

CURE SICKLE CELL.

PRE-GENE THERAPY ASSESSMENT OF PATIENT READINESS AND RESILIENCE:

Best Practices and Recommendations for Implementation in Sickle Cell Disease

PATIENT READINESS AND RESILIENCE WORKING GROUP

Cure Sickle Cell Initiative (CureSCi) Patient Readiness and Resilience Working Group Members

STEVEN HARDY, PHD (CHAIR)
Children's National Hospital

CECELIA VALRIE, PHD
Virginia Commonwealth University

JERLYM PORTER, PHD, MPH
St. Jude Children's Research Hospital

MARIA RIVERA
Sickle Cell Community Consortium

CHARLES JONASSAINT, PHD, MHS
University of Pittsburgh

SOUMITRI SIL, PHD, ABPP
Children's Healthcare of Atlanta

LORI CROSBY, PSYD
Cincinnati Children's Hospital Medical Center

SHAWN BEDIAKO, PHD
*University of Maryland, Baltimore County
National Heart, Lung, and Blood Institute*

CLAYTON ANDREWS, MS, LPC
*Sickle Champions Men's Action Network (SC MAN)
Sickle Cell Mental Health and Wellness Initiative*

TEONNA WOOLFORD
*Sickle Cell Reproductive Health Education
Directive (SC RED)*

VICTORIA COLEMAN-COWGER, PHD
The Emmes Company, LLC



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Introduction

In September 2020, the National Heart, Lung, and Blood Institute (NHLBI) Cure Sickle Cell Initiative (CureSCi) convened the Patient Readiness and Resilience Working Group (PRRWG). The PRRWG was comprised of 10 members spanning mental health clinicians and researchers with expertise in pediatric and adult sickle cell disease (SCD), as well as individuals living with SCD and a parent of a child with SCD. The PRRWG met from 2020 – 2022 to develop best practice recommendations for the assessment of patient readiness and resilience prior to gene therapy for sickle cell disease. Recommendations were developed based on scientific evidence, expert clinical guidance, review of strategic planning documents, and consultation with CureSCi subcommittees and working groups representative of patient, advocate, clinician, and researcher perspectives.

An earlier version of this document was released for public comment in the spring of 2022. The PRRWG completed final revisions in January 2023.

Readiness and resilience are relevant constructs to consider in the setting of potentially life-altering medical procedures such as gene therapy. Individuals with SCD are already at higher risk for developing clinically significant levels of anxiety and depressive symptoms compared to the general population (Lee et al., 2020; Reader et al., 2020). As a result, it is prudent to pay attention to the ways in which existing psychosocial functioning factors into decisions about engaging with new medical treatments and the psychosocial outcomes (positive and negative) experienced following those treatments. The National Academies of Sciences, Engineering, and Medicine (2020) acknowledged this point in their strategic plan and blueprint for action on addressing sickle cell disease, noting for example that hematopoietic stem cell transplant confers a high psychosocial impact and recommending a holistic approach to care beginning with the pre-transplant period (Conclusion 7-4).

Although evidence specific to gene therapy for SCD is currently limited, research suggests psychosocial functioning prior to other major medical procedures (e.g., organ and stem cell transplants) have implications for treatment decision-making and post-procedure outcomes (Andorsky et al., 2006; Khemani et al., 2018; Mishkin et al., 2019). Expectedly, failed treatments and treatments resulting in complications or side effects pose real threats to mental health (Gallo et al., 2019). While successful treatments often lead to improved quality of life (Badawy et al., 2021), this should not be assumed to be a universal experience or necessarily translate into improvements in all aspects of quality of life (Bhatia et al., 2015; Dovert et al., 2023; Krishnamurti et al., 2019). An individual's readiness for major treatments (viewed broadly to include well-accepted physical health indicators of readiness as well as psychosocial indicators) will in most cases moderate treatment response and long-term outcomes. Therefore, the PRRWG asserts that issues of patient readiness, resilience, and psychosocial well-being are not benign or remote concerns in the context of gene therapy for SCD but rather are vital to optimizing treatment outcomes and clinical trial success.

INTENDED USE

This document is focused on best practices for assessing patient readiness and resilience before gene therapy. Ongoing psychosocial monitoring and support are recognized as critical during and after gene therapy; however, recommendations specific to those periods are beyond the current document's scope. The intended audience includes healthcare systems, medical and psychosocial care providers, and clinical research administrators and support staff. However, content presented here may also be relevant to community-based organizations, advocacy groups, managed care organizations and payors, policymakers, and other interested parties.

The assessment described below should not be construed to pressure or persuade anyone to participate in a gene therapy clinical trial, nor should its findings be used to permanently disqualify a person from receiving a potentially therapeutic treatment. In cases where concerns about readiness or resilience are noted, the PRRWG recommends a collaborative approach to developing resolutions that may involve actions or commitments from both investigative teams and patients or families.

As there is presently no evidence-based algorithm or cutoff for determining someone's readiness for gene therapy, readiness should be viewed as existing on

a continuum where people can demonstrate greater or lesser readiness but are rarely definitively ready or not ready. Readiness is also understood to be fluid, rather than static or a trait-like characteristic, and assessment results should only be considered a snapshot of one's readiness at a certain point in time with potential to change.

Results of the assessment should also not be viewed as a "gateway" to participation in a gene therapy clinical trial. Instead, the assessment should be used to gather pertinent data across a range of domains, facilitate meaningful dialogue, foster understanding and trust, and inform team-based and patient-directed discussions about perceived readiness. Interpretations of a patient's readiness for gene therapy are understood to be inherently subjective and biased. However, by providing standard guideposts for assessing readiness, we hope to make incremental progress towards promoting awareness of implicit and explicit bias and reduce the potential for these biases to influence care decisions.

This set of PRRWG best practice recommendations is focused on pre-gene therapy education delivery and assessment of knowledge and understanding, interest and motivation, and psychosocial risk and resilience factors.

THE RATIONALE FOR THESE RECOMMENDATIONS WAS FOUNDED UPON THE FOLLOWING OBSERVATIONS:

1. Invasive and life-altering procedures can introduce stress and influence psychosocial well-being.
2. Premorbid psychosocial factors can influence peri- and post-treatment mental health outcomes.
3. Premorbid psychosocial factors can influence peri- and post-treatment physical health outcomes.
4. Assessing psychosocial factors related to the anticipated experience of undergoing gene therapy for sickle cell disease can produce useful information for determining readiness and optimizing mental and physical health.

Conceptual Framework

The PRRWG determined that knowledge and understanding of gene therapy and clinical trials, interest in and motivation to pursue gene therapy, and psychosocial risk and resilience factors are essential aspects of one's readiness to participate in a gene therapy clinical trial for sickle cell disease (Figure 1). These three domains do not represent all potentially important components of readiness but were identified as shared and critical domains needing assessment. Knowledge and understanding, interest and motivation, and psychosocial risk and resilience are also understood to be interrelated constructs and of equal weight in estimating readiness for gene therapy.

Of note, the act of evaluating patient readiness for gene therapy clinical trials and, in particular, the assessment domains described below, hold relevance to accepted ethical principles outlined in the Belmont Report (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). Assessing an individual's knowledge to ensure they possess an adequate understanding of the treatment and probing for potential threats to autonomous decision-making upholds the principle of respect for persons. Beneficence is grounded in consideration for one's knowledge, motivation, and psychosocial risk and resilience factors, which is key to determining the degree to which participation in a gene therapy clinical trial introduces potential

harm. Careful assessment of knowledge, motivation, and psychosocial risk and resilience also represents an effort to uphold the principle of justice, given the current experimental nature of gene therapy for SCD and possibility that a minoritized group is exposed to disproportionate risk as genetic therapies are advanced for the wider population.

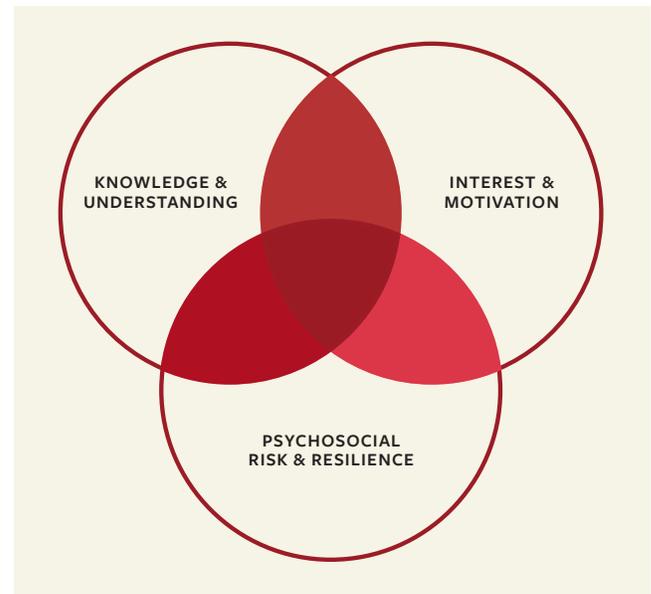


Figure 1. Patient Readiness & Resilience
Conceptual framework of factors underlying the continuum of patient readiness and resilience for gene therapy for Sickle Cell Disease

SUMMARY OF GOALS

The goals of the Pre-Gene Therapy Patient Readiness and Resilience Assessment are to:

1. Gather information about a patient's understanding of and perceived readiness for a gene therapy clinical trial. Premorbid psychosocial factors can influence peri- and post-treatment mental health outcomes.
2. Encourage open dialogue regarding any concerns about gene therapy. Use evidence-based communication strategies to enhance knowledge transfer.
3. Provide a conceptualization of psychosocial factors likely to influence participation in a gene therapy clinical trial and affect relevant outcomes.
4. Identify patient strengths that can be leveraged to promote psychosocial well-being before, during, and after a gene therapy clinical trial.
5. Identify psychosocial risks to be considered and addressed through tailored education, psychosocial support, and community resources.

Summary of Recommendations

INSTITUTIONAL SELF-ASSESSMENT

The recommended progression of the Pre-Genes Therapy Patient Readiness and Resilience Assessment is outlined in Figure 2. An essential first step of implementing this assessment involves an institutional self-evaluation of available psychosocial supports and resources. The PRRWG acknowledges that assessments of patient readiness and resilience will unfold differently depending on institution-specific characteristics. However, regardless of how services are delivered, certain resources should be available to all patients.

Institutions should ensure the availability of qualified and accessible clinicians to conduct the Pre-Genes Therapy Patient Readiness and Resilience Assessment and provide ongoing psychotherapeutic services as determined to be necessary following the assessment. Institutional and community resources (e.g., transportation assistance, temporary housing options, letters for work or school) should also be reviewed to ensure they are sufficient and that processes are in place to connect patients with resources. Flowcharts, communication plans, role definitions, and tracking and monitoring systems should be reviewed and refined and any identified gaps in supports or resources should be addressed before moving to the patient preparation step.

COMPREHENSIVE EDUCATION

Once a program has determined that it is adequately prepared to assess and support patients' psychosocial health, most investigative and clinical teams should begin providing tailored education about gene therapy at least 6–12 months before signing consent. This is consistent with expectations for education delivery prior to other major treatments (e.g., hematopoietic stem cell transplant) but may, on occasion, need to be shortened or lengthened depending on patient circumstances. Although this recommended timeline refers to education specific to the gene therapy clinical trial, it is expected that medical teams are providing information about gene

therapy and other disease-modifying treatments across the lifespan so that this is not the first time a patient is learning about gene therapy.

Recommendations are provided regarding evidence-based strategies to support effective delivery of education about gene therapy (*Table I*). Although the PRRWG favors providing comprehensive education and assessing readiness and resilience prior to informed consent, we recognize that it may be necessary for some trials to obtain consent earlier in the process. However, information obtained from the Pre-Genes Therapy Patient Readiness and Resilience Assessment is viewed as key to informing decisions about: 1) how to carry out informed consent; 2) the extent to which undue pressures to participate in the trial may influence decision-making; and 3) whether psychosocial risks exist that should be addressed before moving forward with treatment.

READINESS AND RESILIENCE ASSESSMENT

After education where patients learn about gene therapy and what to expect during the clinical trial, the PRRWG recommends conducting a comprehensive assessment of patient knowledge and understanding about gene therapy and clinical trials (*Table II*), interest and motivation (*Table III*), and psychosocial risk and protective factors (*Table IV*). The assessment should primarily take the form of a clinical interview, though cognitive testing and validated questionnaires may be used to supplement the assessment. A review of patients' health records should also be conducted to obtain pertinent history. However, clinicians should be cautious when relying on the health record to formulate impressions. Documentation for patients in the U.S. healthcare system who are Black and/or have SCD often contains stigmatizing and biased language that can affect provider behavior (Himmelstein et al., 2022; P Goddu et al., 2019). In cases where the patient's primary treating institution is different from the trial institution, it is essential that the trial team requests patient permission to hold a briefing with providers (particularly psychosocial clinicians) from their home institution.

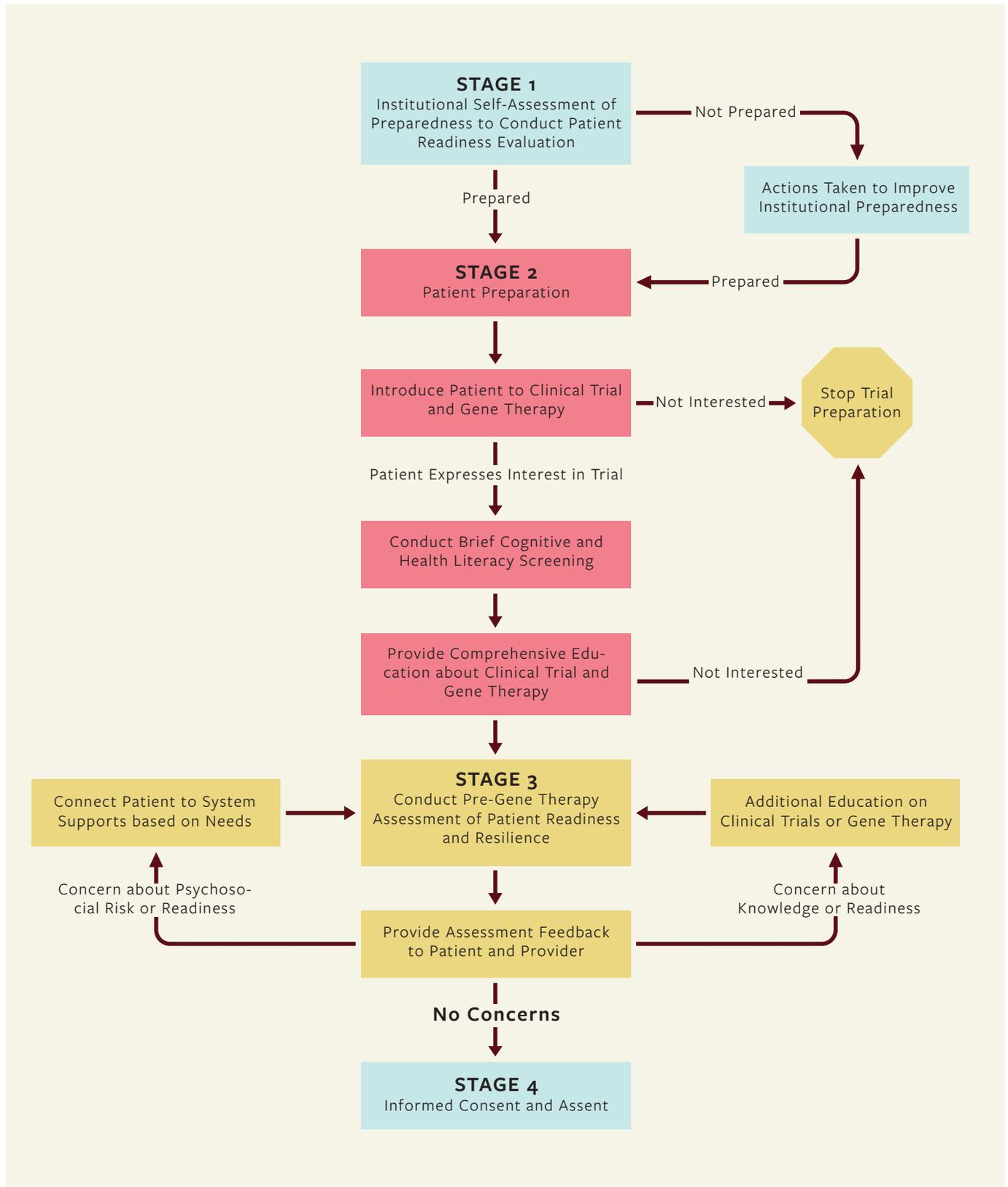
The patient readiness and resilience assessment should be conducted by a member of the psychosocial team with training and expertise in clinical interviewing and psychosocial assessment as well as adequate knowledge of sickle cell disease, gene therapies, medical ethics, and clinical trials. This clinician should also be familiar with details of trial-related education being provided to the patient. While the psychosocial clinician and Principal Investigator (PI) may lead efforts to evaluate readiness, attention to these considerations is the responsibility of all members of the clinical, research, and sponsor teams.

TERMINOLOGY

The term “gene therapy” is used in this document because it reflects the language most referenced in educational materials for the SCD community. However, gene therapy and gene editing are recognized as representing distinct treatments that will necessarily involve unique considerations and risks. With flexible implementation, the PRRWG views the following best practices for assessing patient readiness and resilience as equally appropriate and relevant to gene therapy and gene editing clinical trials.

“Cure” and “curative” are also commonly used terms but were intentionally excluded from this document. The PRRWG discourages use of these terms when discussing gene therapy with patients due to variability in personal definitions of cure and the potentially harmful misunderstandings that could result. For instance, some individuals may define the term cure as implying complete resolution of all SCD-related complications and risks (past and future). However, gene therapy might not reverse all previous complications (e.g., effects of stroke or avascular necrosis) or prevent all future risks (e.g., offspring with sickle cell disease or sickle cell trait). Therefore, the same treatment outcome could be interpreted by different people as successful, unsuccessful, curative, and non-curative. Although investigators would be expected to carefully review these details with patients during education and informed consent, avoiding the terms cure and curative will reduce the potential for misinterpretations.

Figure 2. Patient Readiness & Resilience Pre-Trial Process



**In some circumstances, it may be necessary and appropriate to bypass much of the Pre-Gene Therapy Patient Readiness and Resilience Assessment. Examples of such cases include a very young patient, a patient with severe cognitive limitations, or a patient presenting with a medical indication that raises the urgency for treatment or clearly shifts the risk/benefit balance. However, in these cases, consideration should be given to whether portions of the evaluation can still be completed in some form, whether an evaluation needs to be completed with a guardian or advocate, and whether an ethics consultation is warranted.*

Best Practices for Assessing Patient Readiness and Resilience

A set of best practice recommendations spanning four broad activities are identified: 1) supporting the effective delivery of initial education about gene therapy and clinical trials; 2) assessing an individual's knowledge and understanding of the proposed treatment and trial; 3) assessing an individual's interest in and motivation for gene therapy; and 4) assessing an individual's risk and protective factors that could influence psychosocial well-being, self-care, and health before, during, and after gene therapy.

Specific guidance for implementing these best practices, including sample questions, is provided in a later section of this document (Tables I – IV). An optional extended version of the interview is available in Appendix A: Tables S1 – S3. In these supplemental tables, questions marked as “Tier 1” reflect high priority questions that should be asked in most instances. Tier 1 questions were determined to have a high likelihood of producing clinically useful information. Questions labeled “Tier 2” reflect lower priority questions that may still produce clinically useful information, particularly in cases where a domain is known to be relevant to a patient or there is a concern that necessitates more detailed assessment. Clinicians relying on the extended interview may choose to ask most of the Tier 1 questions, while only asking some of the Tier 2 questions, with selections based on concerns or a desire to clarify information obtained from a Tier 1 question.

The sample questions follow a semi-structured interview format and can be viewed as a general guide for evaluating key areas of patient readiness. However, it is expected that clinicians may need to tailor specific questions for each patient and trial. The goal of the interview is to gather important information and elicit an open dialogue between the clinician and the patient regarding readiness for gene therapy.

Clinicians should be mindful of developmental and cognitive considerations and adapt questions to optimize effective communication. Providers will also need to rely on their clinical judgment to navigate other situational issues, such as those that accompany work with younger patients. For example, when assessing a child, consideration must be given to determining when it is important to meet privately with the child, how to tailor questions that are directed to a child's caregiver, and which tasks would be necessary for a child to master relative to tasks for which a caregiver would be responsible, and tasks for which there is shared responsibility.

Of note, in the remainder of the document, when best practices are implemented with patients under the age of 18, recommendations may also apply to their caregivers (e.g., caregivers completing assessments of health literacy and social support). Institutions and programs may need to further adopt a flexible approach in adhering to the guidance based on patient needs, situational and cultural contexts, and available resources.

1. BEST PRACTICES FOR EFFECTIVE EDUCATION DELIVERY

SEE TABLE I

- Assess relevant cognitive/learning abilities (prior to providing comprehension)
 1. Assess receptive language, working memory, literacy, and health literacy.
- Education delivery
 2. Provide written and audio information that can be easily understood and referenced outside of clinic visits.
 3. Plan to provide education in small chunks starting early in the process.
 4. Use evidence-based communication strategies to enhance knowledge transfer.
 5. Consider and address concerns about trust and bias that could interfere with education delivery.
 6. Monitor comprehension during education delivery.

2. BEST PRACTICES FOR EVALUATING KNOWLEDGE AND UNDERSTANDING

SEE TABLE II

- Assess knowledge of sickle cell disease and sickle cell disease treatment.
- Assess understanding of the clinical trial and gene therapy process.
- Assess understanding of possible short- and long-term outcomes of gene therapy.
- Assess prior knowledge and exposure to information about gene therapy that could impact an individual's perspective.
- Assess awareness of and connectedness with supportive resources and organizations.

3. BEST PRACTICES FOR EVALUATING INTEREST AND MOTIVATION

SEE TABLE III

- Assess values and adopt a non-judgmental approach to assess how gene therapy fits with values.
- Assess overall readiness and current position on continuum of readiness for gene therapy.
- Assess confidence in different components of the gene therapy process.
- Assess potential for pressure or influence from others.
- Assess past experiences of adversity and link to perceived readiness.

4. BEST PRACTICES FOR EVALUATING PSYCHOSOCIAL RISK AND RESILIENCE

SEE TABLE IV

- Assess individual factors using screening instruments.
 1. Pre-existing emotional and physical issues.
- Assess individual factors using clinical interview.
 2. Pre-existing emotional and physical issues.
 3. Schedule of life activities and events.
 4. Current challenges and stressors.
 5. Coping style.
 6. Optimism.
 7. Self-identity.
 8. Expectations.
- Assess family/close social network factors.
 9. Social networks of support.
 10. Primary support person or people.
 11. Family composition.
 12. Family structure.
 13. Family relationships.
- Assess environmental/community factors.
 14. Past relationships with healthcare providers.
 15. Access to the treating center.
 16. Connections with community-based resources and comfort with seeking support.
 17. Professional support for pre-existing issues/conditions.
- Assess cultural and societal factors.
 18. Family and cultural traditions.
 19. Acculturation (to the U.S., society, medical system, other systems and cultures).
 20. Immigration.
 21. Medical mistrust and suspicion.
 22. Experiences of racism, with a focus on the healthcare setting, and associated impact.

TABLE I. Strategies to support implementation of best practices for effective education delivery

ASSESS RELEVANT COGNITIVE / LEARNING ABILITIES (PRIOR TO PROVIDING COMPREHENSIVE EDUCATION)	
BEST PRACTICE	SUGGESTIONS FOR IMPLEMENTATION
<p>1. Assess receptive language, working memory, literacy, and health literacy</p>	<p><i>Review any records of past cognitive or academic testing. Arrange a briefing and discuss with the previous treating team their observations of literacy, health literacy, and cognitive functioning.</i></p> <ul style="list-style-type: none"> ● NIH Toolbox Cognition Battery (for patients aged 3 or older) <ul style="list-style-type: none"> – Picture Vocabulary Test (Ages 3-85) – Oral Reading Recognition Test (Ages 7-85) – List Sorting Working Memory Test (Ages 3-85) ● Health Literacy (for adolescent and adult patients, and caregivers of patients under age 18) <p>*choose one from options below:</p> <ul style="list-style-type: none"> – Brief Health Literacy Screen (BHLS) – Medical Term Recognition Test (METER) – Newest Vital Sign (NVS)
EDUCATION DELIVERY	
BEST PRACTICE	SUGGESTIONS FOR IMPLEMENTATION
<p>1. Provide written and audio information that can be easily understood and referenced outside of clinic visits</p>	<ul style="list-style-type: none"> ● Create a glossary of terms and plain language summary of study procedures, short- and long-term risks, and benefits. ● Include supplemental visual and audio aids to explain complex processes and timelines. ● Consider making study materials available electronically so they can be easily accessed by potential participants.
<p>2. Plan to provide education in small chunks starting early in the process</p>	<ul style="list-style-type: none"> ● Education should occur well enough in advance of consent to allow for varied rates of information acquisition. ● Education should occur over multiple short sessions rather than 1-2 long sessions.
<p>3. Use evidence-based communication strategies to enhance knowledge transfer</p>	<ul style="list-style-type: none"> ● Information should be grouped into small but related sections. ● Key information should be repeated multiple times and not assumed that discussing a topic on a single occasion will lead to adequate comprehension. ● Use engaging methods (e.g., images, videos) to deliver information and increase discussion, reflection, and bidirectional conversation. ● Use relatable terms and analogies when possible to explain complex processes. ● Use vignettes to assist in describing possible outcomes.
<p>4. Consider and address concerns about trust and bias that could interfere with education delivery</p>	<ul style="list-style-type: none"> ● Include familiar medical and psychosocial providers to assist with providing education. ● Allow a patient advocate(s) to join discussions at the patient’s discretion to minimize potential power differentials during the education process (e.g., someone to help ask questions, such as a community member, family member, ethics team member, IRB appointee, or ombudsperson). ● Provide opportunities to hear other patients’ stories (e.g., about decision-making, what questions they asked, what knowledge they felt they needed to be prepared, about outcomes). ● Provide print educational materials not funded or created by industry, individuals, or groups who could be viewed as having conflicts of interest.
<p>5. Monitor comprehension during education delivery</p>	<ul style="list-style-type: none"> ● Education should occur well enough in advance of consent to allow for varied rates of information acquisition. ● Education should occur over multiple short sessions rather than 1-2 long sessions.

TABLE II. Strategies to support implementation of best practices for evaluating knowledge and understanding

BEST PRACTICE	SAMPLE QUESTIONS
<p>1. Assess knowledge of sickle cell disease and sickle cell disease treatment</p>	<ul style="list-style-type: none"> • Sickle cell disease is a complicated illness. I’m interested to hear from you about the parts of sickle cell disease you feel like you have a good grasp on, and what parts feel less clear. <ul style="list-style-type: none"> – In the short-term, what are some of the complications someone with sickle cell disease might experience? What are the longer-term risks • Which sickle cell treatments have you tried in the past and which treatments are you currently receiving? <ul style="list-style-type: none"> – Which treatments have been most helpful? What hasn’t worked? – Have you ever made the decision to stop a treatment? If so, why?
<p>2. Assess understanding of the clinical trial and gene therapy process</p>	<ul style="list-style-type: none"> • Tell me what you know about what will happen if you decide to move forward with the gene therapy treatment? • What have you heard about the schedule for the treatment or clinical trial? <ul style="list-style-type: none"> – What needs to happen before the treatment begins? – Once you are admitted to the hospital for treatment, what happens and when? • What do you know about the prep regimen—the treatments you would need to get before gene therapy starts? For example, what are the names of the treatments, how are they given to you, and when would you receive them? <ul style="list-style-type: none"> – Why is that prep treatment needed? – What risks or side effects do you think you might experience as a result? • Let’s imagine that you decide to move forward with gene therapy. After the treatment is over, what do you think your life would be like in terms of ongoing doctors’ appointments, treatments, and medications? <ul style="list-style-type: none"> – How would that be similar or different to the way things are now? • Since gene therapy is a newer treatment, you will likely need to keep coming back to meet with the research team for many years to make sure the treatment was safe and effective. Do you have any concerns about the need to be followed by the research team for so long?
<p>3. Assess understanding of possible short- and long-term outcomes of gene therapy</p>	<ul style="list-style-type: none"> • Based on what you know about gene therapy, what do you think are the possible short- and long-term outcomes, ranging from worst case to best case scenario? <ul style="list-style-type: none"> – What does a successful treatment outcome look like to you? How likely do you think it is that you will experience this kind of outcome? – What would an unsuccessful outcome look like? How likely do you think it is that you will experience this kind of outcome? – Is it possible that the outcome of your gene therapy could be somewhere in the middle? For example, something that doesn’t feel like a total failure but also doesn’t feel like a complete success. What might that look like? • What new problems, if any, might you experience during and after the gene therapy treatment? <ul style="list-style-type: none"> – Do you think these would be short-term or long-term problems? – Do these seem like major problems or minor problems to you?
<p>4. Assess prior knowledge and exposure to information about gene therapy that could impact an individual’s perspective</p>	<ul style="list-style-type: none"> • Before you started talking to the healthcare team in charge of the gene therapy trial, what had you heard (e.g., from family, social media, doctors) about gene therapy in general or specifically for sickle cell disease?
<p>5. Assess awareness of and connectedness with supportive resources and organizations</p>	<ul style="list-style-type: none"> • Are you familiar with any sickle cell community organizations or resource or advocate groups locally or nationally (e.g., SCDA, Sickle Cell Consortium, CBOs, CureSCi, SC RED)? <p><i>If needed, provide information about resources (within treating and referring institutions, SCD advocacy groups, insurance-specific resources) to support patient knowledge and readiness. This may entail working closely with the team at the referring institution to identify local resources.</i></p>

TABLE III. Strategies to support implementation of best practices for evaluating interest and motivation

BEST PRACTICE	SAMPLE QUESTIONS
<p>1. Assess values and adopt a non-judgmental approach to assess how gene therapy fits with values</p>	<ul style="list-style-type: none"> • Everyone finds meaning in life in different ways. We all have different values and life priorities. For some people, their family is the thing they value most. For others, it's their spirituality, health, friendships, or other things. What are the things in life that are most important to you? • What are some reasons you are interested in gene therapy? If you moved forward with gene therapy, how would your life change? What concerns do you have about gene therapy?
<p>2. Assess overall readiness and current position on continuum of readiness for gene therapy</p>	<ul style="list-style-type: none"> • Obviously, coming here and talking to me is a big step towards preparing for gene therapy. What other steps, either in the hospital or at home, school/work, or in your community, have you taken to get ready for gene therapy? • Getting to this point in exploring a treatment like gene therapy can be similar to a roller coaster where there are frequent ups and downs. Sometimes you might feel ready for or confident in gene therapy, but other times you might feel uncertain or nervous about that same treatment. Imagine a scale that ranges from 0 to 10 where 0 is “Not ready at all for gene therapy” and 10 is “I’m totally ready for gene therapy.” Where do you think you fall on that continuum? <ul style="list-style-type: none"> – Talk to me about how you reached that place and what kept you from rating your readiness as higher or lower.
<p>3. Assess confidence in different components of the gene therapy process</p>	<ul style="list-style-type: none"> • How comfortable are you feeling about some of the changes that you will likely experience because of gene therapy? For example, having to devote a lot of time to medical appointments leading up to treatment and potentially having to stop other therapies like hydroxyurea. <ul style="list-style-type: none"> – How prepared are you feeling about being separated from your support system and disconnected from responsibilities and important activities? – What do you know about fertility preservation and how gene therapy may affect your ability to have children in the future? • How do you think you will handle the treatment once it starts? I’m wondering specifically about things you might experience during treatment like receiving chemotherapy, not feeling well, possibly feeling anxious or sad. • How do you think you will handle things after gene therapy is over? For example, I’m wondering about things like managing frequent medical appointments, having to take medications, dealing with activity limitations, potential infertility, or changes in family, peer, or community relationships.
<p>4. Assess potential for pressure or influence from others</p>	<ul style="list-style-type: none"> • It’s common for people considering serious treatments like gene therapy to ask for thoughts and advice from people they trust—like family or friends. Sometimes those people have strong feelings one way or another about treatment. To what extent are you feeling pressured by others to make a decision about gene therapy that you aren’t comfortable with?
<p>5. Assess past experiences of adversity and link to perceived readiness</p>	<ul style="list-style-type: none"> • Tell me about some of the challenges you have experienced living with sickle cell disease. How have you coped with those challenges and how have those experiences led you to this point where you are considering gene therapy?

TABLE IV. Strategies to support implementation of best practices for evaluating psychosocial risk and resilience

ASSESS INDIVIDUAL FACTORS USING SCREENING INSTRUMENTS	
ASSESSMENT AREA	SUGGESTIONS FOR IMPLEMENTATIONS
1. Pre-existing emotional and physical issues	<p><i>Review any records of past emotional and physical issues and treatments. Arrange a briefing and discuss with the previous treating team their observations of pre-existing emotional and physical issues making sure to include psychosocial team members.</i></p> <ul style="list-style-type: none"> ● Assess for comorbid psychiatric or medical conditions (measures can be identified from the CureSci Common Data Elements or PhenX Toolkit) <ul style="list-style-type: none"> – Depression – Anxiety – Stress – Sleep/fatigue problems – Poor health-related quality of life – Other medical/pain conditions (e.g., chronic pain, stroke, avascular necrosis)
ASSESS INDIVIDUAL FACTORS USING A CLINICAL INTERVIEW	
ASSESSMENT AREA	SAMPLE QUESTIONS
1. Pre-existing emotional and physical issues	<ul style="list-style-type: none"> ● What challenges, if any, have you dealt with in managing sickle cell disease or other medical concerns (e.g., chronic pain, asthma), mental health issues, or other aspects of your health? <ul style="list-style-type: none"> – What treatments (e.g., medical, psychological/psychiatric, integrative/alternative) have you previously explored to try to manage these symptoms or conditions? ● How do you feel you are doing now from an emotional standpoint in terms of coping with sickle cell disease or other health issues? ● Unfortunately, many people say they have experienced traumas or other significant life events that are distressing. Have you ever experienced any traumas or other distressing life events? This could include health-related traumas, but you could also think about traumas unrelated to sickle cell disease or your health. If so, when was the last time you experienced a trauma or distressing life event? <p><i>Review medical charts and then follow-up with patients concerning any issues not discussed based on previous questions.</i></p>
2. Schedule of life activities and events	<ul style="list-style-type: none"> ● Do you anticipate any problems that might come up with school or work before, during, or after the gene therapy trial? If so, how might you navigate those problems? ● Are there any additional activities that you participate in regularly? Do you think they will be impacted at all by the gene therapy trial? <ul style="list-style-type: none"> – Are there any big events or commitments coming up over the next year or two?
3. Current challenges and stressors	<ul style="list-style-type: none"> ● Stress is a normal part of life that everyone experiences from time to time. What’s the most stressful thing you are dealing with right now? How might that affect your readiness for gene therapy? ● A lot of people identify finances as a source of stress. How often do you worry about having enough money for things like food, gas, the power bill, or rent or the mortgage? What would you do if there were significant unexpected costs that came up during the trial (e.g., gas or travel costs, extra meals)
4. Coping style	<ul style="list-style-type: none"> ● How do you usually cope with stressful situations? <ul style="list-style-type: none"> – What do you do to manage the stress specifically related to SCD or other health issues? – Do you think the things you do to cope with stress work? Which strategies are more or less effective than others?
5. Optimism	<ul style="list-style-type: none"> ● How would you rate your level of confidence that things will generally work out on a 0 to 10 scale where 0 is “No hope at all that things will work out positively” and 10 is “Total confidence that things will work out positively”?

ASSESSMENT AREA	SAMPLE QUESTIONS
6. Self-identity	<ul style="list-style-type: none"> To what extent is having sickle cell disease and being a Sickle Cell Warrior an essential part of who you are (your identity)? <ul style="list-style-type: none"> How might going through gene therapy change that, if at all?
7. Expectations	<ul style="list-style-type: none"> What are your goals and expectations for gene therapy? What do you think life will be like after the trial? What are your life goals? Do you think participating in this trial will have any effect on your ability to meet those goals? Have you thought about if this does not work out the way you expect it to (e.g., some of your previous sickle cell complications don't go away)?

ASSESS FAMILY / CLOSE SOCIAL NETWORK FACTORS

ASSESSMENT AREA	SAMPLE QUESTIONS
1. Social networks of support	<ul style="list-style-type: none"> Everyone needs help at one point or another and it's good to have a community of people you can go to for help. We also find that people usually seek out different people for different types of support. For example, we might go to a good listener for emotional support, someone knowledgeable and trustworthy for information, and someone dependable for practical support like giving you a ride to the doctor. Who would you go to for each of these things—someone for emotional support, someone to get information, and someone to help you do something or handle a problem? <ul style="list-style-type: none"> Do you feel comfortable asking for support from these people? Do you feel confident that they would help you if you needed help?
2. Primary support person or people	<ul style="list-style-type: none"> Other than your doctor, who would be the first person or first people you called if you needed help with something related to your health during the gene therapy trial? Why? <ul style="list-style-type: none"> Is there anything that might get in the way of them helping you (e.g., responsibilities or commitments, limited familiarity with medical topics, mental/physical health challenges)?
3. Family composition	<ul style="list-style-type: none"> Who lives at home with you (e.g., parents, caregivers, significant others, children, extended family, friends)? Does anyone else in the family have sickle cell disease or other special healthcare needs (either developmental, psychological, or physical health issues)? Do you feel like your family has mostly everything it needs to get by (e.g., transportation, money, food, housing, etc.)?
4. Family structure	<ul style="list-style-type: none"> In some families, one person is clearly in charge and makes decisions for the family but in other families, multiple people seem to share that responsibility. How do decisions get made or problems get solved in your family?
5. Family relationships	<ul style="list-style-type: none"> How does everyone in your family get along? <ul style="list-style-type: none"> Are there any strained or challenging relationships? Do people in your family feel comfortable expressing their honest feelings?

ASSESS ENVIRONMENTAL / COMMUNITY FACTORS

ASSESSMENT AREA	SAMPLE QUESTIONS
1. Past relationships with healthcare providers	<ul style="list-style-type: none"> Do you and your doctor/healthcare team communicate effectively with each other? If not, what gets in the way? How would you describe your relationship, in general, with doctors, medical teams, hospitals, etc.? <ul style="list-style-type: none"> To what extent do you feel that your doctors and healthcare team respect and trust you? To what extent are you able to trust your doctors and healthcare team? How involved in treatment decisions do you like to be? <ul style="list-style-type: none"> Do members of your healthcare team(s) seek out and seem to value and honor your opinions/preferences?

ASSESSMENT AREA	SAMPLE QUESTIONS
2. Access to the treating center	<ul style="list-style-type: none"> • How do you typically get to the center? Do you have reliable transportation? • Are transportation costs manageable for the duration of treatment and follow-up care? • Do you know of any resources that are available to help with access and/or transportation to the treatment center (e.g., staying overnight, travel, parking, modes of transportation available)?
3. Connections with community-based resources and comfort with seeking support	<ul style="list-style-type: none"> • Are you involved in any religious/spiritual organizations or community groups? Do you feel like you can get support from them before, during, and after the trial? • Are you involved in any community organizations that specifically support or advocate for people with sickle cell disease?
4. Professional support for pre-existing issues/conditions	<ul style="list-style-type: none"> • What existing relationships do you already have in place for medical, mental health, or school/work needs? For example, is there someone you would go to for help with medical issues, mental health concerns, and school/work problems? • Do you have a primary care provider? Are they aware that you are considering gene therapy? Does your primary care provider ever talk with your medical specialist teams?

ASSESS CULTURAL AND SOCIETAL FACTORS

ASSESSMENT AREA	SAMPLE QUESTIONS
1. Family and cultural traditions	<ul style="list-style-type: none"> • Families and cultures often have different expectations for how people should be involved in each other's life. Who are the people that play an important role in your life? These people might include biological family members, spouses, caregivers, chosen or adopted family, relatives, or family friends or religious leaders. <ul style="list-style-type: none"> – Would you say that there are cultural expectations for involving certain people in your important life decisions (e.g., based on gender, seniority, or authority)? If so, have they been involved in discussions about the gene therapy clinical trial? • What family or cultural traditions (e.g., prayer, affirmations) bring you resilience or strength that can be called upon during times of stress?
2. Acculturation (to the U.S., society, medical system, other systems and cultures)	<ul style="list-style-type: none"> • Are there established family/cultural expectations or norms for who communicates with members of the healthcare team? <ul style="list-style-type: none"> – What are your/your family's preferred ways of communicating with members of the healthcare team? • Although the sickle cell disease care team and the gene therapy clinical trial team are both made up of healthcare professionals, the teams may act and communicate in different ways. Sometimes, that takes a while for people to get used to. What have you found to be helpful ways of working and communicating with your sickle cell team?
3. Immigration	<ul style="list-style-type: none"> • Are there any current or past immigration issues that would be helpful to discuss related to you or other family members? <p><i>If care has been primarily provided outside of the U.S., consider potential differences (both positive and negative) between care and experiences in the U.S. and previous place of living/origin.</i></p>
4. Medical mistrust and suspicion	<ul style="list-style-type: none"> • To what extent does it feel like members of your healthcare team or teams have your best interests at heart? • Has there ever been a time when you felt that someone on your healthcare team was actively working against you? If so, would you be comfortable telling me about that experience?
5. Experiences of racism, with a focus on the healthcare setting, and associated impact	<ul style="list-style-type: none"> • In what ways have you been treated differently in healthcare settings because of your race or because you have sickle cell disease? Does this seem to depend on the settings (e.g., emergency department vs. inpatient setting vs. sickle cell care clinic) or is it like that everywhere?

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TABLE S1. Strategies to support implementation of best practices for evaluating knowledge and understanding

BEST PRACTICE	SAMPLE QUESTIONS
<p>1. Assess knowledge of sickle cell disease and sickle cell disease treatment</p>	<p>TIER 1</p> <ul style="list-style-type: none"> ● Sickle cell disease is a complicated illness. I’m interested to hear from you about the parts of sickle cell disease you feel like you have a good grasp on, and what parts feel less clear <ul style="list-style-type: none"> – In the short-term, what are some of the complications someone with sickle cell disease might experience? What are the longer-term risks? ● Which sickle cell treatments have you tried in the past and which treatments are you currently receiving? <ul style="list-style-type: none"> – Which treatments have been most helpful? What hasn’t worked? – Have you ever made the decision to stop a treatment? If so, why? <p>TIER 2</p> <ul style="list-style-type: none"> ● The causes of sickle cell problems are complicated, but treatments can be complicated too. There are also new treatments being developed all the time and it can be hard to keep up with all of them. What sickle cell treatments are you familiar with? What have you heard about what they treat and how they work? What do you see as the pros and cons to each treatment?
<p>2. Assess understanding of the clinical trial and gene therapy process</p>	<p>TIER 1</p> <ul style="list-style-type: none"> ● Tell me what you know about what will happen if you decide to move forward with the gene therapy treatment? ● What have you heard about the schedule for the treatment or clinical trial? <ul style="list-style-type: none"> – What needs to happen before the treatment begins? – What needs to happen before the treatment begins? ● What do you know about the prep regimen—the treatments you would need to get before gene therapy starts? For example, what are the names of the treatments, how are they given to you, and when would you receive them? <ul style="list-style-type: none"> – Why is that prep treatment needed? – What risks or side effects do you think you might experience as a result? ● Let’s imagine that you decide to move forward with gene therapy. After the treatment is over, what do you think your life would be like in terms of ongoing doctors’ appointments, treatments, and medications? <ul style="list-style-type: none"> – How would that be similar or different to the way things are now? ● Since gene therapy is a newer treatment, you will likely need to keep coming back to meet with the research team for many years to make sure the treatment was safe and effective. Do you have any concerns about the need to be followed by the research team for so long?
<p>3. Assess understanding of possible short- and long-term outcomes of gene therapy</p>	<p>TIER 1</p> <ul style="list-style-type: none"> ● Based on what you know about gene therapy, what do you think are the possible short- and long-term outcomes, ranging from worst case to best case scenario? <ul style="list-style-type: none"> – What does a successful treatment outcome look like to you? How likely do you think it is that you will experience this kind of outcome? – What would an unsuccessful outcome look like? How likely do you think it is that you will experience this kind of outcome? – Is it possible that the outcome of your gene therapy could be somewhere in the middle? For example, something that doesn’t feel like a total failure but also doesn’t feel like a complete success. What might that look like?

BEST PRACTICE	SAMPLE QUESTIONS
	<ul style="list-style-type: none"> • What new problems, if any, might you experience during and after the gene therapy treatment? <ul style="list-style-type: none"> – Do you think these would be short-term or long-term problems? – Do these seem like major problems or minor problems to you?
4. Assess prior knowledge and exposure to information about gene therapy that could impact an individual’s perspective	<p>TIER 1</p> <ul style="list-style-type: none"> • Before you started talking to the healthcare team in charge of the gene therapy trial, what had you heard (e.g., from family, social media, doctors) about gene therapy in general or specifically for sickle cell disease?
5. Assess awareness of and connectedness with supportive resources and organizations	<p>TIER 1</p> <ul style="list-style-type: none"> • Are you familiar with any sickle cell community organizations or resource or advocate groups locally or nationally (e.g., SCDA, Sickle Cell Consortium, CBOs, CureSCi, SC RED)? <p><i>If needed, provide information about resources (within treating and referring institutions, SCD advocacy groups, insurance-specific resources) to support patient knowledge and readiness. This may entail working closely with the team at the referring institution to identify resources.</i></p>

TABLE S2. Strategies to support implementation of best practices for evaluating interest and motivation

BEST PRACTICE	SAMPLE QUESTIONS
1. Assess values and adopt a non-judgmental approach to assess how gene therapy fits with values	<p>TIER 1</p> <ul style="list-style-type: none"> • Everyone finds meaning in life in different ways. We all have different values and life priorities. For some people, their family is the thing they value most. For others, it’s their spirituality, health, friendships, or other things. What are the things in life that are most important to you? • What are some reasons you are interested in gene therapy? If you moved forward with gene therapy, how would your life change? What concerns do you have about gene therapy?
	<p>TIER 2</p> <ul style="list-style-type: none"> • How might treating sickle cell disease with gene therapy interfere with or get in the way of your values?
2. Assess overall readiness and current position on continuum of readiness for gene therapy	<p>TIER 1</p> <ul style="list-style-type: none"> • Obviously, coming here and talking to me is a big step towards preparing for gene therapy. What other steps, either in the hospital or at home, school/work, or in your community, have you taken to get ready for gene therapy? • Getting to this point in exploring a treatment like gene therapy can be similar to a roller coaster where there are frequent ups and downs. Sometimes you might feel ready for or confident in gene therapy, but other times you might feel uncertain or nervous about that same treatment. Imagine a scale that ranges from 0 to 10 where 0 is “Not ready at all for gene therapy” and 10 is “I’m totally ready for gene therapy.” Where do you think you fall on that continuum? <ul style="list-style-type: none"> – Talk to me about how you reached that place and what kept you from rating your readiness as higher or lower.
	<p>TIER 2</p> <ul style="list-style-type: none"> • What alternatives to gene therapy are you considering, or have you considered?
3. Assess confidence in different components of the gene therapy process	<p>TIER 1</p> <ul style="list-style-type: none"> • What alternatives to gene therapy are you considering, or have you considered? How comfortable are you feeling about some of the changes that you will likely experience because of gene therapy? For example, having to devote a lot of time to medical appointments leading up to treatment and potentially having to stop other therapies like hydroxyurea.

BEST PRACTICE	SAMPLE QUESTIONS
	<ul style="list-style-type: none"> – How prepared are you feeling about being separated from your support system and disconnected from responsibilities and important activities? – What do you know about fertility preservation and how gene therapy may affect your ability to have children in the future? • How do you think you will handle the treatment once it starts? I’m wondering specifically about things you might experience during treatment like receiving chemotherapy, not feeling well, possibly feeling anxious or sad. • How do you think you will handle things after gene therapy is over? For example, I’m • wondering about things like managing frequent medical appointments, having to take medications, dealing with activity limitations, potential infertility, or changes in family, peer, or community relationships.
4. Assess potential for pressure or influence from others	<p>TIER 1</p> <ul style="list-style-type: none"> • It’s common for people considering serious treatments like gene therapy to ask for thoughts and advice from people they trust—like family or friends. Sometimes those people have strong feelings one way or another about treatment. To what extent are you feeling pressured by others to make a decision about gene therapy that you aren’t comfortable with?
	<p>TIER 2</p> <ul style="list-style-type: none"> • What do the important people in your life think about the possibility of you undergoing gene therapy for your sickle cell disease? • Other than yourself, who else in your family, friend, or community group has the loudest voice or strongest opinion about your option to undergo gene therapy?
5. Assess past experiences of adversity and link to perceived readiness	<p>TIER 1</p> <ul style="list-style-type: none"> • Tell me about some of the challenges you have experienced living with sickle cell disease. How have you coped with those challenges and how have those experiences led you to this point where you are considering gene therapy?
	<p>TIER 2</p> <ul style="list-style-type: none"> • Can you tell me about a time when you experienced adversity or something really difficult? How did you handle or cope with that situation? • In what ways, if at all, have your past experiences of adversity moved you towards gene therapy or prepared you for what you think your gene therapy experience will be like?

TABLE S3. Strategies to support implementation of best practices for evaluating psychosocial risk and resilience

ASSESS INDIVIDUAL FACTORS USING SCREENING INSTRUMENTS	
ASSESSMENT AREA	SUGGESTIONS FOR IMPLEMENTATION
1. Pre-existing emotional and physical issues	<p><i>Review any records of past emotional and physical issues and treatments. Arrange a briefing and discuss with the previous treating team their observations of pre-existing emotional and physical issues making sure to include psychosocial team members.</i></p> <ul style="list-style-type: none"> • Assess for comorbid psychiatric or medical conditions (measures can be identified from the CureSCI Common Data Elements or PhenX Toolkit) <ul style="list-style-type: none"> – Depression – Anxiety – Stress – Sleep/fatigue problems – Poor health-related quality of life – Other medical/pain conditions (e.g., chronic pain, stroke, avascular necrosis)

ASSESS INDIVIDUAL FACTORS USING A CLINICAL INTERVIEW

ASSESSMENT AREA	SAMPLE QUESTIONS
<p>1. Pre-existing emotional and physical issues</p>	<p>TIER 1</p> <ul style="list-style-type: none"> ● Do you anticipate any problems that might come up with school or work before, during, or after the gene therapy trial? If so, how might you navigate those problems? ● Are there any additional activities that you participate in regularly? Do you think they will be impacted at all by the gene therapy trial? <ul style="list-style-type: none"> – Are there any big events or commitments coming up over the next year or two?
<p>2. Schedule of life activities and events</p>	<p>TIER 1</p> <ul style="list-style-type: none"> ● What challenges, if any, have you dealt with in managing sickle cell disease or other medical concerns (e.g., chronic pain, asthma), mental health issues, or other aspects of your health? <ul style="list-style-type: none"> – What treatments (e.g., medical, psychological/psychiatric, integrative/alternative) have you previously explored to try to manage these symptoms or conditions? ● How do you feel you are doing now from an emotional standpoint in terms of coping with sickle cell disease or other health issues? ● Unfortunately, many people say they have experienced traumas or other significant life events that are distressing. Have you ever experienced any traumas or other distressing life events? This could include health-related traumas, but you could also think about traumas unrelated to sickle cell disease or your health. If so, when was the last time you experienced a trauma or other distressing life event? <p>TIER 2</p> <ul style="list-style-type: none"> ● How would you describe your health currently? <p><i>Review medical charts and then follow-up with patients concerning any issues not discussed based on previous questions.</i></p>
<p>3. Current challenges and stressors</p>	<p>TIER 1</p> <ul style="list-style-type: none"> ● Stress is a normal part of life that everyone experiences from time to time. What’s the most stressful thing you are dealing with right now? How might that affect your readiness for gene therapy? ● A lot of people identify finances as a source of stress. How often do you worry about having enough money for things like food, gas, the power bill, or rent or the mortgage? What would you do if there were significant unexpected costs that came up during the trial (e.g., gas or travel costs, extra meals)? <p>TIER 2</p> <ul style="list-style-type: none"> ● What are some things that commonly get in your way when you are trying to achieve goals or get things done?
<p>4. Coping style</p>	<p>TIER 1</p> <ul style="list-style-type: none"> ● How do you usually cope with stressful situations? <ul style="list-style-type: none"> – What do you do to manage the stress specifically related to SCD or other health issues? – Do you think the things you do to cope with stress work? Which strategies are more or less effective than others? <p>TIER 2</p> <ul style="list-style-type: none"> ● Do you ever use your religious or spiritual beliefs or practices to manage stress or SCD? What does this usually include? Has that worked for you?
<p>5. Optimism</p>	<p>TIER 1</p> <ul style="list-style-type: none"> ● How would you rate your level of confidence that things will generally work out on a 0 to 10 scale where 0 is “No hope at all that things will work out positively” and 10 is “Total confidence that things will work out positively”? <p>TIER 2</p> <ul style="list-style-type: none"> ● How would you handle a situation where there is evidence that things might not work out?

ASSESSMENT AREA	SAMPLE QUESTIONS
6. Self-identity	<p>TIER 1</p> <ul style="list-style-type: none"> To what extent is having sickle cell disease and being a Sickle Cell Warrior an essential part of who you are (your identity)? <ul style="list-style-type: none"> How might going through gene therapy change that, if at all?
7. Expectations	<p>TIER 1</p> <ul style="list-style-type: none"> What are your goals and expectations for gene therapy? What do you think life will be like after the trial? What are your life goals? Do you think participating in this trial will have any effect on your ability to meet those goals? Have you thought about if this does not work out the way you expect it to (e.g., some of your previous sickle cell complications don't go away)?
	<p>TIER 2</p> <ul style="list-style-type: none"> Are you concerned you could lose your job/get demoted or that your schoolwork will be disrupted?

ASSESS FAMILY / CLOSE SOCIAL NETWORK FACTORS

ASSESSMENT AREA	SAMPLE QUESTIONS
1. Social networks of support	<p>TIER 1</p> <ul style="list-style-type: none"> Everyone needs help at one point or another and it's good to have a community of people you can go to for help. We also find that people usually seek out different people for different types of support. For example, we might go to a good listener for emotional support, someone knowledgeable and trustworthy for information, and someone dependable for practical support like giving you a ride to the doctor. Who would you go to for each of these things – someone for emotional support, someone to get information, and someone to help you do something or handle a problem? <ul style="list-style-type: none"> Do you feel comfortable asking for support from these people? Do you feel confident that they would help you if you needed help?
	<p>TIER 2</p> <ul style="list-style-type: none"> What resources are available to help with home/family responsibilities like childcare? Do you have people beyond your primary caregiver who can help with these obligations?
2. Primary support person or people	<p>TIER 1</p> <ul style="list-style-type: none"> Other than your doctor, who would be the first person or first people you called if you needed help with something related to your health during the gene therapy trial? Why? <ul style="list-style-type: none"> Is there anything that might get in the way of them helping you (e.g., responsibilities or commitments, limited familiarity with medical topics, mental/physical health challenges)?
3. Family composition	<p>TIER 1</p> <ul style="list-style-type: none"> Who lives at home with you (e.g., parents, caregivers, significant others, children, extended family, friends)? Does anyone else in the family have sickle cell disease or other special healthcare needs (either developmental, psychological, or physical health issues)? Do you feel like your family has mostly everything it needs to get by (e.g., transportation, money, food, housing, etc.)?
4. Family structure	<p>TIER 1</p> <ul style="list-style-type: none"> In some families, one person is clearly in charge and makes decisions for the family but in other families, multiple people seem to share that responsibility. How do decisions get made or problems get solved in your family?
	<p>TIER 2</p> <ul style="list-style-type: none"> How would you describe each person's role in your family?

ASSESSMENT AREA	SAMPLE QUESTIONS
5. Family relationships	<p>TIER 1</p> <ul style="list-style-type: none"> • How does everyone in your family get along? <ul style="list-style-type: none"> – Are there any strained or challenging relationships? – Do people in your family feel comfortable expressing their honest feelings?
ASSESS ENVIRONMENTAL / COMMUNITY FACTORS	
ASSESSMENT AREA	SAMPLE QUESTIONS
1. Past relationships with healthcare providers	<p>TIER 1</p> <ul style="list-style-type: none"> • Do you and your doctor/healthcare team communicate effectively with each other? If not, what gets in the way? • How would you describe your relationship, in general, with doctors, medical teams, hospitals, etc.? <ul style="list-style-type: none"> – To what extent do you feel that your doctors and healthcare team respect and trust you? – To what extent are you able to trust your doctors and healthcare team? • How involved in treatment decisions do you like to be? <ul style="list-style-type: none"> – Do members of your healthcare team(s) seek out and seem to value and honor your opinions/preferences?
	<p>TIER 2</p> <ul style="list-style-type: none"> • Tell me about some challenging experiences you have had, if any, with a healthcare provider or the medical system more generally. • Tell me about a positive relationship you have had with a healthcare provider or team. What made that relationship positive? • Do you feel like your doctor or members of your medical team spend enough time when providing information? Do they give you enough time to process information before making a decision? • How confident do you feel about your doctors' knowledge of sickle cell disease?
2. Access to the treating center	<p>TIER 1</p> <ul style="list-style-type: none"> • How do you typically get to the center? Do you have reliable transportation? • Are transportation costs manageable for the duration of treatment and follow-up care? • Do you know of any resources that are available to help with access and/or transportation to the treatment center (e.g., staying overnight, travel, parking, modes of transportation available)?
	<p>TIER 2</p> <ul style="list-style-type: none"> • How far away is the center from where you live? How long does it take to get there?
3. Connections with community-based resources and comfort with seeking support	<p>TIER 1</p> <ul style="list-style-type: none"> • Are you involved in any religious/spiritual organizations or community groups? Do you feel like you can get support from them before, during, and after the trial? • Are you involved in any community organizations that support or advocate for people with sickle cell disease?
	<p>TIER 2</p> <ul style="list-style-type: none"> • Have you ever been involved in advocacy efforts to change things for people with sickle cell disease? • Are you familiar with the Sickle Cell Disease Association of American (SCDAA) and any of their local chapters or other advocacy groups/organizations (e.g., the Sickle Cell Reproductive Health Education Directive–SC RED)?

ASSESSMENT AREA	SAMPLE QUESTIONS
4. Professional support for pre-existing issues/conditions	<p>TIER 1</p> <ul style="list-style-type: none"> • What existing relationships do you already have in place for medical, mental health, or school/work needs? For example, is there someone you would you go to for help with medical issues, mental health concerns, and school/work problems? • Do you have a primary care provider? Are they aware that you are considering gene therapy? Does your primary care provider ever talk with your medical specialist teams?

ASSESS CULTURAL AND SOCIETAL FACTORS

ASSESSMENT AREA	SAMPLE QUESTIONS
1. Family and cultural traditions	<p>TIER 1</p> <ul style="list-style-type: none"> • Families and cultures often have different expectations for how people should be involved in each other's life. Who are the people that play an important role in your life? These people might include biological family members, spouses, caregivers, chosen or adopted family, relatives, or family friends or religious leaders. – Would you say that there are cultural expectations for involving certain people in your important life decisions (e.g., based on gender, seniority, or authority)? If so, have they been involved in discussions about the gene therapy clinical trial? • What family or cultural traditions (e.g., prayer, affirmations) bring you resilience or strength that can be called upon during times of stress? <p>TIER 2</p> <ul style="list-style-type: none"> • I want to understand more about the family and/or cultural beliefs, values, and structures that are important to you. How would you describe your culture? What family or cultural traditions are central to your life?
2. Acculturation (to the U.S., society, medical system, other systems and cultures)	<p>TIER 1</p> <ul style="list-style-type: none"> • Are there established family/cultural expectations or norms for who communicates with members of the healthcare team? – What are your/your family's preferred ways of communicating with members of the healthcare team? • Although the sickle cell disease care team and the gene therapy clinical trial team are both made up of healthcare professionals, the teams may act and communicate in different ways. Sometimes, that takes a while for people to get used to. What have you found to be helpful ways of working and communicating with your sickle cell team?
3. Immigration	<p>TIER 1</p> <ul style="list-style-type: none"> • Are there any current or past immigration issues that would be helpful to discuss related to you or other family members? <p><i>If care has been primarily provided outside of the U.S., consider potential differences (both positive and negative) between care and experiences in the U.S. and previous place of living/origin.</i></p>
4. Medical mistrust and suspicion	<p>TIER 1</p> <ul style="list-style-type: none"> • To what extent does it feel like your members of your healthcare team or teams have your best interests at heart? • Has there ever been a time when you felt that someone on your healthcare team was actively working against you? If so, would you be comfortable telling me about that experience?
5. Experiences of racism, with a focus on the healthcare setting, and associated impact	<p>TIER 1</p> <ul style="list-style-type: none"> • In what ways have you been treated differently in healthcare settings because of your race or because you have sickle cell disease? Does this seem to depend on the settings (e.g., emergency department vs. inpatient setting vs. sickle cell care clinic) or is it like that everywhere? <p>TIER 2</p> <ul style="list-style-type: none"> • Have you heard of other people having negative experiences with the healthcare system because of their race or having sickle cell disease? • How do these experiences affect the trust that you are able to develop with doctors, healthcare teams, hospitals, and/or researchers?