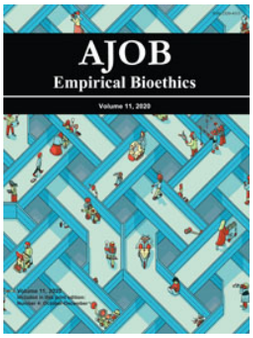

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The Meaning of Informed Consent: Genome Editing Clinical Trials for Sickle Cell Disease

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ABSTRACT

Background: A first therapeutic target of somatic genome editing (SGE) is sickle cell disease (SCD), the most commonly inherited blood disorders, affecting more than 100,000 individuals in the United States. Advancement of SGE is contingent on patient participation in first in human clinical trials. However, seriously ill patients may be vulnerable to overestimating the benefits of early phase studies while underestimating the risks. Therefore, ensuring potential clinical trial participants are fully informed prior to participating in a SGE clinical trial is critical. **Methods:** We conducted a mixed-methods study of adults with SCD as well as parents and physicians of individuals with SCD. Participants were asked to complete a genetic literacy survey, watch an educational video about genome editing, complete a two-part survey, and take part in focus group discussions. Focus groups addressed topics on clinical trials, ethics of gene editing, and what is not understood regarding gene editing. All focus groups were audio-recorded, transcribed, and analyzed using conventional content analysis techniques to identify major themes. **Results:** Our study examined the views of SCD stakeholders regarding what they want and need to know about genome editing to make an informed decision to participate in a SGE clinical trial. Prominent themes included stakeholders' desire to understand treatment side effects, mechanism of action of SGE, trial qualification criteria, and the impact of SGE on quality of life. In addition, some physicians expressed concerns about the extent to which their patients would understand concepts related to SGE; however, individuals with SCD demonstrated higher levels of genetic literacy than estimated by physicians. **Conclusions:** Designing ethically robust genome editing clinical trials for the SCD population will require, at a minimum, addressing the expressed information needs of the community through culturally sensitive engagement, so that they can make informed decisions to consider participation in clinical trials.

KEYWORDS
Sickle cell disease; CRISPR; somatic genome editing; informed consent; clinical trials

Background

Sickle cell disease (SCD) is an inherited genetic disorder affecting approximately 100,000 people in the United States and millions worldwide whose ancestors descend from sub-Saharan Africa, Saudi Arabia, India, and Mediterranean countries (Hankins and Wang 2009; Piel, Steinberg, and Rees 2017). Complications include acute vaso-occlusive pain episodes, pulmonary hypertension, leg ulcers, and acute chest syndrome (Jain, Bakshi, and Krishnamurti 2017; Kato et al. 2018; Dessap et al. 2008). Despite its discovery over 100 years ago (Herrick 1910), few treatments exist for individuals living with SCD (Kato et al. 2018; Piel, Steinberg, and Rees 2017).

A current curative therapeutic approach for SCD is bone marrow transplantation, which involves replacing the hematopoietic stem cells carrying the SCD mutation with stem cells from a matched donor without SCD (Fitzhugh et al. 2014). However, as over 80% of candidates do not have a matched donor and there is risk of graft rejection, experimental gene therapies

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are currently being pursued (Demirci, Uchida, and Tisdale 2018). These include stable gene addition using lentiviral vectors to express normal copies of the hemoglobin gene in hematopoietic cells as well as newer genome editing techniques which appear to be more efficacious, as they modify genomes with better precision, speed, and efficiency than previous methods (Bak, Dever, and Porteus 2018; Demirci, Uchida, and Tisdale 2018). One such revolutionary technique, CRISPR (clustered regularly interspaced short palindromic repeats) genome editing, has emerged as a novel tool with the potential to cure numerous genetic conditions, including SCD (DeWitt et al. 2016).

Currently, two methods of CRISPR somatic genome editing are being investigated for future SCD treatments: deactivating *BCL11A* to allow fetal hemoglobin (HbF) levels to persist later in life (Bauer et al. 2013; Canver et al. 2015) and correcting the mutated hemoglobin gene (*HBB*) (Dever et al. 2016; DeWitt et al. 2016) in hematopoietic stem cells which will be re-inserted into the individual receiving treatment. Both treatment pathways have the potential to either drastically reduce the severity of symptomology or cure SCD (Orkin and Bauer 2018). However, as these treatments are experimental, there are many unknown risks and safety concerns (Orkin and Bauer 2018; Shinwari, Tanveer, and Khalil 2018).

In light of the extensive discussions taking place on both the national and global stage regarding genome editing, it is imperative to keep patients at the center and involved in decision-making throughout all aspects of the clinical trial developmental process (Shinwari, Tanveer, and Khalil 2018; Ormond et al. 2019). The Human Genome Editing Science, Ethics, and Governance Report, released in 2017 by the National Academies of Sciences, Engineering, and and Medicine (2017), emphasized the importance of public engagement efforts and concluded that endeavors to advance genome editing will be strengthened by public dialogue. While recommendations detailing approaches for assessing societal risks and benefits of genome editing have been erected, drawing insights from patient communities on the clinical use of somatic genome editing will also be key to developing ethically-sound research approaches related to this emerging technology (Shinwari, Tanveer, and Khalil 2018; Howard et al. 2018).

One of the foundational principles of research ethics is respect for a person's autonomy to make an informed decision about whether or not to participate in a research study (Adashi, Walters, and Menikoff 2018). The primary function of informed consent is commonly described as facilitating research participation decisions that are consistent with an individual's values (Beauchamp and Childress 2001). Genome editing trials present particular challenges for the informed consent process due to the complexity and uncertain risks of this type of intervention, as well as the likely eagerness of potential participants to receive a potentially curative intervention.

Understanding information about a clinical trial is a core component of the consent process and a prerequisite of a participant's autonomous authorization (World Medical Association General Assembly 1964), yet this information is often highly technical and difficult for participants to appreciate for a variety of reasons. Desperate participants may be vulnerable to overestimating the benefits of early phase studies while underestimating the risks, a concern sometimes referred to as the "therapeutic misconception" (Appelbaum et al. 1987). There is some disagreement among bioethicists about the prevalence of therapeutic misconception, however; some view participants' optimistic attitudes as reasonable expressions of hope that are balanced with an understanding of the low likelihood of benefit (Pentz et al. 2012). Written consent documents are an important component of a robust consent process that should help potential research participants distinguish between hope and unreasonable expectations of benefit. These documents should provide potential participants with balanced information about the scientific uncertainty surrounding an experimental intervention, risks and potential benefits of that intervention, and alternatives to participating in a given clinical trial.

Prior research on the quality of the consent process for gene transfer suggests that these goals can be elusive for research involving widely-publicized interventions for desperate patient populations. For example, a 2005 content analysis of consent forms from 321 early gene transfer protocols found that the forms included vague, inconsistent, and overstated language about the nature of gene transfer research and the low likelihood of benefit in the earliest phases (King et al. 2005). A companion study that interviewed research participants who were enrolled in these same gene transfer protocols found that many tended to overestimate the potential benefit of the gene transfer intervention. Importantly, however, participants were less likely to overestimate benefit for studies in which both researchers and consent forms clearly stated that benefit was unlikely (Henderson et al. 2006). This suggests that it is worthwhile to strive to craft consent

forms that carefully present information about complex emerging technologies in a balanced manner.

As somatic genome editing clinical trials are now being initiated with the hope of alleviating the burden of SCD, understanding what SCD stakeholders need to know in order to provide informed consent becomes more critical. Currently, few studies are investigating the process of informed consent related to curative genetic therapies clinical trials (Cho et al. 2020), let alone the intersection of informed consent, somatic genome editing, and SCD. The aim of our study is to explore the views of SCD stakeholders on what they believe they need to know about CRISPR genome editing so that they are informed. We also assessed the genetic literacy of adults with SCD and parents of individuals with SCD, as well as physicians' perceptions of the genetic literacy of their SCD patients.

Methods

Study population and recruitment

We conducted a mixed methods study [NCT03167450], which included an educational video on CRISPR genome editing, pre- and post-video surveys, and 15 moderated focus groups: six groups of adults with SCD, six parent groups, and three physician groups (Persaud et al. 2019). Inclusion was limited to English-speaking adults at least 18 years of age. Eligible participants included: individuals diagnosed with SCD; parents with at least one child (pediatric or adult) diagnosed with SCD; and hematologists who have delivered care to at least five individuals living with SCD (pediatric or adult) for a minimum of 12 months. Participants were recruited from the mid-atlantic and southern regions of the United States between April and December 2017. Demographic information was collected, and each participant received a $75 gift card for their participation.

Educational video

A fourteen-minute educational video on CRISPR-genome editing was developed by the research team in collaboration with researchers conducting relevant work in the field, a science writer, a graphic artist, and an educator at the National Human Genome Research Institute. The video was presented to participants in each focus group. The topics of the video included the mechanisms of CRISPR genome editing, the utility of CRISPR genome editing to treat SCD, the difference between somatic and germline editing, ethical issues related to genome editing, and current advancements in somatic genome editing.

Measures of genetic literacy and comprehension of genome editing

Two surveys were used to assess baseline genetic literacy and understanding of CRISPR genome editing: the Genetic Literacy and Comprehension instrument (GLAC) (Abrams et al. 2015), and a measure developed by the research team to assess knowledge of CRISPR genome editing based on information presented in the video tool. The GLAC survey gathers information about how the public understands genomics and applies the knowledge in non-technical settings. It presents eight terms commonly used in genomics: genetic, chromosome, susceptibility, mutation, variation, abnormality, heredity, and sporadic. For each of the eight terms in the GLAC, adults with SCD and parents were asked to rank their familiarity on a scale from 1-7, and to complete fill-in-the-blank and multiple-choice questions aimed at assessing their understanding of the term. The other measure, an 11-item questionnaire, was developed by the research team to assess participants' understanding of CRISPR genome editing before and after watching the educational video. Physicians completed a modified version of the GLAC measure which assessed their beliefs regarding the genetic literacy of their own SCD patient population.

Administration of focus groups and study instruments

Three pilot focus groups (adults with SCD, parents, and physicians) were conducted, and surveys were administered. The survey instrument and interview guide were refined and finalized based upon pilot focus groups. Trained moderators (A.P. and V.B.) led groups using an interview guide. Adults with SCD, parents, and physicians participated in focus group sessions separately. Before the focus groups began, all participants completed the pre-video tool survey which included both the GLAC survey and CRISPR knowledge questionnaire. The participants watched the educational video and then completed the post-video survey which included the CRISPR knowledge questionnaire they took prior to the video. Focus groups were audio recorded with the participants' permission, transcribed verbatim, and anonymized.

Analyses

To explore what stakeholders wanted to know about somatic genome editing and its potential use in treating SCD, focus group comments were analyzed using content analysis, a form of qualitative inquiry that aims to identify and distill themes, ideas, and topics from text. Two independent reviewers (A.P. and S.D.) reviewed all transcripts to establish initial categories and themes. Transcripts were then analyzed for additional categories, which resulted in themes including informed consent, information participants desired before deciding to participate in genome editing clinical trials, and questions about somatic genome editing. The interpretation of these codes included comparing theme frequencies, identifying theme co-occurrence, and identifying relationships between different themes. Coding compliance between the two coders obtained a final kappa coefficient of 0.82 and percentage agreement scores of >90% across all transcripts (Persaud et al. 2019). Analyses were performed using R (R: A language and environment for statistical computing 2008), and NVivo 11 (Bazeley and Jackson 2013). Descriptive statistics were calculated for demographic variables. Chi squared tests were used to compare physicians' perceptions of patients' and parents' familiarity with common genetic terms to the familiarity scores of adults with SCD and parents. Lastly, pre- and post-CRISPR knowledge scores were compared using a paired sample t-test.

Results

The study sample consisted of 46 adults with SCD, 41 parents, and 23 hematologists. The mean age was 37.8 ± 12.6, 54.3 ± 9.6, and 53.6 ± 16 for adults with SCD, parents, and hematologists, respectively. Across the groups, most participants were female (74%) and over the age of 30 (57%). The largest single self-identified racial or ethnic group was Black/African American for adults with SCD (85%) and parents (88%). Many of the adults with SCD (46%) and parents (58%) had some college education but did not receive a bachelor's degree (Table 1).

Literacy levels of individuals with SCD and parents

On the GLAC, 89% of both individuals with SCD and parents scored >70% on the fill-in-the-blank questions, compared with 57.6% in the U.S. general population (Abrams et al. 2015). The mean GLAC score for patients and parents were 6.44 (SD 1.34) and 6.88 (SD 0.86), respectively, on a score range of 1 to 7. Correlation analysis with education levels indicated a moderate positive correlation, meaning that higher education levels corresponded to higher GLAC scores for both patients (rho = 0.34, p=.02) and parents (rho = 0.45, p=.005). GLAC levels were high compared with a general U.S. population sample for both groups (Abrams et al. 2015). Physicians expected their SCD patients to have significantly low familiarity levels in response to seven out of the eight genetics-related terms ($p < 0.05$). These include familiarity with the following concepts: Genetic, chromosome, susceptibility, mutation, variation, abnormality, heredity, and sporadic. Only in the instance of genetic abnormality, did physicians accurately estimate patients' familiarity scores ($p = 0.16$). Their expectations were largely inconsistent with the familiarity scores of the participants in this study.

The qualitative data captured diverse concerns, interests, and misconceptions held among the focus groups. All three types of focus groups, adults with SCD, parents, and physicians, discussed clinicians doubts about patients' ability to understand the scope of genetics and genome editing. Both adults with SCD and parents felt they were often restricted to routine medications or procedures because no one was willing to take the time to explain specifics about clinical trials.

As you see, this is a very well-educated group and it's not that we don't understand or that we're resistant to research, but you need to explain in a way that people will understand, also be a credible source… (Philadelphia Adult with SCD Group)

There were mixed attitudes across physician focus groups related to this theme.

Drawing from their previous encounters with adults with SCD, some physicians questioned whether patients would be able to understand the complexity of the details regarding genome editing, fearing patients might become overwhelmed and in danger of missing important information about the risks of the therapies such as infertility, toxicities of myeloablative chemotherapy, and off target effects (Brodsky and DeBaun 2020). Yet other physicians felt that the capacity for patients and parents to process this information and make informed decisions was being severely undermined:

I feel like there are two different questions: can someone absorb information when it is… in an abstract sense, just [general] information… and when it is communicated [as] this is what could happen to

Table 1. Characteristics of focus group participants.

Characteristic	Adults with SCD N = 46 (%)	Parents[a] N = 40 (%)	Physicians[b] N = 23 (%)
Sex			
Female	34 (74)	31 (78)	14 (61)
Male	12 (26)	8 (20)	9 (39)
Age Group, years			
18-30	18 (39)	1 (3)	2 (9)
31-40	9 (20)	13 (33)	4 (17)
40-50	11 (24)	14 (35)	2 (9)
50-65	4 (9)	11 (28)	10 (43)
>65	2 (4)	1 (3)	3 (13)
Ethnicity			
African American	39 (85)	35 (88)	6 (26)
White	0	0	7 (30)
Asian	0	0	6 (26)
Hispanic/Latino	1 (2)	1 (3)	0
Mixed/Other	4 (9)	4 (10)	1 (4)
Educational level			
High school or less	3 (7)	3 (8)	0
Some college	17 (40)	20 (50)	0
Bachelor's degree	9 (20)	4 (10)	0
Master's degree	13 (28)	9 (23)	0
Doctoral degree	2 (4)	4 (10)	23 (100)
Health insurance			
Private	15 (33)	21 (53)	n/a
Medicare	19 (41)	5 (13)	n/a
Medicaid	14 (30)	14 (35)	n/a
Military healthcare	0	1 (3)	n/a
No coverage	2 (4)	4 (10)	n/a
Other	3 (7)	0	n/a
Marital status			
Married	11 (24)	22 (55)	n/a
Widowed	1 (2)	2 (5)	n/a
Divorced/separated	4 (9)	7 (18)	n/a
Never married	20 (43)	7 (18)	n/a
Living with partner	7 (15)	1 (3)	n/a
Attended US medical school?			
Yes	n/a	n/a	11 (48)
No	n/a	n/a	11 (48)
PI or Investigator**			
Yes	n/a	n/a	16 (70)
No	n/a	n/a	7 (30)

**Represents physician participants who report being the principal investigator (PI) or investigator in a current or past clinical trial.
[a]Missing demographic data for one parent.
[b]Missing demographic data for physicians (age 2 physicians), (ethnicity 3 physicians), (medical education 1 physician).

you or this is what could happen to your child? I think, for one thing, they want to understand it in a lot more detail… I mean for any of us doing consents for any kind of treatment, it is a time… of overwhelming information overload. I think there is great risk of information overload in these sorts of situations then, too… (Fort Lauderdale Physician Group)

[Patients have said], "We want to know where things are going." I think that people are quite capable of taking this complex information and seeing it in their point of view, according to the good, bad, and the ugly about the treatment… People accept that [their] body has faced the consequences of all my misdeeds [of past recommendations for treating SCD]. "I can accept that and try to do better today." People are sort of willing to see it in that way. (Fort Lauderdale Physician Group)

Although physicians expressed concerns about patients' ability to understand genetic concepts, adults with SCD and parents demonstrated greater understanding of the genetic concepts tested than the physicians expected of their patients.

Desired information about CRISPR genome editing

CRISPR's promise to treat, or possibly even cure, SCD has given birth to new hope that positive, catalytic change is coming for a community that has limited treatments. We explored what information individuals who may consider participation in a clinical trial or treatment would want to know to feel informed prior to consenting to the procedure. Qualitatively, the stakeholders described four topic areas of interest: 1) explanations of treatment side effects, 2) mechanism

of action, 3) study eligibility for trial participation, and 4) the impact of treatment on quality of life.

Concerns about side effects of treatment

One issue many participants discussed was the desire to understand the spectrum of side effects that may occur after a genome editing-mediated treatment, especially regarding how the effects may vary by individual. To be properly informed, adults with SCD and parents want to understand both the promise and pitfalls of treatment. By addressing these questions and concerns, autonomous decisions can be made toward future participation in somatic genome editing if given the opportunity. Concerns about side effects came up in every adult with SCD focus group. (Supplemental Table S1).

What are the different side effects for the… different type of sickle cell that you have. (Charlotte Adult with SCD Group)

I guess I would more or less want to know what [side] effects happen. Because with hydroxyurea I know I have some type of [side] effects… (Charlotte Adult with SCD Group)

Parents vocalized their obligation to be cognizant of the potential adverse reactions that can occur in their children prior to finalizing a decision regarding participating in a clinical trial.

Everything has side effects. And that's really important. And you could give us a child with sickle cell, if they start the treatment, and then they start having all these other issues… what it's doing to the other organs in their bodies… most of the people that pass [away] from sickle cell, [it] is [from] the side effects and what it does to the other organs in their bodies. (Atlanta Parent Group 2)

Parents also discussed how the sickle cell community is a vulnerable population that may be inclined to ignore the potential side effects that can occur from treatments due to an intense desire for relief from severe symptoms. This vulnerability and desperation for symptom relief was a theme throughout the focus groups.

This community's so wary of anything, because everybody just always passes something off. "Oh, look, this person got cured." But they never tell you about all the people that are still living with just horrible side effects. (Atlanta Parent Group 2)

While adults with SCD were concerned with understanding side effects in a more general sense, physicians and parents specifically discussed side effects related to the need for myeloablative chemotherapy, which carries its own risks, such as loss of fertility.

And then fertility. We know that is always something that needs to be discussed up front with potential subjects and their families, to address what information we do have, but also what we don't have. (Bethesda Physician Group)

Mechanism of action: How does it work?

During the focus group discussions, adults and parents expressed a desire to understand how genome editing works. These groups want to comprehend exactly what happens on a procedural and molecular level, in addition to how genome editing will affect health outcomes (Supplemental Table S1).

I'm not clear on how exactly it works. Is it something they do in a thing and then they put it in your body? How does that work? Do they inject it in your bone marrow, in your blood?… How does the CRISPR get on your DNA chain to make the changes? (Atlanta Adult with SCD Group 1)

How much repair can you do? …What if it's two or three [genes] that's cut? Now, how is that going to affect [me] and how is that going to be repaired? And what does that repair look like? We understand that it can be done on a cellular level. Now, how does that turn out for our child? Do we eliminate sickle cell, but now create something different? (Atlanta Parent Group 1)

This desire was sometimes expressed through misconceptions about the genome editing procedure itself.

I think it was when she talked about the embryo and changing the DNA of the embryo. In my mind, that's what I saw, a pregnant lady sitting on the table and they were digging in her belly button to get DNA from the embryo that's inside her and then changing it. (Charlotte Parent Group)

As adults and parents spoke about their current understanding of gene editing procedures and requested clarity on the processes that were ambiguous to them, physicians emphasized that it was important to communicate to potential participants and parents the mechanism, as well as the limitations of the treatment.

I think we don't know enough about the current level of treatments, which may have the outcome of behaving like a genetic version of hydroxyurea and make the disease milder because at least the currently advancing approaches are to do just that. They are not correcting the underlying sickle cell disease mutation. Even when it does do that, it may not have 100 percent efficiency. There may still be issues that it is not really a cure. It may make things better. It is also possible that it will have a totally curative-type effect. I think we are not confident yet. I think that

uncertainty is not conveyed in any of the conversations so far. (Fort Lauderdale Physician Group)

In summary, all stakeholder groups expressed a desire to understand how genome editing works on both a molecular and macro level.

Inclusion criteria for being a study participant

Eligibility is another factor which surfaced as an issue in need of clarification for each stakeholder group. Among adults with SCD and parents, discussions ranged from finances to past medical history of prospective participants. Would they be able to afford the sacrifices needed for participation? Would this only be for a young adult patient with no history of kidney disease? Parents wanted to know if all individuals with SCD, regardless of age or disease severity, would have equal access to genome editing trials (Supplemental S1):

What candidate level do you have to be at, [for example] you have to be a [certain] candidate to [be] consider [for a] bone marrow [transplant]. Just because your child has a sickle cell, [does not mean a] doctor is going to do [the procedure] unless it's life and death candidate. There is pretty much where they draw a line where, hey, this is our last resort. (Charlotte Parent Group)

Similarly, adults with SCD were also interested in the criteria used to determine which individuals would qualify for clinical trials. They wondered if only individuals with severe disease or those who were not responding to other treatments would qualify:

I definitely believe that it depends on what you're going through at the time… if you are at a point where you feel like nothing is working and this comes up, you say okay, well I need to try something, and something is better than nothing. I can't keep doing nothing so perhaps this will work. (Charlotte Adult with SCD Group)

Who is a good candidate for it? Is it people who are like me who can't work, who can't get transfusions every month? If there's a way that you can prevent [pain and suffering], especially if you can prevent it at a young age and they can go a lifetime without knowing it. And even if they aren't young, like they have worked for a while, I think everyone should be able to access [gene editing]. (Philadelphia Adult with SCD Group)

Most physicians within the groups agreed that the current condition of the patient was a critical factor when considering how genome editing would affect the patient's health in the future. In contrast to adults with SCD and parents who expressed uncertainty surrounding the eligibility criteria, physicians expressed more concrete opinions on what should be considered when deciding if an individual is a candidate for a clinical trial. Several physicians stated that trials should be focused on individuals with severe disease who do not have other options:

It's going to be the five-year-old with a hemiparesis, that first big stroke, and that patient is going to go on to have repeated strokes and it's going to get worse, and they're finally going to die, or they're going to end up with iron overload and a ferritin of 20-, 30-, 40,000 that's poorly managed. You know, you could pick some sickle patients who are at predictably greater risk and those are the ones that you'd start on. (New York Physician Group)

I think if your patient had no other alternative. In a sense, if your patient has severe disease and is not a bone marrow transplant candidate, has failed on hydroxyurea and other things were not working for them and they fit the criteria; that would be a situation where I would be more encouraged to do it. (Bethesda Physician Group)

However, there was also discussion among physicians that the complications experienced by individuals with severe disease would not be helped by gene editing, suggesting that there is a spectrum of ideas regarding who would be the best candidates for clinical trials.

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 other – and organ damage does occur, even if you have gene therapy, this is not going to reverse the damage that has already occurred. In that sense, it is not really a cure the way I think patients think it is a cure. Maybe I am projecting. I think the patients think they are going to get gene therapy and they are going to be cured. (Fort Lauderdale Physician Group)

While stakeholder groups have varying opinions on who should be considered for genome editing clinical trials, it is clear that understanding the criteria for participation is an important aspect of being informed.

Impact on quality of life

Each stakeholder group reported wanting information about the quality of life the participant would have after the procedure. This included health maintenance such as follow ups with a hematologist, ability to work as usual, and if long-term medication would be needed (Supplemental Table S1).

Are there drugs they have to take afterwards to, you know, be able to maintain this? (Atlanta Parent Group 2)

Some participants inquired about burdens that may interfere with their ability to be present with their families and to carry out personal responsibilities. Many wanted to know whether they would be restricted to a specific regimen for the rest of their life.

What regimen will I have to follow after I have [gene editing]? Am I going to be immunosuppressed where I can't be around my kids and family for six months to a year? I want to know about everything that's going to happen in the process and afterwards. Because that's important, you can't decide to not take care of your family. (Charlotte Adult with SCD Group)

Physicians were more inclined to focus on the measurable physical functioning metrics of patients following the procedure as well as outcomes on quality of life, along with how somatic genome editing would compare in terms of efficacy to the use of other currently approved treatments for sickle cell. The last consideration was mentioned with an emphasis on tailoring and choosing treatments based on an individual's unique needs and desires.

How many days would they be in the hospital? How sick would they be? How long after would they feel normal again? (New York Physician Group)

What does it actually do for them on a daily basis? Will they have less pain? Will it halt like renal failure progression? Plus, any complications. (New York Physician Group)

I also feel with the range of therapies that we have in sickle cell disease, like transfusion, hydroxyurea, recently, Endari™, [L-glutamine oral powder] drugs that are coming out. I think patients would want to know where gene editing fits in with all of that, according to their own life basically, and how it compares with those individual therapies. Whether they should go for it or whether they shouldn't go for it, depending on what their own sort of trajectory or course is. (Bethesda Physician Group)

All stakeholder groups mentioned wanting specific information on the potential short-term and long-term effects of genome editing on quality of life. Furthermore, physicians stressed being transparent with potential participants and other individuals affiliated with the sickle cell community. Establishing trust between patient and provider was mentioned as one of the most important components when discussing genome editing with potential participants. Some physicians expressed that establishing trust takes time and may involve other providers in the patient's life, in addition to those involved in the clinical trial.

I also have to think that you have to take into account the trust issue that the patient has with the provider. It may be the most trusted clinician in the conversation … their most trusted person may be the educator who is in their area. Maybe somebody - a counselor to CBO [Community Based Organization]. It may be their primary care provider. It may not be the hematologist that is involved in the trial. So, it would probably have to be at least collaborative. (Bethesda Physician Group)

Discussion

The objective of this study was to investigate the views of adults with SCD, parents, and healthcare providers on what information is required to sufficiently understand the risks and benefits of consenting to participate in a genome editing clinical trial. SCD stakeholders' interests centered around the side effects, mechanisms of action, criteria to qualify as a clinical trial candidate, and the impact of genome editing on quality of life. We also found the genetic literacy of individuals with SCD to be underestimated by physicians.

As genome editing clinical trials are launched, it is crucial to determine the information that is relevant for potential participants to understand regarding the risk and benefits of participation. Individuals with SCD will now be faced with the decision to participate in a clinical trial that could cure their disease, but also carries uncertain yet potentially significant risks of side effects. To make an informed decision about participation, adults and parents of children living with SCD need access to clear and comprehensible information about the state-of-the-art of genome editing and gene therapies (Strong et al. 2017), especially details differentiating general, germline, and somatic therapies for SCD. An ethically designed consent process can enhance a patient's autonomy and invite them to participate in research when it is consistent with their values and personal goals, while also enabling them to advance the frontiers of scientific knowledge. It is critically important to present data to potential participants in a way that is understood in order to ensure the consent given is valid (Beskow and Weinfurt 2019). Identifying the information that participants will need for informed consent will help clinicians and researchers better prepare and support individuals who are interested in genome editing-

based clinical trials. It will also help integrate new requirements from recent revisions to the U.S. Common Rule to improve prospective participant understanding of research via the use of better organized consent forms and the provision of "key information" in a concise and focused manner (Federal Policy for the Protection of Human Subjects 2017). This study suggests specific items that can be included in the "key information" section of consent documents for genome editing trials to facilitate a more robust, well-informed decision-making process for prospective participants.

The general goal of informed consent for genome editing trials is the same as for other clinical trials: ensuring the participant understands the aims of the trial; procedures, risks and benefits; sources of financial conflicts of interest; and researchers' affiliations (World Medical Association General Assembly 2018), among other relevant details. Understanding genome editing trials is especially complex, however, due to the nature of the treatment and potential for misunderstanding the treatment, its goal, and its process. The decisions influencing what participants need to know to be informed is almost always determined by researchers, with feedback from an Institutional Review Board. Achieving an improved informed consent process requires an understanding of what potential participants need to comprehend about the trial, in addition to what the researchers want to convey.

While consent is most commonly understood as a mechanism to facilitate autonomous decision-making by individual research participants, the consent process can also serve other important functions such as providing transparency about the nature of the research, promoting public trust regarding the social value of the research, and ensuring the professional integrity of the research enterprise (Dickert et al. 2017). Designing a consent process that is effective for somatic gene editing clinical trials requires an awareness of the range of potential goals of informed consent for this specific context. The findings from this study touch upon several important policy-related goals of consent for genome editing trials related to the vulnerability and desperation of the sickle cell community, and the historical marginalization of this specific patient population. In addition, this study identified an awareness among physicians of the need for both researchers and clinicians to be transparent and trustworthy in their discussions of genome editing trials with prospective participants to support a robust informed consent process.

In the age of genomic technological advances within a complex health care system, it is becoming more challenging – yet more important – for patients and medical professionals to have the same understanding and have aligned goals for the treatment. Prior to exploring what information potential participants need to be truly informed in genome editing clinical trials, it is important to gauge a perception of what they already understand; for this reason, we assessed genetic literacy of adults living with the disease and parents of children with SCD. In this study, we found that the genetic literacy of adults with SCD and parents was higher than the physicians' expectations of their patients' genetic literacy. The genetic literacy level of the patients and parents in this study does not substantiate the concerns physicians expressed about patients' ability to understand genetic information. It is important to note that our sample did have a higher genetic literacy than the general population (Abrams et al. 2015). We anticipate that this may be due to lifelong experience with a genetic disorder. However, it remains critical for physicians and researchers who are conducting clinical trials to not underestimate the ability of potential participants and parents to understand genome editing concepts. This can lead to frustration and mistrust among the community and may serve as a critical deterrent to clinical trial participation.

After understanding the capabilities of potential participants to grasp genome editing concepts, it is important for researchers to consider what these participants want to know, need to know, and how best to communicate information about genome editing to the community. Once a clearer picture of what participants want to know about gene editing has been identified, the onus is on the research team and referring physicians to facilitate understanding through community-informed methods that are well-tailored to the needs of prospective participants. We believe that a successful consent approach in this context will need to be interactive, with engagement and education taking place over a more extended period of time rather than a one-time interaction. This is both to help facilitate patient understanding of the vast amount of information and detail regarding gene editing, SCD, and gene editing clinical trials, as well as to build more engaged relationships between research teams and participants in service of a transparent and trustworthy approach to informed consent.

Where should the field go from here?

Concerns around the trustworthiness of biomedical researchers as well as biotechnology and

pharmaceutical companies have created a critical gap between the developers of genome editing technologies and individuals living with the disease. This is especially important to consider within the context of SCD given its unique past (Bonham and Smilan 2019). Historically, SCD has experienced inequities in research funding compared to other rare diseases (Bahr 2015). This, combined with the paucity of treatments available for SCD and the documented neglect the SCD community has faced from the healthcare system, warrants extra care and consideration with respect to engagement. A primary step to be taken includes directly engaging with SCD stakeholders to build trust and address specific concerns. Although conversations about the ethics of genomic research and its impacts on racial and ethnic minorities have been ongoing for many years, there continues to be a need for resources devoted to effectively inform people who have been taken advantage of in the past (Hildebrandt and Marron 2018; Bussey-Jones et al. 2010; Michie et al. 2011; Bonham et al. 2009). Engaging communities of color in the dialogue around public policy and genomics is important for the translation of genetics research into inclusive strategies aimed at improving health (Bonham et al. 2009).

While the outcomes of these deliberations offer useful, high-level advice, there has been little discussion of the critical ethical issues involved with providing the desired information about genome editing sought by key stakeholders in the community, as well as what it will take for a prospective participant to be adequately informed about the procedure. We hope to have added a community voice to the scholarly dialogue regarding ethics, genome editing, and participation in clinical trials by exploring what it means for potential participants to be informed and what information they would like prior to deciding to participate in a clinical trial.

As reported previously (Persaud et al. 2019), our study has some limitations. Thirty two percent of the adults with SCD 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 (United States Census Bureau 2016). We recruited the participants from national sickle cell conferences and advocacy groups. Therefore, the study population may be more actively involved in clinical trial research compared to the general SCD population; 65% of the adults with SCD reported previous participation in a clinical trial. These attributes may restrict the generalizability of our findings to the broader SCD population; however, the population included in this study is likely to reflect individuals who will be offered participation in future clinical trials and therefore is a relevant population for this analysis. Studies have found under-representation of lower socioeconomic status groups in cancer clinical trials (Sharrocks et al. 2014). Finally, all the data presented in this study were collected prior to the controversial report of the birth in November 2018 of the first babies modified with heritable genome editing, which may have since influenced opinions about genome editing (Cyranoski and Ledford 2018).

Future research should examine strategies to effectively address the information needs of individuals living with SCD when deciding to participate in genome editing clinical trials, as well as study approaches to meaningfully engage the disease community in clinical trial awareness and recruitment. In addition, future studies should explore individuals' perspectives of somatic genome editing from other diverse disease populations and compare the results to our study to identify any overlap in desired information around gene editing, as well as to address existing misconceptions around the research and its therapeutic capacity. It will also be important to assess inaccuracies in understanding that may result when obtaining consent from patients. Studies should be conducted to evaluate the underlying causes of the disconnect between the participant's goals and the objectives of the study. Our study suggests the SCD community is optimistic about the promises of somatic genome editing; however, it is important to recognize that lack of information and misconceptions about the technology may influence one's decision to participate in a clinical trial.

Conclusion

As genome editing continues to push the frontiers of gene therapy, ethically robust clinical trials must be designed to be attentive to the voices of SCD stakeholders on what they need to know about genome editing. This will allow informed decisions to be made when considering participation in genome editing clinical trials (Hildebrandt and Marron 2018). Biotechnology companies, researchers, and clinicians must continue to build partnerships with SCD stakeholders and advocates within the community in order to promote equitable access to these new curative and life-changing technologies. Maintaining the stakeholders' trust and interest in this process is critical to moving the field forward in a fair, ethical manner.

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Author's contributions

- Conceived and designed the study Vence L. Bonham and Anitra Persaud
- Moderated focus groups and collected data: Vence L. Bonham and Anitra Persaud
- Data Coding: Anitra Persaud and Stacy Desine
- Qualitative data analysis: Stacy Desine, Anitra Persaud, Brittany M. Hollister
- Statistical analysis: Stacy Desine and Brittany M. Hollister
- Data analysis, interpretation and drafted the article: Stacy Desine, Brittany M. Hollister, Khadijah E. Abdallah, Anitra Persaud, Sara Chandros Hull, Vence L. Bonham
- Acquisition of funding: Vence L. Bonham
- Administrative support: Stacy Desine, Khadijah Abdallah
- Supervision: Vence L. Bonham

Conflicts of interest

The authors declare that no conflicting financial interests exist.

Ethical approval

This study was reviewed and approved by the Institutional Review Board at the National Human Genome Research Institute at the National Institutes of Health.

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