

Comparative Effectiveness of a Decision Aid for Therapeutic Options in Sickle Cell Disease

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Title: Comparative Effectiveness of a Decision Aid for Therapeutic Options in Sickle Cell Disease

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PI: Dr. Lakshmanan Krishnamurti

Coordinator: Diana Ross, MSN, RN

Abstract:

Background: Sickle cell disease (SCD) is an inherited disorder with chronic multi-system manifestations affecting 100,000 individuals in the US, largely of minority origin and associated with substantial morbidity, premature mortality, individual suffering, healthcare costs and loss of productivity. Disease modifying treatments such as Hydroxyurea, chronic blood transfusion and curative bone marrow transplantation are offered to patients based on physician preference and current practice informed by clinical trials. Decision aids are tools that could help translate evidence from these sources into practice by helping clinicians involve patients in making deliberate choices based on accessible information about the options available and their outcomes and to help them make decisions based on their values and preferences.

Objective: The overarching goal of this project is to develop and implement a web based decision aid individualized to patient characteristics to help patients with SCD achieve more accurate perception of risks and benefits of treatment options and make decisions in congruence with their values and preferences.

Methods: We will conduct needs assessments interviews as indicated by the data for saturation and validation of findings. We will conduct beta testing of the web-based decision aid to clarify development and validate findings. We will use a randomized controlled trial of the effectiveness of a web based decision aid to give patients accurate information about risks and benefits of therapies and enable them to make decisions based on their individual values and preferences.

Outcomes: To provide accurate information to patients and caregivers about the risks and benefits of various treatments for sickle cell disease and to enable them to make informed and involved therapeutic decisions based on their values, preferences and stated goals.

Background:

Sickle cell disease (SCD) is a major public health problem in the United States with an estimated 100,000 individuals living with this disease 1. It is associated with significant morbidity caused by pain crises, acute chest syndrome, stroke, pulmonary hypertension, leg ulcers and irreversible organ damage 2. Quality of life is impaired in children and adults with this disease 3-6 and productivity is impaired, with a 40-60% unemployment rate in adult patients 7. The disease results in premature mortality, with a median age of death of 38 years 2, 8, 9. In 2010 there were approximately 100,000 hospital discharges in the United States for which SCD was the principal diagnosis. Mean hospital charges per admission were \$15,000, with the total annual charges in the US exceeding \$1.5 billion 12. Approximately 70% of the patients were on

government sponsored medical insurance, predominantly Medicaid and Medicare. Sickle cell disease is thus the archetype of the chronic multisystem disease predominantly affecting a minority, disadvantaged population.

Hydroxyurea (HU) has been demonstrated in placebo controlled multi-center clinical trials to be efficacious in reducing complications such as vasoocclusive pain crises and acute chest syndrome in children and adults with SCD and in improving survival in adults 13-17. It is the only disease-modifying therapy and the only drug approved by the FDA for use in patients with SCD. While early studies demonstrated the benefit of HU therapy in adults with SCD 17, recent safety and efficacy data from the BABY-HUG study support the consideration of this therapy even in very young children 13. Patients who are adherent to treatment have been shown to have reduced health care utilization 18-21. Significant barriers remain, however, in the effectiveness of HU in real world circumstances 18. It is under prescribed, and when prescribed, underutilized by patients. Approximately 85% of SCD patients who receive an HU prescription never fill it 22-25, and the average refill prescription rate is reported as being as low as 58% 26. Patient-related barriers to adherence include time and transportation to a clinic and to pharmacy to obtain refills 20. Over 20% of families refuse Hydroxyurea because of reasons such as fear of cancer or other side effects, concern about lack of efficacy, and unwillingness to take the medicine or come to clinic or pharmacy 22,23.

Hematopoietic stem cell transplantation has been demonstrated to be curative in patients with SCD 27, 28. Only a minority of patients who meet eligibility criteria for transplantation, however, proceed with the treatment even when a matched sibling donor is available 29. The low utilization of curative strategies for SCD appears to be partly attributable to a lack of information about the technologies available to facilitate transplantation 30. Thus, the low uptake by patients of therapeutic interventions proven in clinical trials suggests, on the one hand, a lack of awareness of therapeutic options and, on the other, a potential discordance between endpoints in clinical trials and outcomes that are considered important by patients.

There are minimal data about patient-related barriers to, and attitudes towards, the use of curative therapies in SCD. A systematic review of the research on barriers to care in patients with SCD did not identify any studies that specifically addressed patient-related barriers to the use of Hydroxyurea 31. The attitudes of patients with SCD toward the use of hydroxyurea (HU) therapy may contribute to the underutilization of HU in the United States, yet our understanding of these attitudes is limited 32. Of patients who have never taken HU, half reported receiving no information about HU, and 85% report believing that they would receive no improvement if they were to take HU 32. In making choices regarding transfusion, transplantation or HU, families are most influenced by perceived efficacy and safety 33. Thus significant gaps remain in the understanding of patient perspectives, in the provision of accurate information about risks and benefits of therapies and of incorporating patients' values and preferences in offering treatment options. Thus, there is a need for research that helps to understand patient values and preferences and determines how to help patients make informed treatment decision in congruence with their values and preferences.

Significance:

The Salzburg statement 34 recognizes that clinicians have an ethical imperative to share important decisions with patients. Much of the care patients receive is based on the ability and readiness of individual clinicians to provide it, rather than on widely agreed standards of best practice or patients preferences for treatment. There is thus, a need to stimulate a two-way flow of information that encourages patients to ask questions, explain their circumstances, and express their personal preferences, and prompts clinicians to provide accurate information

about options and the uncertainties, benefits, and harms of treatment in line with best practice for risk communication. Further, information must be tailored to individual patient needs, it must be acknowledged that most decisions do not have to be taken immediately, and patients and their families should be given the resources, time and help to reach decisions.

Decision aids are designed to help patients improve their knowledge of the options, achieve a more accurate perception of risk and benefits of treatment, participate actively in decision making, and make choices more in keeping with their values and preferences. In randomized controlled trials (RCTs) evaluating the efficacy of decision aids for people facing difficult treatment or screening decisions, decision aids performed better than usual care interventions in terms of: greater knowledge; lower decisional conflict related to feeling uninformed, c) lower decisional conflict related to feeling unclear about personal values; d) reduced the proportion of people who were passive in decision making ; and e) reduced proportion of people who remained undecided post-intervention¹¹. When simpler decision aids were compared to more detailed decision aids, the relative improvement was significant in knowledge and there was some evidence of greater agreement between values and choice.

The proposed study will create and pilot test, for the first time, a web based decision aid for therapeutic options in sickle cell disease and test in a randomized clinical trial the comparative effectiveness of a decision aid and standard clinical care in patients with SCD facing treatment decisions. Thus, this decision aid has the potential to helping patients make decisions on their treatment based upon high quality information according to their values and in accordance with their preferences, thus producing improvement in their health, wellbeing and quality of care in a manner which is meaningful to them.

There exists a significant a gap between results of clinical trials and patient uptake and adherence with disease modifying therapies for SCD. An effective decision aid is likely to empower patients with accurate information tailored to their clinical condition and their values and preferences. We anticipate this is likely to help them better navigate treatment choices. Further, the web based decision aid is also likely to serve as a tool for clarification of patient values to themselves and to their healthcare providers. This is likely to influence the course of research in the direction of development of therapies that are in line with the values and preferences important to patients.

Hypothesis:

Our overarching hypothesis is that a web based decision aid individualized to patient characteristics can improve knowledge and help patients with SCD achieve more accurate perception of risks and benefits of treatment options and is associated with lower decisional conflict than standard care. To test our hypothesis we propose the following specific aims:

Aim 1: Develop a health literacy sensitive, web based, decision aid to help patients with sickle cell disease make informed choices about treatment options such as hydroxyurea, chronic blood transfusion, bone marrow transplantation and standard comprehensive care.

Aim 2: To estimate in a randomized clinical trial the effectiveness of the decision aid tailored to individual patient characteristics on patient knowledge, patient involvement in decision-making and decision-making quality, when compared with usual care.

Aim 3: To validate decision aid in Hindi language

Research Questions:

1. What are the needs of patients with sickle cell disease and their parents/caregivers when considering treatment options for sickle cell disease?
2. Does the use of a decision aid result in improvement of patient knowledge, patient involvement in the decision, the congruence of their decision with their values and preferences?
3. Is the Hindi version understandable and useable by patients?

Expected Outcomes:

1. Collection and analysis of qualitative interviews using an open-ended semi-structure interview guide will provide understanding of patient and parent/caregiver knowledge, expectations, values, barriers and needed support that needs to be provided in a decision aid tool.
2. Based on the goals of the decision aid to provide accurate information to patients and caregivers about the risks and benefits of various treatments and to enable them to make informed and involved therapeutic decisions based on their values, preferences and stated goals we propose the following outcomes:
 - a) Impact on patient knowledge and understanding of treatment risks and benefits. Patient knowledge will be tested by using a knowledge questionnaire. Since knowledge is different from understanding we will design questions that test understanding e.g., if they understand the concepts and meaning for e. g., of an 80% survival by using different scenarios.
 - b) Impact of the decision aid on the decision making process and on the treatment decision, including the extent of patient involvement, the specific decision made, satisfaction with the decision-making process and with the decision. Patient involvement in decision making will be tested using a Patients' Perceived Involvement in Care Scale^{38,39}.
 - c) Psychological impact of decision aids on decisional burden, decisional conflict and decisional regret. Decisional conflict will be measured using a decisional conflict scale. Decisional conflict is evaluated using a validated decisional conflict scale^{40,41}. Decisional regret will be evaluated by using a validated decision regret scale⁴². Decisional burden will be evaluated using a validated decision burden scale⁴³.
 - d) Uptake, adherence and satisfaction with therapeutic option discussed. Within 4 months following discussion with the physician/healthcare provider we will also survey patients to determine their uptake, adherence with, and satisfaction with, the therapeutic option discussed.
3. The Hindi version of the decision aid will be comprehensible and useable as demonstrated by beta testing.

Methods

Study Design for Qualitative Interviews Decisional Needs Assessment

After consenting by a research team member via telephone or in-person, an in-depth needs assessment of participants age ≥ 8 years with sickle cell disease and parents/legal guardians/caregivers of individuals (of any age) with sickle cell disease and will be scheduled for an interview within 6 weeks of consent. Additionally, stakeholders and healthcare providers may be recruited for participation. Interviews will be completed via in-person or telephone interaction. Interviewers will use a semi-structured open-ended question guide developed based on the Ottawa Decisions Support Framework workbook, *Decisional Needs Assessment in Populations*. Interviews may also be based on a need to expand knowledge of previous interviews. Using qualitative iterative process, questions design will be analyzed after every 3 to 5 interviews, allowing for increased focus of questions based on themes and issues identified during ongoing analysis. Per qualitative data collection and analysis methods, this process allows for greater clarification of emerging themes and concepts. Interviews will take up to 45 to 60 minutes. Interviews will be audio recorded and transcribed verbatim for later analysis. Interviews will be conducted in a private setting, away from parents, family, caregivers and clinical staff. Research staff may visit the clinic for observation and to collect field notes related to clinic management prior to and during recruitment. These field notes will allow the research team to better understand current practice related to clinical practice and allow for better refinement of the decision aid. No patients will be identified in the field notes and identifiable incidents will not be recorded. There will be no audio recording of these clinic observational visits.

Demographic information will be collected including but not limited to age, gender, marital status, education level and role in sickle cell disease (patient, caregiver, stakeholder, provider). Additionally patients and parents/legal guardians of patients will be asked to self-report information regarding themselves or the patient they care for including but not limited to patient age, gender, education level, marital status, genotype, insurance type, history of HLA typing, number of hospitalizations for sickle cell related complications in the past 2 years. No PHI will be accessed for these qualitative interviews.

Study Design for Beta Testing

After consenting by a research team member in person or via telephone, review of the web-based Sickle Cell Decision Aid will be reviewed with participants, age ≥ 8 years with sickle cell disease and parents/legal guardians/caregivers of individuals (of any age) with sickle cell disease will be scheduled for an interview and review of the website within 6 weeks of consent. Additionally, stakeholders and healthcare providers may be recruited for participation.

Interviewers will demonstrate in-person or describe over the telephone use of the website, including navigation and the elements of the site. Participants will then be asked to navigate the site. As the participant navigates the site, the interviewer will ask the participants to describe thoughts about the site, including but not limited to ease of navigation, content and construction. Beta testing may be performed in-person or via telephone. Using qualitative iterative process, questions design will be analyzed after every 15-30 interviews, allowing for increased focus of questions based on themes and issues identified during ongoing analysis. Per qualitative data collection and analysis methods, this process allows for greater clarification of emerging themes and concepts. Interviews will take up to 60 to 90 minutes to complete. Interviews will be audio recorded and transcribed verbatim for later analysis. Interviews will be conducted in a private setting, away from parents, family, caregivers and clinical staff.

Demographic information will be collected including but not limited to age, gender, marital status, education level and role in sickle cell disease (patient, caregiver, stakeholder, provider). Additionally patients and parents/legal guardians of patients will be asked to self-report information regarding themselves or the patient they care for including but not limited to patient age, gender, education level, marital status, genotype, insurance type, history of HLA typing, number of hospitalizations for sickle cell related complications in the past 2 years. No PHI will be accessed for these qualitative interviews.

Hindi Beta Testing

After consenting by a research team member review of the web-based Sickle Cell Decision Aid will be completed with the participant (physician, parent/caregiver, or patient) using a computer or smart phone. Participants who are patients will be 16 years or older. Physicians will be hematologists, general practice physicians or bone marrow transplant specialists who provide health care services for patient with sickle cell disease. Research interviewers will record the interaction for later transcription and analysis. The interviewer will demonstrate logging onto the website then will ask the participant to navigate the site, reading and commenting on the various pages of the site. Interviewers will keep track of which pages were viewed by participants to ensure that the majority of, if not all, web pages are viewed during beta testing. The participant will be asked to discuss ease of navigation and the various educational elements and features of the site, including content and construction. Interviews will take up to 60 to 90 minutes to complete. Interviews will then be transcribed and analyzed for like themes. Interviews will be conducted in a private setting, away from parents, family, caregivers, and medical staff.

Demographic information will be collected, including but not limited to age, gender, marital status, education level and role in sickle cell disease (patient, parent/caregiver or health care provider. Additionally, Parents/caregivers of patients and patients will be asked to self-report information regarding the person they care for with sickle cell disease or themselves, including but not limited to patient age, gender, education level, marital status, type of sickle cell disease, number of hospitalizations or emergency room visits in past year due to sickle cell pain. No medical records will be accessed for the purpose of collecting private health information.

Study Design for Testing of Decision Aid

For **Cohort A**, we will use a randomized controlled trial for the use of a web based decision aid to give patients with sickle cell disease and parent/legal guardian of children with sickle cell disease accurate information about risks and benefits of therapies and enable them to make decisions based on their individual values and preferences. Participants will complete surveys before, soon after and within 4 months following their discussion with their health care provider to determine impact of the decision aid on knowledge, involvement in the decision and on decisional conflict, quality and uptake and adherence with the therapies.

For **Cohort B** we will use a mixed methods descriptive study design to determine the impact of the decision aid on quality and comprehension of information, and impact on daily life relating to management of sickle cell disease in patients <18 years of age.

Cohort C - To better understand the effect of the decision aid in decision making and patient involvement as reported by the physicians consenting these patients (child and adult) for treatment will be asked to participate in the study. Health care providers will not be randomized.

Randomization

After the consenting process is completed, adult participants will be assigned to **Cohort A** and will be randomized to the clinical trial control or intervention group. Further subdivision will be done by age, to include three age groups:

1. Parent/legal guardian of children (age group of child < 18 years)
2. Individuals with sickle cell disease =>18 years to <28 years
3. Individuals with sickle cell disease =>28 years

Participants <18 years will be assigned to **Cohort B** and will not be randomized.

Health care providers will be assigned to **Cohort C** and will not be randomized.

Cohort A

Consenting/Visit 1

After consenting in-person or via telephone, we will collect demographic information from adults with sickle cell disease including but not limited to age, gender, race, education, marital status, employment, religion, number of full and half siblings, as well as relationship, age and education of individual(s) who assists with sickle cell related healthcare decision making.

We will collect demographic information from parent/legal guardian of children (<18 years of age) including but not limited to age, gender, race, education, marital status, employment and religion. Additionally we will collect demographic information about the child including but not limited to age, gender, race, education, number of full and half siblings). Additionally patients and parents/legal guardians of patients will be asked to self-report information regarding themselves or the patient they care for including but not limited to patient age, gender, education level, marital status, genotype, insurance type, history of HLA typing, number of hospitalizations for sickle cell related complications in the past 2 years. No PHI will be accessed.

Participants will be asked to complete the following study surveys at within 2 weeks following their office/clinic visit, questionnaires will be available in paper version and electronically:

- Acceptability of education (*8 multiple choice, 2 short answer*)
- Decision Self-Efficacy Scale (*11 multiple choice*)
- Decisional Conflict Scale (*16 multiple choice*)
- Values survey (*14 multiple choice, 6 fill in the blank*)
- Realistic Expectations (*multiple choice*)
- Preparation for Decision Making Scale (*10 multiple choice*)
- Knowledge Survey (*25 multiple choice*)
- Choice Predisposition and Decision (*1 multiple choice and 4 fill in the blank*)
- Stage of Decision Making (*10 multiple choice*)

Participants => 18 years of age will complete:

- Emotional distress Anxiety – short form 6a – participant version
- Depression – short form 6a – participant version
- Fatigue – short form 6a – participant version
- Pain interference – short form 6a – participant version
- Physical Function – short form 8b – participant version

- Ability to participate in social roles and activities – short form 6a – participant version

Participants of children <18 years of age will complete:

- Fatigue – short form 10 – parent proxy
- Mobility – short form 8 – parent proxy
- Peer relations – short form 7 – parent proxy
- Anxiety – short form 8b – parent proxy
- Depressive symptoms – short form 6b – parent proxy

It is anticipated that these surveys will take 20-30 minutes to complete within 2 weeks following each visit. Surveys may be available via paper version and electronically.

Participants in Cohort A who are assigned to the control group will receive education regarding treatment consideration from their healthcare provider/team as per standard practice (usual care).

Participants in Cohort A who are assigned to the intervention group will receive education regarding treatment consideration from their healthcare provider/team as per standard practice. Additionally, they will be provided access to the decisional aid and will be provided with a unique access ID and password for purposes of this study. Participants will receive follow-up monthly via telephone call and/or e-mail to verify ability to access and navigate through website.

Visit 2

Participants will be scheduled for the second research visit to coincide with the completion of education presented by the healthcare provider/team. Participants will be asked to complete the study surveys within 2 weeks following the office/clinic visit via paper version or on-line. Self-report information regarding themselves or the patient they care for will be updated relating to sickle cell disease management and complications since Consent/Visit 1. Participants will receive follow-up monthly via telephone call and/or e-mail to verify ability to access and navigate through website.

Visit 3

Participants will be scheduled for the final research visit within 4 months of the completion of education and discussion with their healthcare provider/team. Participants will be asked to complete the study surveys as well as either via paper versions or online within 2 weeks following this office/clinic visit:

- Decision Regret Scale (*5 multiple choice*)
- Additionally, a qualitative interview will be conducted with the participants within 4 weeks of visit 3 to evaluate the extent to which the method of educational tools (standard practice or decision aid) helped the participant to recognize that a decision needs to be made regarding treatment of sickle cell disease, to understand the values that affect the decision, and understand if and how these values were addressed with the health care provider. Interviews will take approximately 30-45 minutes for completion. Interviews will

be audio recorded and transcribed verbatim for later analysis. Interviews will be conducted in a private setting, away from family members and clinical staff.

Self-report information regarding themselves or the patient they care for will be updated relating to sickle cell disease management and complications since Visit 2.

Cross-Over

After completion of final study visits/surveys and data collection, participants in the control group for Cohort A will be offered opportunity to visit the Decision Aid website. Participants will be given 4 weeks to review this site, at which time they will be asked to complete a series of questionnaires via paper version or electronically:

- Acceptability of education (*8 multiple choice, 2 short answer*)
- Decision Self-Efficacy Scale (*11 multiple choice*)
- Decisional Conflict Scale (*16 multiple choice*)
- Stage of Decision Making (*10 multiple choice*)
- Values survey (*14 multiple choice, 6 fill in the blank*)
- Realistic Expectations (*multiple choice*)
- Preparation for Decision Making Scale (*10 multiple choice*)
- Knowledge Survey (*25 multiple choice*)
- Choice Predisposition and Decision (*1 multiple choice and 4 fill in the blank*)
- Decision Regret Scale (*5 multiple choice*)

Participants => 18 years of age will complete:

- Emotional distress Anxiety – short form 6a – participant version
- Depression – short form 6a – participant version
- Fatigue – short form 6a – participant version
- Pain interference – short form 6a – participant version
- Physical Function – short form 8b – participant version
- Ability to participate in social roles and activities – short form 6a – participant version

Participants of children <18 years of age will complete:

- Fatigue – short form 10 – parent proxy
- Mobility – short form 8 – parent proxy
- Peer relations – short form 7 – parent proxy
- Anxiety – short form 8b – parent proxy
- Depressive symptoms – short form 6b – parent proxy

A qualitative interview will be conducted within 4 weeks of completion of the questionnaires to understand participant-perceived comparison of supportive care in decision making versus use of the Decision Aid tool. Participants will be asked to discuss the affect, if any, on their treatment decision prior to use of the Decision Aid tool. Participants will receive follow-up monthly via telephone call and/or e-mail to verify ability to access and navigate through website after receiving access to the decision aid.

Cohort B

Consenting/Visit 1

After consenting in-person or via telephone, we will collect demographic information from children (<18 years of age) including but not limited to age, gender, race, education, number of full and half siblings as well as information about the parent/legal guardian of the child including but not limited to age, gender, race, education, marital status, employment, and religion.

Participants will be asked to complete the following study surveys within 2 weeks following each clinic/office visit:

- Decision Self-Efficacy Scale (*11 multiple choice*)
- Pediatric fatigue – short form 10a
- Pediatric mobility – short form 8a
- Pediatric pain interference – short form 8a
- Pediatric peer relationship – short form 8a
- Pediatric anxiety – short form 8b
- Pediatric depressive symptoms – short for 8b

Surveys may be available on-line for distant participation.

Visit 2

Participants will be scheduled for the second research visit to coincide with their next clinic appointment or within 4 months of Visit 1. Participants will be asked to complete the study surveys via paper version or online within 2 weeks following the office/clinic visit.

Self-report information regarding themselves or the patient they care for will be updated relating to sickle cell disease management and complications since Consent/Visit 1.

Visit 3

Participants will be scheduled for the final research within 4 months of Visit 2. Participants will be asked to complete the study surveys via paper version or online within 2 weeks following clinic/office visit.

Additionally, a qualitative interview will be conducted with the child within 4 weeks following visit 3 to understand the implications of education regarding sickle cell disease using the web-based decision aid tool on their daily lives: implementation of learned information to manage sickle cell disease, discussion with parent/legal guardian and/or healthcare provider regarding information gleaned from the decision aid tool, including conversations about potential treatment options. Interviews will take approximately 30-45 minutes for completion. Interviews will be audio recorded and transcribed verbatim for later analysis. Interviews will be conducted in a private setting, away from parents and clinical staff.

Self-report information regarding themselves or the patient they care for will be updated relating to sickle cell disease management and complications since Visit 2.

Cohort C

After consenting to participate in the study in-person or via telephone demographic information will be collected from health care providers including but not limited to education, years of practice, age, and gender after Cohort A visit 3. Health care providers will be asked to complete one questionnaire after Cohort A visit 3 interview and again after Cohort A visit 4 interview. It is anticipated that this survey will take no more than 5 minutes to complete.

- Physician determination of patient readiness for treatment decision making in sickle cell disease

Study Population

Study population may be drawn from among sickle cell patients, any patient who is post-bone marrow transplant for sickle cell disease, and the caregivers of pediatric patients who receive care at the Aflac Cancer and Blood Disorders Center of Children's Healthcare of Atlanta (Egleston, Hughes Spalding, and Scottish Rite locations) and various sickle cell clinics across the United States. Contact will be made with physicians and sickle cell foundations through listserves, professional conferences, and seminars regarding this study. Recruitment flyers will be provided for placement in patient/parent/caregiver common areas to physicians, clinics, and sickle cell foundations known to the research team across the country after permission has been obtained from these entities. Recruitment flyers will request individuals to contact the research team if interested in participation. Discussion with physicians will occur prior to placement of flyers for Decision Aid website testing to obtain physician understanding of the study.

Recruitment of Women and Minorities as Research Subjects. Equal number of women and men are likely to be recruited. Majority of the patients will be of minority ethnic origin because of the demographics of distribution of SCD. The racial, gender and ethnic characteristics of the proposed subject population reflects the demographics of the study sites. We shall attempt to recruit subjects in respective proportion to these demographics. No exclusion shall be based on race, ethnicity, or gender.

There is a minimal risk of breach of confidentiality of health information even though no medical data will be collected from official medical records/charts and only self-reported information will be collected from participants. Participants have the right to refuse to answer self-reported questions regarding their health or the health of family members. Any private data reported by participants related to sickle cell disease will be maintained in a confidential file within the secure offices of the Hematology/Oncology Department. When collecting data from third parties (i.e. parents, caregivers, family) no names of patients with sickle cell disease, names of health care providers/medical facilities will be obtained. This is meant to decrease any possibility of patient identification. Participants in Cohort A and Cohort B will be informed that health care

providers will be made aware of their participation in Testing of Decision Aid due to the participation of health care providers in this study, Cohort C.

Age range

8 to 80 years, inclusive

Inclusion Criteria

Qualitative Needs Assessment Interviews and Beta Testing

1. Individuals with sickle cell disease ages 8 to 80 years, inclusive
2. Individuals who are post- bone marrow transplant for sickle cell disease
3. Parents/legal guardians/caregivers (including significant others, family and friends) of individuals with sickle cell disease (newborn to 80 years) directly involved in decision making with/for that individual
4. Parents/legal guardians/caregivers (including significant others) of individuals who are post-bone marrow transplant for sickle cell disease who are directly involved in decision making with/for that individual
5. Stakeholders involved in any aspect of sickle cell disease
6. Healthcare providers who are directly involved in sickle cell healthcare, including but not limited to physicians, nurse practitioners, physician assistants, social workers, and nurses.
7. All participants will be able to comprehend English
8. Patients <18 years may also participate in Testing of Decision Aid only if they complete the Needs Assessment Interview first.

Beta Testing (additional)

1. Access to the internet via smartphone, personal computer, tablet or other device allowing for access to the decision aid website for telephone interviews. (Computers may be provided for access during in-person interviews by the research team.)
2. Patients will have sickle cell disease.
3. Parents/caregivers will be directly responsible for care of child <18 years of age with sickle cell disease.
4. Health care providers will provide direct care to patients with sickle cell disease.
5. Participants will speak and read fluent Hindi for enrollment into the Hindi Beta testing portion of the study.

Testing of Decision Aid

1. Individuals with sickle cell disease ages 8 to 80 years, inclusive
OR
2. Parent/legal guardian of patients (age < 18 years) with sickle cell disease who are directly involved in decision making regarding sickle cell disease healthcare treatment
OR
3. Health care provider directly involved in care of individuals with sickle cell disease, including child of parent/legal guardian enrolled in study
4. Patients/parents/caregivers who have made a past decision to not obtain treatment of the considered option or who have not obtained treatment of the chosen option in past 12 months.
5. All participants will be able to comprehend English

6. Patients/Parent/Legal guardian will have access to the internet from iPad, smart phone or personal computer
7. Patients <18 years may participate in Testing of Decision Aid, Cohort B, if they have participated in the Qualitative Needs Assessment Interviews only if they complete the Needs Assessment Interview first.

Exclusion Criteria

Qualitative Needs Assessment Interviews

1. Family members/Individuals/Caregivers not directly involved in decision-making regarding sickle cell disease healthcare.
2. Family members/Individuals/Caregivers not directly involved in decision-making regarding healthcare for post-bone marrow transplant patients with sickle cell disease.
3. Adult patient/parent/legal guardian participant in Testing of Decision Aid aspect of this study
4. Healthcare providers who are not directly involved in care of sickle cell patients
5. Stakeholders who are not involved in any aspect of sickle cell disease

Testing of Decision Aid

1. Family Members/Individuals/Caregivers not directly involved in decision-making regarding sickle cell disease healthcare.
2. Patient/parent/legal guardian who has already made a decision to begin and has started the treatment option.
3. Parent/legal guardian of child who is participating in Cohort B of this study.
4. Child < 18 years of parent/legal guardian who is participating in Cohort A of this study and randomized to the control arm and not the decision aid arm.
5. Spouse, significant other, or other family member involved in decision making for child <18 years if parent/legal guardian of child already enrolled into this study.

Total number of subjects to be studied (including those screened for eligibility) in Qualitative Needs Assessment Interviews and Beta Testing:

Up to 50. Sample size is dependent on data saturation during analysis and need for verification of findings.

Total number of subjects to be studied in Hindi Beta Testing

Up to 50 individuals will be consented for participation in the Hindi Beta Testing study. Sample size is dependent on data saturation during analysis and need for verification of findings.

Total number of subjects to be studied (including those screened for eligibility) in Testing of Decision Aid:

Cohort A: 120

Cohort B: 25

Cohort C: Up to 50 (depending on number of health care providers providing care to patient population in this study).

Sample Size Calculations for the Randomized Clinical Trial (Cohort A)

We assume that patient involvement is 30% with standard care and we can double this with the intervention. Based on 90% power and 0.05 significance level we will require 110 patients, 55 in each group for comparing 2 binomial proportions⁴⁴. To account for attrition we propose to recruit 120 patients, 60 in each group treatment group with 20 in each of 3 age groups.

Total Duration of Participation

Qualitative Needs Assessment Interviews: 6 weeks

Decision Aid Testing: Up to 12 months

Recruitment Methods

Potential participants may be recruited from the Aflac Cancer and Blood Disorders Center of Children's Healthcare of Atlanta (Egleston, Hughes Spalding, and Scottish Rite locations) and the Georgia Comprehensive Sickle Cell Center at Grady Health System. Physicians will be notified via list-serves, at conferences and seminars of study recruitment. They will be asked to contact the study coordinator if interested in participating. We will provide patient recruitment flyers for placement in patient/parent/caregiver common areas in their office or clinic. Additionally, we will contact sickle cell foundations for assistance. We will ask that the recruitment flyers be placed on their websites. Recruitment flyers will request interested individuals to contact the research team if interested in participation. Discussion with physicians will occur prior to enrollment of subjects to obtain physician understanding of study. Patients and/or caregivers may be approached directly by research team members for participation in the needs assessment.

Flyers with study information for study sections will be provided to the clinics and to the healthcare providers.

Needs Assessment Interviews: Patients and/or caregivers may be approached directly by research team members for participation in the needs assessment. Physicians and other healthcare providers may also refer patients for possible participation. Potential participants may also contact the study coordinator directly using the contact information provided on the flyer if interested in hearing more about the study.

Hindi Beta Testing Recruitment

Health care providers will be notified by physicians involved in the study of the beta testing study. If interested, research staff will be notified and consent will be obtained if they desire participation. Physicians will be asked to identify potential patient and parent/caregiver participants. If potential participants agree to talk with research staff, the study will be introduced and, if interested, consent will be obtained.

Decision Aid Testing: Sickle cell healthcare providers who see patients at these sites will be provided with study information and asked to present the study to patients who are considering a therapy new to their care (chronic blood transfusion, hydroxyurea, bone marrow transplantation). After the healthcare provider obtains permission from the patient, a research team member will approach the patient to introduce the study.

Consenting

Needs Assessment Interviews: Potential participants may be introduced to the study by a member of the sickle cell healthcare team who will obtain permission for the individual to be approached by a member of the research team. Patients and/or caregivers may be approached directly by research team members for participation in the needs assessment. The potential participant may also directly contact the study coordinator via contact information provided on the study flyer. Screening for eligibility will be completed. If eligible, and the individual is interested, the consent will be verbally reviewed, including expected study activities, and potential risks and benefits. The individual will have an opportunity to discuss potential study participation with significant others, including caregivers and other family prior to consenting. All questions will be answered by a member of the research team and/or the PI. If the individual agrees to participate, he/she will be verbally consented in-person or via telephone.

Beta Testing

Potential participants will be introduced to the study by a member of their healthcare team who will obtain permission for the individual to be approached by a member of the research team. If permission is obtained for discussion with the research staff, the research staff will introduce the study. The consent will be reviewed. All questions will be answered. If the individual is interested in participation verbal consent will be obtained.

Decision Aid Testing: Potential participants will be introduced to the study by their primary sickle cell healthcare provider who will obtain permission for the patient to be approached by a member of the research team. The potential participant will be screened for eligibility. If eligible, and the individual is interested, the consent will be reviewed, including expected study activities, and potential risks and benefits. The individual will have an opportunity to take the consent home to discuss it with significant others, including caregivers and other family. The individual will also be given the opportunity to discuss it with his/her hematologist. All questions will be answered by a member of the research team and/or the PI. If the individual agrees to participate, he/she will be consented. A copy of the signed consent will be given to the participant.

Analytic Methods

Qualitative analysis will be performed using qualitative descriptive methods which is influenced and a similar to interpretive descriptive analysis. Qualitative descriptive^{45,46} analysis requires less interpretation than other types of qualitative analysis, such as phenomenological or interpretive description. Qualitative description lends itself to a more straightforward analysis that, by the nature of its methods, lends itself to this study. Analysis of these data will rely on components of the Ottawa Decision Support Framework for development of a codebook. This framework provides operational definitions of needs in the decision making process, such as decisional conflict (uncertainty), knowledge and expectations, personal values, and support/resources available. Additionally, data will be quantized or translated to numerical data for improved understanding of results⁴⁷. This method of analysis allows for quantification of themes, patterns, and idiosyncrasies unique to qualitative research that may otherwise be discarded as outliers in quantitative analysis⁴⁷.

We propose a randomized controlled trial of decision aid vs. usual care to determine its impact on previously defined endpoints measuring decisional process and decisional quality.

Avoidance of bias

Selection biases occur when the groups to be compared are different. We anticipate that randomization will avoid selection bias as well as volunteer or referral bias. A *drop out analysis will be carried out to determine the contribution of attrition bias*. Measurement biases involve systematic error that can occur in collecting relevant data and include, insensitive measure bias, expectation bias, recall or memory bias, attention bias, and verification or work-up bias. Systematic validation of the decision aid will avoid *insensitive measure bias* which occurs when instruments used are not sensitive enough to detect what might be important differences in the variable of interest. The risk of *Expectation bias*, when observers may err in measuring data toward the expected outcome will be avoided by masking or blinding the reviewer of the survey about the arm to which the patient was randomized. Recall or memory bias which can occur if outcomes being measured require that subjects recall past events will be avoided by administering surveys within days of the interaction with their health care provider.

Human Subjects

Protected Health Information

Name, address, telephone number, and email address (if appropriate) will be recorded to facilitate contact with study subjects and to mail gift cards. No other PHI will be collected or recorded.

Third Party Information

1. Information will be gathered from participants with sickle cell disease regarding individuals/family members (caregivers/parents/legal guardians) who assist with sickle cell healthcare decision making, including but not limited to relationship to participant, age, gender, marital status, education level of individuals/family members.
2. Parent/legal guardian of the child with sickle cell disease will be asked information including but not limited to their relationship to that child, the child's role in decision making regarding sickle cell healthcare, number of siblings the child has, demographic information such as gender, age, and education level of the child.

Potential Risks

There is a risk of breach of confidentiality. The web-based decision aid is maintained on a secure server and requires a unique individualized identification and password to log on. Users will be instructed to protect their log-on information, to not share it with anyone else, and to be aware of the presence of others when logging on to the site. All efforts will be made to avoid breach of confidentiality.

There is a risk of discomfort with qualitative interviews. The participant is not required to answer and question he/she does not feel comfortable answering. The participant may speak with the primary investigator, his/her physician or a member of the healthcare team as needed.

Potential Benefits

There are no direct benefits for participation in the Needs Assessment interviews though information learned may be used to benefit others in the future. There is a potential benefit of participating in Testing Decision Aid secondary to increased access to information that may increase the ability to make an informed values based decision regarding sickle cell treatment.

Data and Safety Monitoring Plan

Research staff directly involved in the study will have access to data collected during this study. Paper documents will be filed in a locked filing cabinet in a secure office setting. Electronic data will be maintained on a secure Hematology/Oncology share-drive with limited access behind a secure firewall at Emory University. Participant data will be identified with a unique number. The key connecting the participant to the ID number will be maintained separately from the study data and will be destroyed upon completion of the study, to include dissemination of findings. The ID key will be accessible only to members of the research team. All audio recordings will be identified on the recording with the unique participant identification number. All transcripts will be identified using the participant identification number and names of parents and health care providers will be indicated with "XXX" in the transcription. Audio transcriptions will be destroyed after transcription is complete and verified, analyzed and findings are disseminated.

The data and safety monitoring team will include the Principal Investigator and the study coordinator. Meetings will occur every 3 months from time of enrollment of the first patient. DSMP reports will be generated for each meeting. Any information regarding increased risks, modifications necessary to ensure patient safety, and adverse events will be discussed and submitted to the IRB according to established guidelines. All study data reviewed and discussed during these meetings will be kept confidential. Any breach in confidentiality will be reported to the IRB and regulatory agencies. The investigator will continue to review all available information and study results regarding this patient population. The PI will report to the IRB within 24 hours any serious adverse event occurring that is associated with this research study. Unexpected adverse events of moderate severity in association with the research intervention will be reported to the IRB within 5 business days. Reporting of adverse events to sponsors and federal agencies will be the responsibility of the investigator.

Withdrawal from Study

The participant may withdraw from the study at any time by notifying the PI and/or the research team. All data collected up until the point of withdrawal will be included in data analysis. No further data will be collected.

The participant may be withdrawn from the study if the participant does not participate in the educational process of usual care or if the participant assigned to intervention does not view the website prior to the next scheduled clinic appointment or does not show for the next appointment and does not reschedule that appointment within 4 weeks of the originally scheduled appointment.

Compensation

Study participants, (patients, parents/legal guardians) will be provided with a \$25 gift card for each completed set of survey questions.

Participants (patients, parents/legal guardians and caregivers) will be provided with a \$25 gift card for completion of each qualitative interview.

Healthcare providers and stakeholders will be given a sickle cell tie, bowtie or scarf for their participation in this study.

There will be no compensation provided for participation in the Hindi beta testing.