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A CRISPR Focus on Attitudes and Beliefs Towards Somatic Genome Editing from Stakeholders Within the Sickle Cell Disease Community

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Abstract

Purpose: Genome editing holds both tremendous therapeutic promise and significant potential risk. Sickle cell disease (SCD), the most commonly inherited blood disorder, is a frontline candidate for the clinical applications of this tool. However, limited knowledge of patient community values and concerns regarding this new technology exists. This study aims to investigate the perspectives of three key decision-makers (patients, parents, and physicians) towards participation in future CRISPR-mediated somatic genome editing clinical trials.

Methods: We utilized a mixed-methods approach, involving an educational video tool, two-part survey, and fifteen moderated, audio-recorded focus groups, which were conducted in seven US cities.

Results: Study participants expressed hope that genome editing technology would re-chart the course for SCD, but concerns related to involvement burden, uncertainty of clinical outcomes, and equity in access were identified. Major themes emerged from the focus groups: facilitators, and barriers to, participation in future somatic genome editing clinical trials; information pertinent to the decision-making process; persons from whom participants would seek counsel before making a decision; and recommendations for the research community on meaningful engagement as clinical trials are designed and approved.

Conclusion: The advent of genome editing has renewed hope for the SCD community, but caution tempers this optimism.

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Conflict of Interest Statement

The authors have NO commercial association that might pose, create or create the appearance of a conflict of interest with the information presented in any submitted manuscript.

Keywords

Sickle Cell Disease; Somatic Genome Editing; CRISPR; Clinical Trials; ELSI

INTRODUCTION

One of the first targets of CRISPR-mediated somatic genome editing will likely be sickle cell disease (SCD).[1–6] SCD affects millions of people, particularly those in regions where malaria is highly prevalent, such as sub-Saharan Africa, India, and the Mediterranean.[7,8]

SCD is caused by a single point mutation (A→T) in the sixth codon of the β-globin gene. Affected individuals inherit two abnormal copies of the gene, resulting in the production of malformed hemoglobin. This diminishes the oxygen carrying capacity of erythrocytes, resulting in medical complications, including pain crises, strokes, pulmonary hypertension, leg ulcers, priapism, and acute chest syndrome.[7,8,9]

Despite being identified over a century ago and posing a significant global health burden, those living with SCD have limited treatments available to them.[9,10] Hematopoietic stem cell transplantation (HSCT) remains the only non-experimental cure for SCD.[11,12] However, while the event-free survival rate of HSCT exceeds 90%, few patients can access this curative therapy due in part to stringent eligibility criteria.[11,12]Further, while the life expectancy of the general adult SCD population has increased over the past 40 years, premature death continues.[8,9]

Because SCD is a well-studied molecular disorder impacting the blood system, it comprises an ideal candidate for gene editing therapies, with different approaches under current investigation. One mechanism involves promoting fetal hemoglobin (HbF) levels, which can reduce the disease's severity by inhibiting HbS polymerization.[5,7,13] However, HbF expression is typically suppressed after birth.[13] Genome editing can be used to deactivate the B-cell lymphoma/leukemia 11A (BCL11A) transcription factor promoter, allowing HbF to persist.[5,13] Other researchers have displayed proof of principle success in removing hematopoietic stem and progenitor cells (HSPC) from the bone marrow, correcting the mutation itself with CRISPR, and re-populating the bone marrow with the edited cells.[2,4,14]

Given these preliminary results, clinical trials are soon expected. On September 13, 2018, the National Heart Lung and Blood Institute launched the Cure Sickle Cell Initiative to accelerate the development of the most promising genetic-based curative therapies. However, given the fraught history of the SCD community's medical marginalization, the community's views must be a central consideration if the goal is to deliver successful, socially responsible research and healthcare.[15,16,17,18] Michie and Allyse, in their study of parents of children with Down syndrome, concluded that genome editing interventions cannot succeed without input and support from patient communities.[16] International policy positions have been enacted recommending stakeholder engagement, education and bidirectional dialogue.[17,19] "Publics must not only be asked to engage in the discussion, but they should also be given proper information and education regarding the known facts, as well as the uncertainties regarding the use of gene editing in research and in the clinic."[17] To

this end, we sought to capture the perspectives of key stakeholders in the SCD community towards CRISPR-mediated somatic genome editing.

MATERIALS AND METHODS

Recruitment

Participants were recruited through collaborations with hematologists, community-based SCD organizations, and at national SCD conferences. Inclusion was limited to English-speaking adults. Eligible patients were required to have a diagnosis of SCD; parents had to have at least one child, pediatric or adult, diagnosed with SCD; and, hematologists must have delivered care to at least five individuals living with SCD, pediatric or adult, for a minimum of twelve months.

Study Design

Fifteen focus groups were conducted in the Southern and mid-Atlantic regions of the United States between April 2017 and December 2017: six patient groups, six parent groups, and three physician groups (See Table S1). After providing informed consent and demographic data (See Table 1), participants viewed a short educational video. The objective of the video was to provide participants with baseline scientific information about somatic genome editing and its potential use for SCD. The content of the video was reviewed by genomic researchers, genomic education specialists, and a science writer. Participants then answered survey questions related to genome editing and participation in future clinical trials. Focus group discussions followed. Trained moderators (A.P. and V.B.) led groups using a discussion guide, while another team member observed and took notes. Focus group questions were initially developed from topics identified through literature review and discussion. These questions were refined after the first three pilot groups. Each participant received a $75 gift card for their participation. This study was reviewed and approved by the Institutional Review Board at the National Human Genome Research Institute [].

Analysis

Debriefing sessions followed each focus group (A.P and V.B.). An a priori list of codes, based on the focus group questions, was developed. These initial codes were modified, and other codes were added as needed to best capture the focus group data. Each code was defined. The interactions between participants and differences in opinion throughout the discussion topics were captured. Transcripts were independently reviewed by A.P and S.D. using the qualitative analytic software, NVIVO 11. Textual data were categorized using conventional content analysis techniques, as described by Shannon and Hsieh.[20] Coded transcripts were compared, discrepancies were discussed, and inter-coder reliability metrics were calculated. Discrepancies were resolved by re-examining the context of the quote within the transcript and returning to the original definitions assigned to the codes. The final kappa coefficient averaged 0.82, and percentage agreement scores of > 90% were reached across all transcripts. Descriptive statistics were calculated for demographic variables and item-level attitudes towards gene editing and clinical trials.

RESULTS

Forty-six patients, 41 parents, and 23 hematologists participated in the study. Average age was 37.8 ± 12.6, 54.3 ± 9.6, and 53.6 ± 16, respectively. The majority of patients (88%) and parents (85%) self-identified as African American and/or Black. Forty-three percent of patients reported previous participation in clinical trials. 70% of hematologists reported having previously conducted SCD research (See Table 1).

Four broad themes emerged from this work: (1) factors influencing one's decision to participate, (2) information requirements for decision, (3) groups of individuals patients and parents would solicit guidance from, and (4) advice to the research community on meaningful engagement.

Decisional Factors

Motivators—All three stakeholder groups were hopeful that gene editing could be the overdue, impactful treatment for SCD many have been waiting for, often referencing the lack of treatments available compared to other diseases. Patients and parents discussed willingness to support future CRISPR-based clinical trials if suffering and social isolation are attenuated as a result (See Table 2):

> "With me sitting here in pain right now…if there's something that can be done to heal that, then I'm for it." (Patient) "I'm very optimistic. It's another possible option for sickle cell patients and unfortunately we don't have many."
>
> (Patient)

Parents described the frustrating experience of seeing their children in pain, but feeling helpless to reduce the disease's burden. Other patients and parents mentioned wishing they could have foreseen the toll SCD would take, or been given predictions of the trajectory of the disease's severity:

> "She can hardly breathe…the quality of life is just so horrible for them, and we have no control over it. As parents, we always want to fix things for our children, and we can't…all I could do was get in bed with her, and hold her hand…and she's 35" (Parent) "My son, he's had five strokes…As a young mother, would I have considered? Probably, if someone would have said that your child might avoid having strokes."
>
> (Parent)

For many patients, altruism was a salient motivator (See Table 2). Some were driven by the possibility that their participation could help family members living with the disease. Others saw participating as a way to promote social justice and support the SCD community at large. They felt participating might help reverse the lack of attention given to SCD, and encourage a more equitable distribution of resulting therapies:

> "Because it's a minority illness, it doesn't get the consideration that it should. So, I would like to participate just so I can help somebody who's coming behind me not to have it."

(Patient)

Of patients reporting prior participation in clinical trials, 65% cited “helping others” as a primary incentive (See Table S2). In addition, 97% of patients indicated they would participate in a future CRISPR-based clinical trial to help other patients with SCD. 75% said they would do so “for the sake of loved ones” (See Table 3).

Altruism surfaced far less among parents and was completely absent among physicians. Five times the number of parents and physicians cited lack of direct benefit to child or patient as a barrier compared to patients (See Table 3). While many parents viewed their child’s best interests as the main priority and expressed ambivalence over having their child participate, a few recognized the value of research participation in accelerating treatment development and said they would let their child participate.

The perceived shortcomings of existing treatments, especially bone marrow transplantation (BMT), comprised another motivating factor (See Table 2):

> “By age 10, I was in the hospital once a month. If I was given that decision, I probably would have said, ‘Mom, let’s do it,’, but unfortunately, I was so unhealthy that I couldn’t go through with BMT”. (Patient), “I can only speak for my one. There’s times where he’s just tired of taking pills…you got to take [it] every single morning, every single day.” (Parent) “Is it like transplant and afterwards I have to take these pills the rest of my life?”

(Patient)

Lastly, in two physician focus groups, there was mention of patients and parents being increasingly aware of, and willing to try, experimental treatments:

> “They are wanting to know what the latest thing is, why can’t I have it, where are the trials?”

(Physician)

Deterrents—Fear of participation stemmed from uncertainty about potential complications, the “editing genes” aspect of the CRISPR system, and the permanency of doing so (See Table 2). All three stakeholder groups were concerned about the unknown long-term effects of gene editing, a theme that surfaced in twelve of the fifteen focus groups. 56% of patients and 68% of parents cited “I don’t want to mess with [my/my child’s/my patient’s] genes” as a strong or moderate reason against participation, compared to 24% of physicians (See Table 3). Other patients and parents expressed anxiety over the possibility of exchanging one condition for another:

> “Why is it so permanent? Once the DNA is cut and made, it can’t be undone, so that concerns me as well.”

(Patient)

Parents were afraid to make a decision that could potentially exacerbate their child’s disease severity. Issues around fertility and inheritance were raised. While these concerns surfaced among parents, they were absent from patient groups. Several parents wanted to avoid

treatments that could limit their children's reproductive viability, and a few were worried about possibly violating the fidelity of one's family line:

> "Are they going to be connected to me… as with my DNA? Are they going to be connected to my mother… and her mother and all of that?"
>
> (Parent)

The continued ability to pass down SCD was deemed a downside of somatic gene editing among patients and parents (See Table 2). Several participants asked about the complete eradication of SCD, mentioning the psychosocial implications of doing so, such as easier family planning. Physicians predicted this question and felt it was important to convey that somatic gene editing would not achieve this end.

All stakeholder groups noted the potential burden of trial involvement (See Table 2). These included questions regarding how many school days their child might miss, time off from work needed, possible relocation, the extent of follow-up, the length and nature of the recovery process, and its impact on family dynamics:

> "We were considering a clinical trial and we had to go to Augusta and be there for two weeks, three weeks…that's a lot. That's a sacrifice to your family."
>
> (Parent)

Many patients and parents also expressed apprehension around the research enterprise's trustworthiness and transparency (See Table 2). However, a few expressed confidence in the research process and regulatory bodies governing the enterprise. Several participants remarked that distrust could be mitigated by hearing from researchers who have committed their lives to helping those with SCD:

> "I want to make sure that you don't do this overnight just to get funding and put your name on something." (Patient), "I'm going to accept it more if it's coming from my community…it has to be somebody who has been working to better this community before gene editing was a possibility."
>
> (Patient)

All three stakeholder groups worried about who would ultimately benefit (See Table 2). Many believed cost would be an issue in the future, and that those with the greatest need would have the least access:

> "Are [we] going to be used to get whatever information…and then somebody else benefits from it [who] doesn't even have the same disease?"
>
> (Patient)

Mediators—Religious beliefs, arising in eight groups, influenced decision-making in polarizing ways (See Table 2). Some participants viewed gene editing as "playing god" and inappropriately crossing a line, regardless of the goal, while others perceived it as a gift given by god to provide relief:

> "From a spiritual perspective, I really disagree with it. At a DNA level, that's how god intended you to be." (Patient) "I am fully supportive of using what god has given us to make our lives better."
>
> (Patient)

In fourteen groups, the patient's stage of life and capacity to manage the disease's severity arose as another mediator (See Table 2):

> "… in my 20s it was hard. I think that if this came up in my 20s, my husband and I would have said well maybe let's try it. I've been dealing with this for 45 years, I can deal with it for 45 more."
>
> (Patient)

Information Needed to Make Decision

In addition to knowing the risks and benefits, participants cited three types of information pertinent to decision-making: clear specifics of the procedure and clinical expectations; interpretation of inter-patient variation; and the track record of the research (See Table 2).

Patients and parents wanted to better understand the "cutting" and "repairing" aspects of CRISPR, details on the procedure itself, and contingency plans in the event the treatment goes awry. For many, reduction of pain was the central consideration. Others, however, inquired about improvements in other SCD comorbidities:

> "And for those groups who have chronic iron overload, would that help us with our liver problems, would it help us with our avascular necrosis?"
>
> (Patient)

Physicians were particularly concerned by drawbacks of the procedure and urged communication of the limitations of gene editing:

> "We change the genes in one of these patients, so they won't have crisis but they've still got liver malfunction…all that stuff is still going to be there…So, it's not magic."
>
> (Physician)

All stakeholder groups wanted more details about the research supporting this type of treatment. Participants were interested in the length of the experiments, the duration of therapeutic effects, instances and causes of failures, on whom or what the experiments have been performed, and percentages of adverse events and successes:

> "Show me every animal that died and why."(Patient), "I need to see that the red blood cells don't go back to sickling… Is it for a year and then it goes back?" (Patient), "Where are the current numbers on clipping [editing DNA] in the wrong place?"
>
> (Parent)

.

Lastly, participants asked how researchers are approaching the heterogeneity of the SCD population and determining eligibility criteria. All stakeholder groups thought it was important to determine conditions and critical windows for maximal effectiveness:

> "Are success rates different for the different types of sickle cell?" (Patient) "Is this treatment going to be the last resort, everything failed, or would it be first resort, before anything wrong goes on?"
>
> (Physician)

Seeking Guidance

Patients and parents cited five groups of people to consult before deciding to participate in clinical gene editing research: physicians, family members, other individuals with SCD who have previously participated in research, researchers, and religious leaders and/or god. Among potential advisors, trusted physicians with whom a long-standing, trusting relationship exists were identified as the group most patients and parents would consult. One parent, discussing his child's physician, remarked:

> "I think that relationships are extremely important, and when you build that trust with someone, they could tell you to ride this rocket ship to the moon, and you believe that they have your child's best interests at heart."
>
> (Parent)

In addition, survey data revealed one third of patients and parents previously participated in clinical trial research upon physician recommendation (See Table S2). Researchers, on the other hand, were least likely to be consulted. Patients and parents mentioned wanting to consult their physician two and a half more times across focus groups than they referenced research personnel:

> "But you have people who did research and don't want to give you the information. They just want you to participate."
>
> (Patient)

Recommendations for Meaningful Engagement

Each focus group was given an opportunity to leave the research community with some last thoughts on how to move forward. First, emphasis was placed on reaching out to the community to raise awareness and build credibility. Participants particularly stressed doing this sooner, rather than later. Many questioned why they were only hearing of CRISPR for the first time when the research has been ongoing for several years:

> "Before you start saying, hey we've got this. Let me try this. Get the name out there more. Go to colleges, schools, urban communities, centers…"
>
> (Patient)

Across all groups, participants repeatedly mentioned giving SCD patients, parents, and advocates the chance to be actively involved throughout the entire research process; avoiding a one-size-fits-all approach, noting differences in culture and attitudes; and, investing time to understand the lived experiences of SCD patients:

> "I would want them to remember that they are doing this for real, live humans… these people have lives, families, and that this research should be conducted with care and consideration of those trying to benefit." (Patient), "I would say to listen. Don't just ask us for opinions."
>
> (Parent)

Patients and parents also wanted open access to information and complete transparency in the way this information is communicated. Patients, parents, and physicians urged information be relayed through common communication modalities, specifically news channels, social media, talk shows, and other frequently used information distribution platforms:

> "It should perhaps be set up a little bit different than what scientific communications have been before, which is all through these kinds of channels or journals or NYT science page. It should be on the talk shows and on more ordinary communication." (Physician), "Present it in a presentation just like it was presented to us…on a ground-level understanding."
>
> (Patient)

Finally, many participants noted injustice, often citing greater support given to other diseases with far lower rates of incidence. All stakeholder groups urged the research community to develop policies that promote equitable resource allocation and long-term access to novel treatments:

> "To have the sickle cell population move this forward and then not have this available for them equally, would be extremely traumatic to the community."
>
> (Physician)

Physicians particularly stressed presenting the range of therapeutic options available both within, and outside of the gene editing realm, as a way of avoiding inadvertent coercion and prioritizing patient interests. Emphasis was placed on clearly explaining the purpose of phase 1 clinical trials, and the implications of participation. Lastly, participants urged researchers to act in a manner sensitive to the fraught past between this patient community and the research enterprise:

> "I think it is really important to also discuss what other cures or therapies may or may not be available…" (Physician), "I feel like we have one shot with this community. If things wane and we can't maintain whatever is the production of the cure, then will they have something else that they can move forward with?"
>
> (Physician)

Discussion

As the voices of disease communities grow louder and clinical trial development continues onward, the needs of the patients and families whose lives are likely to be altered by these new interventions must be prioritized.[19] To our knowledge, this is the first study investigating SCD stakeholder views on somatic genome editing.

Despite long-standing claims that racial and ethnic minorities are less inclined to participate in clinical research, many participants in our study expressed excitement over this potential new treatment modality, but had needs and concerns they wanted addressed. An increasing number of studies suggest minorities are as willing as non-Hispanic whites to participate in clinical research.[21,22,23,24]Research has shown there may even be an overrepresentation of minority communities in early phase clinical trials, when direct benefit is less likely.[21] Physicians in our study also remarked that patients and parents in the SCD community often come to them seeking information about new experimental treatments. In 2014, Haywood and colleagues reported highly positive attitudes toward clinical trials among adults with SCD, with important facilitators being education, prior research participation, and perception of greater potential benefits.[24] This study demonstrates a similar position towards somatic genome editing. Together, the mounting evidence against traditional theories of unwillingness to participate in clinical trials warrants a more nuanced examination of the barriers impeding enrollment.[25,26]

Patients, parents, and physicians also expressed fear of community exclusion from the long-term benefits of research. There was a pervasive concern that SCD patients might be used to help validate and improve the tool's utility, after which profit-based incentives and efforts to treat other diseases would overshadow those who risked their lives to make these therapies a reality. Participants were also dissatisfied with how little they knew about gene editing prior to this study and felt that it was a key example of a gap needing attention. They proposed mechanisms of meaningful engagement they believed would be effective in building trust and increasing participation. These include partnering with advocacy organizations and trusted physicians and/or researchers, providing opportunities for patients and advocates to be actively involved, disseminating information about the current status of research via communication platforms frequently accessed by the community, and designing and supporting initiatives that promote the SCD community's welfare. In an attempt to heed this advice ourselves, we have returned to the community and presented our findings since the conclusion of the study.

Our study also demonstrated that physicians were the group most participants would seek counsel from when deciding whether to participate in a CRISPR-based clinical trial. While patients and parents have often recounted bad experiences with clinicians in the emergency department, many mentioned having excellent, long-standing relationships with their hematologists. This suggests researchers should forge collaborations with these trusted physicians, be prepared to address their concerns, and work with them to better understand patient needs and establish rapport.[27,28,29]

This study had several limitations. First, 32% of patients and parents who self-identified as Black or African American reported some degree of college education. National census statistics estimate 8% of individuals with similar racial/ethnic backgrounds have obtained this level of education.[30] Furthermore, most participants reported advocacy group engagement, which may not reflect the average SCD patient or parent. Our study population also appeared to be more actively involved in clinical trial research compared to the general SCD population, with 65% of our patients reporting having previously participated in a clinical trial. These attributes may restrict the generalizability of our findings to the broader

SCD population. However, the research engaged patient population are the patients more likely to participate in Phase 1 gene editing clinical trials. Lastly, while the ability to draw conclusions from the quantitative data was limited by the small sample size, this data nevertheless was able to inform and complement focus group results.

The search for curative treatments using gene editing has renewed hope across the SCD community, providing a glimpse of a future with less pain, stigma, and neglect. However, there are cautionary, apprehensive undertones to this hope, partially due to the medical disenfranchisement of the SCD community. Using insights gained from this and subsequent studies to inform the design and conduct of clinical trials will be crucial, especially with respect to consent and engagement. This exploration of SCD stakeholder views may also serve as a model through which to approach and understand the values of other patient communities, particularly those for whom CRISPR applications are currently being explored.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Demographics of Focus Group Participants

Characteristic	Patients N=46(%)	Parents N=41(%)[4]	Physicians N=23 (%)
Sex			
Female	34 (74)	32 (78)	14 (61)
Male	12 (26)	8 (20)	9 (39)
Age Group, y			
18–30	18 (39)	1 (2)	2 (9)
31–40	9 (20)	13 (32)	4 (17)
41–50	11 (24)	14 (34)	2 (9)
51–65	4 (9)	11 (27)	10 (43)
>65	2 (4)	1 (2)	3 (13)
Ethnicity			
African American	39 (85)	35 (85)	6 (26)
White	0	0	7 (30)
Asian	0	0	6 (26)
Hispanic/Latino	1 (2)	1 (2)	0 (0)
Other	4 (9)	4 (10)	1 (4)
Educational Level			
High school or less	3 (7)	3 (7)	0
Some college	17 (37)	20 (49)	0
Bachelor’s degree	9 (20)	4 (10)	0
Master’s degree	13 (28)	9 (22)	0
Graduate school degree	2 (4)	4 (10)	n/a
Health Insurance			
Private	15 (33)	21 (51)	n/a
Medicare	19 (41)	5 (12)	n/a
Medicaid	14 (30)	14 (35)	n/a
Military healthcare	0	1 (2)	n/a
No coverage of any type	2 (4)	4 (10)	n/a
Other	3 (7)	0	n/a
Marital Status			
Married	11 (24)	22 (54)	n/a
Widowed	1 (2)	2 (5)	n/a
Divorced or separated	4 (9)	7 (17)	n/a
Never married	20 (43)	7 (17)	n/a
Living with partner	7 (15)	1 (2)	n/a
How much do you try to carry your religion over into all other dealings in your life?			
A great deal	20 (43)	19 (48)	n/a
Quite a bit	6 (13)	12 (29)	n/a
Some	4 (9)	4 (9)	n/a

Characteristic	Patients N=46(%)	Parents N=41(%)[4]	Physicians N=23 (%)
Not at all	6 (13)	0 (0)	n/a
How spiritual would you say you are?			
Very spiritual	22 (48)	22 (54)	n/a
Moderately spiritual	12 (26)	14 (34)	n/a
Not spiritual at all	2 (4)	1 (2)	n/a
Are you involved in a SCD support or advocacy group(s)?			
Yes	34 (74)	25 (61)	n/a
No	9 (20)	14 (34)	n/a
Attended US Medical School?			
Yes	n/a	n/a	11 (48)
No	n/a	n/a	11 (48)
PI or Investigator[2*]			
Yes	n/a	n/a	16 (70)
No	n/a	n/a	7 (30)

[1] Numerical data are presented as number (percentage) of study participants unless otherwise indicated.

[2*] Represents physician participants who report previously having been, or currently being, the PI or Investigator of a clinical trial.

[3] Numbers may appear higher than normal due to participants selecting numerous options.

[4] Missing demographic data for one parent.

Table 2.

Decision-Making Factors Related to Future Somatic Gene Editing Clinical Trial Participation

Theme	Subtheme	Quotes
Motivators	Reduce Suffering, Prevent Disease Progression, and Promote Quality of Life	"I think if more research was done, I would consider it. I have suffered a lot from sickle cell, and at this point, I deal with chronic pain. I would do it in the hopes that this illness doesn't continue to destroy my body." *(Patient)* "With sickle cell, I can't just hop up and run and go do something. I have to think about it, weigh it out. Is it worth my time? Do I really want to do it? Like yesterday, we wanted to go to the pool…Because the sun was starting to go down and the temperature was dropping, I couldn't just go and jump in the pool because I could go into crisis…sometimes it is hard for me to pick my daughter up when she wants me to." *(Patient)* "How it would improve or affect their level of function after? Like on a daily basis. Like patients with sickle cell disease want to know if they will have less painful crises. That they are able to get to work more. Not miss as many school days." *(Physician)*
	Altruism	"My participation would only be to benefit my 13-year-old niece. Anything that would make her life different and better than mine was at her age, that would be my only reason to participate." *(Patient)* "I think about how can this help all of our children. And so, I would probably be the flip parent and say where do I sign up because I've been down this road. I've seen what some of my friends have gone through. It can be very dark. It can be very lonely." *(Parent)*
	Shortcomings of Current Treatment Options	"I'm not going to lie. If I knew that I could change something in my bone marrow with DNA and not feel pain anymore, I would do it. I don't want to get chemotherapy, though. That's probably the one reason why I haven't already been to the bone marrow transplants." *(Patient)* "I don't think we always think about the social implications that it has, you know, like bone marrow transplant sounds wonderful if it cures your sickle cell disease but nobody talks about the fact that nobody is going to be able to come see you for six months and what that does to a child, you know." *(Parent)* "I think of it this way: That my patients have been waiting so long for this. Because there's such limitations to transplantation." *(Physician)*
Deterrents	Permanency of Changing DNA, Uncertainty of Risks and Long-Term Impact	"I'm really talking about changing someone's DNA. There is always that unintended consequence. You do A, but with the unknown potential?" *(Parent)* "I think that you have to talk about the fact that a lot of the risks are unknown. We don't know what is going to happen 20 years from now if we edit your genes when you are a little baby." *(Physician)*
	Trial Involvement Burden	"Getting to and from, yeah. How much time is it going to take, even though right now she's not working, but I am. I'm the only person working in our household." *(Parent)* "If the schedule is intense then that may not work with my lifestyle because I wouldn't want to have to miss days of work and things like that…because I feel like with trials you can't like miss things." *(Patient)* "Some more details about, you know, what would it look like? How many days would they be in the hospital? How sick would they be? How long after would they feel normal again?" *(Physician)*
	Mistrust of Intent Due to Historical Marginalization	"What is your real reason of researching it? Can I really invent this to, you know, to make some money off of?" *(Parent)* "'Oh, look, this person got cured' But they never tell you about all the people that are still living with just horrible side effects." *(Parent)* "You have to think about intent. We have also seen how malicious intent has made advancements go very wrong in our society. There was a question about do you trust your government to do the right thing. Well, I used to." *(Patient)*
	Reproduction and Genetic Inheritance	"Families are going to ask…I know many of us have been in the situation where we are talking about transplant and cure, one of the things that you have to discuss, because I don't think it is intuitive, is that you will still have the ability to pass on the sickle gene." *(Physician)* "The other thing that concerns me is that this just fixes the problem for the patient now. What happens when my son has a son, the future generations… I would like to see something that maybe is permanent…" *(Parent)* "Would you be able to have another child with someone who has sickle cell. Like will this change that? Would that change the whole game up where you can go and do that without having the worry of who you are dating and what they have and everything." *(Patient)*
	Concerns over Cost and Access	"If this treatment becomes available to the public, will it be available to everyone equally? I am not rich, but I qualify. I have sickle cell. I struggle with it daily… I don't want the reason why I can't get it done is because, oh, your insurance or you don't have the money." *(Patient)* "The companies are all thinking they will make about a million to a million and a half dollars for each procedure I think that the money might be a problem." *(Physician)*
Mediators	Religiosity and Spirituality	"If they can go in and snip out this illness and give you a better quality of life, I think God would appreciate that doctor doing that for his child." *(Patient)* "I have a child with sickle cell. I have other family members with sickle cell and I still would be on the fence. Because I feel like we're kind of – we're playing with God so-to-speak." *(Parent)*

Theme	Subtheme	Quotes
	Capacity to Manage Disease and Stage of Life	"Well, being 47, I would want to know what benefit -- like, is this going to extend my life? How -- because I've managed now, and I'm comfortable with it for the most part." *(Patient)* "I'm sort of at a crossroads. For me to do it, it would be like for me, right now, it would be like – because I'm so used to the pain now and knowing how to control and how to get ahead of it, it would have to be a life or death decision." *(Patient)*
Information Desired	Specific Details on Procedure and Clinical Expectations	"I'd also like to know if some things could possibly be reversed …will it correct my vision problems?" *(Patient)* "How long is the gene is going to hold up for? Do you have to keep going back for some new genes, like, how are they putting it into my body?"*(Patient)* "A patient needs to know that gene therapy may cure you only if you do it at birth. If you wait until you have already suffered a stroke, renal disease, whatever… even if you have gene therapy, this is not going to reverse the damage that has already occurred." (*Physician)*
	Inter-Patient Variability & Rationale Behind Eligibility Criteria	"What are the different results or side effects for the different traits and the different types of sickle cell that you have? *(Patient)* "Then how do you decide? Like in a family like ours where you have two children with sickle cell disease. When they were both a part of the sickle cell trial, and one got the treatment and the other did not. That wasn't that big a deal, but in something like this, that is more of a big deal." *(Parent)*
	Track Record of Research	"What made it effective? How many rats did they use based on this type? How many humans did they use on this type?" *(Patient)* "Chances of success, chances of failure, chance of death, chance of irreversible complications, known possible things that could go wrong. How many people have been through this already?" *(Physician)* "There's a saying, there's proof in the pudding. I want you to show me evidence and your findings and your result, whether it's 25 percent, 50 percent." *(Parent)*

Table 3.

Facilitators and Barriers to Participation in Future Somatic Gene Editing Clinical Trials

Facilitators	**Patients N=32 (%)[1]**	**Parents N=31 (%)**	**Physicians N=17 (%)**
I want to help other patients with SCD	31 (97)	27 (87)	13 (76)
I want to contribute to science	15 (47)	22 (71)	11 (65)
It would be better to do something rather than just wait for [my/my child's/my patient's] SCD to get worse	26 (81)	24 (77)	11 (65)
I hope it would help [my/my child's/my patient's] SCD	27 (84)	27 (87)	15 (88)
I expect that it would help[my/my child's/my patient's] SCD	22 (69)	26 (84)	15 (88)
Maybe it would help [my/my child's/my patient's] SCD in the long run, if the research succeeds	21 (66)	29 (94)	14 (82)
For the sake of my loved ones	24 (75)	21 (68)	n/a
Barriers			
It seems too dangerous	20 (63)	18 (58)	8 (47)
It seems like a lot of work for [me/my child/my patient] to be involved in the study	12 (38)	10 (32)	6 (35)
I don't want [me/my child/my patient] to be a guinea pig	11 (34)	17 (55)	2 (12)
I don't like the idea of messing with [my/my child's/my patient's] genes	18 (56)	21 (68)	4 (24)
The purpose of the study would not solely benefit [me/my child/my patient] directly	2 (6)	9 (29)	5 (29)

[1] Responses included 0=Not a Reason, 1=Minor Reason, 2=Moderate Reason, 3=Strong Reason. Scores of 2 and 3 were used to calculate the numbers/percentages above.

[2] This survey measure was adapted from Kim, et al. Sham Surgery Controls in Parkinson Disease Clinical Trials: Views of Participants. Mov Disord. 2012;27(11):1461–1465. doi:10.1002/mds.25155.C

Table 4.

Major Themes Related to Recommendations for the Research Community on Meaningful Engagement

Theme	Quotes
Keep all aspects of the approach patient- and community- centric	"We need a seat at the table. When this clinical trial is going on and you've got the researchers setting up protocols, setting up how it is going to work – advocacy, CBO…people that have sickle cell, need to be involved in every aspect of the trial." *(Patient)* "I think for me the education component of it is really big. Everybody who has sickle cell knows somebody with sickle cell…The more educated we are, the more powerful we become. And then we don't have to worry about our community being underserved because they'll be able to advocate for themselves…" *(Parent)* "One of the things I am working with in utero stem cell transplantation for SCD is going back to that community and saying, what is your understanding of IVF, PGD? Of stem cell transplants? And really trying to address, not just the barriers, but the opportunity– let's do it the right way. Let us understand the population that we are trying to help a little bit better by figuring out how we can best prepare them." *(Physician)*
Dedicate resources to SCD because this disease has not received the attention it deserves	"I would say don't mess it up…if you are really talking about it impacting the sickle cell population, you have to be very careful that the other rare diseases that have more resources don't take it over and the sickle cell population gets left in the dust. Because they have been left in the dust with so many other things that they already are skeptics." (*Physician)* "Dedicate the resources because we as a community deserve it. Sickle cell should be the first…No excuses. We don't have treatments." *(Parent)*
Be trustworthy, transparent, and provide easy access to clear information	"Make it accessible. Not so hidden that you have to go through hoops and back doors to find it because oftentimes that is a problem. We know the research is out there. We know the information is out there. But accessing that information is sometimes very, very difficult." *(Parent)* "I would just want them to keep us in the loop, like, really. With the good and the bad." *(Patient)*