outside of sickle cell, and I have to learn my body all over again since I don’t have sickle cell… (Participant #2, post full matched transplant) |
| Partial response, good decision | No, I have no regrets. Even with what I’ve been through, I have no regrets. (Participant #4, post gene therapy) |
| Successful response but serious complications, good decision | It was a great decision. (Takes a deep breath) It’s been a longer road than I had anticipated it being… I mean I was wondering why I wasn’t feeling the way I thought I might feel, but of course, not knowing what my new normal would be, I couldn’t say that this just wasn’t what it was. (Participant #1, post gene therapy) |
| Successful response but serious complications, mixed feelings about decision | Generally, it’s a good decision. I’m not looking at it in a selfish [way]. Like, you know, they could get results for somebody else, doesn’t necessarily have to be just me, on how to deal with future patients. (Participant #19, post full matched transplant) |
| Unsuccessful response, good decision | Oh, I made a good decision… It’s also about the experience. I met great people and then I learned more about me. Um I feel I became a better person. (Participant #20, post full matched transplant) |

* Patient said he would make the same decision again if given the choice.
† Patient said he would not make the same decision again if given the choice.