Title: Engaging Parents of Children with Sickle Cell Disease and their Providers in Shared-Decision Making for Hydroxyurea (ENGAGE HU)

Principal Investigator: Lori E. Crosby, PsyD.
Division of Behavioral Medicine and Clinical Psychology
Cincinnati Children’s Hospital Medical Center

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1. **ABSTRACT:**

Sickle cell disease (SCD) is a genetic blood disorder that places children at risk for serious medical complications, early morbidity and mortality, and high healthcare utilization. In the U.S., SCD primarily affects African-American and Latino children. Hydroxyurea is the only disease-modifying treatment for this devastating and life-threatening disease. National Evidence-Based Guidelines recommend the use of a shared decision making approach to offer hydroxyurea to all children with SCD as early as nine months of age. Hydroxyurea uptake remains low because parents lack information about hydroxyurea and have concerns about its safety and potential long-term side effects (e.g. cancer, infertility, birth defects). Clinicians do not have the training or tools to facilitate a shared discussion with parents that provides medical evidence and considers parent preferences and values. The current study compares two methods for disseminating hydroxyurea guidelines and facilitating shared decision-making: the American Society of Hematology’s hydroxyurea clinician pocket guide (usual care method) and a clinician hydroxyurea shared decision-making toolkit (H-SDM toolkit). The specific aims of the study are to evaluate the effectiveness of the usual care dissemination method (clinician pocket guide) and the H-SDM clinician toolkit dissemination method on: parent report of decisional uncertainty (primary outcome chosen by parents of children with SCD), parent perception of experiencing shared decision-making, parent knowledge of hydroxyurea, the number of children offered hydroxyurea, hydroxyurea uptake (those with active prescriptions), and child health outcomes (pain, neurocognitive functioning, sickle cell related quality of life and healthcare utilization). Eligible children must be between the ages of 0 and 5 and a candidate for hydroxyurea to participate. The trial will use a stepped-wedge design (clinic is the unit of randomization). The long-term objective of the research team is to improve the quality of care for children with SCD. We propose that suboptimal care for patients with SCD is preventable with the use of multicomponent dissemination methods if developed with key stakeholders and designed to address barriers to high quality care at multiple levels (patient, clinician, healthcare system, and community).

2. **STUDY PURPOSE:**

The purpose of the study is to answer the following research question: will use of the hydroxyurea shared decision making toolkit (H-SDM toolkit) dissemination method be more effective than the ASH clinician pocket guide dissemination method (usual care) at increasing clinicians’ ability to implement sickle cell specific evidence-based guidelines and improve/maintain patient-centered health outcomes?

3. **BACKGROUND:**

Sickle cell disease (SCD) is a genetic blood disorder that affects approximately 100,000 individuals in the United States (US). (Hassell, 2010) Approximately 1 in 2500 babies born in the US has SCD, making it the most common disorder identified by newborn screening. (American Academy of Pediatrics, 2007) SCD is chronic and associated with early mortality (average lifespan of 40-50 years). A daily dose of oral hydroxyurea has been shown to significantly reduce the frequency of pain (two fold decrease) and serious medical complications: dactylitis, severe pain and swelling in the bones of the hands or feet (fivefold decrease), acute chest syndrome, a life-threatening condition where the lungs do not get the oxygen they need (three
fold decrease). (Wang et al., 2011) Children taking hydroxyurea require fewer transfusions and spend less time in the hospital for fewer dactylitis (50 fewer days), pain (100 fewer days), and acute chest syndrome (300 fewer days). (Wang et al., 2011) This medication may also protect organs from the effects of chronic sickling.

Because the benefits of hydroxyurea outweigh the risks, in 2014, the National Heart, Lung, and Blood Institute (NHLBI) published Evidence-Based Guidelines for the Management of Sickle Cell Disease that recommended hydroxyurea therapy be offered to children with SCD as early as 9 months of age using a shared decision-making process. Prior to the release of the NHLBI guidelines, children with SCD were only offered hydroxyurea if they had frequent pain or other serious SCD-related complications. (National Heart, Lung and Blood Institute, 2017) In contrast, the new guidelines state that all children with the most severe genotypes (HbSS and HbS/β0thalassemia) be offered hydroxyurea. This has resulted in a change in practice, from a prevention model to an intervention model. It also means that the number of children eligible for hydroxyurea has significantly increased (about a 2-fold increase at our institution).

Shared decision-making is one method of targeting the worries, fears and uncertainty noted by parents, which is one reason the NHLBI recommended its use. Currently, the only tool to assist providers with implementing hydroxyurea guidelines for SCD is a clinician pocket guide developed by the American Society of Hematology (ASH). Pocket guides are widely used and are usually rated as useful at the point of care by clinicians, (Korn, Reichert, Simon, & Halm, 2003; Siebens, Tucker, & Leander, 2004) but the majority of pocket guides only target clinician motivation. They do not provide training to increase motivation, guided practice in communication skills to elicit preferences that build clinician self-efficacy, audit and feedback to reinforce behavior change or decision support tools to help clinicians engage parents and support parents in decision-making.

We used Agency for Healthcare Research & Quality (AHRQ) funding to develop, test, and begin to disseminate a parent-centered, technology-enhanced decision-support toolkit, the Hydroxyurea Shared Decision Making Toolkit (H–SDM toolkit), to assist clinicians in implementing shared decision-making for hydroxyurea and parents in feeling more confident about their decision. This toolkit targets factors noted in the Cochrane reviews (Légaré et al., 2010; Légaré et al., 2014) and the literature on behavior change (Godin, Bélanger-Gravel, Eccles, & Grimshaw, 2008), motivation, self-efficacy, and patient readiness; we hypothesize that this dissemination method will lead to increased shared decision-making, less parent uncertainty about the decision, increased offering of hydroxyurea, and ultimately improve hydroxyurea uptake. The current study proposes to address a critical gap in the literature by comparing two dissemination methods (ASH clinician pocket guide and the H–SDM toolkit) for improving adoption of the NHLBI guideline recommended practice of shared decision-making about hydroxyurea for children with SCD. We will also examine the impact of these dissemination methods on patient/parent-centered outcomes.

This project is significant because it will improve the quality of the evidence available for parents and clinicians to make an informed decision about hydroxyurea, thereby improving care and health outcomes for young children with SCD. There is high potential for study findings to be adopted into clinical practice and improve care delivery. Furthermore, the project focuses on outcomes identified by parents and clinicians as important to a child’s health.

4. STUDY DESIGN:
Overview

Cincinnati Children’s Hospital Medical Center (CCHMC) is the Coordinating Center (CC) for this multisite comparative effectiveness trial. As such, CCHMC will be overseeing the study conduct, regulatory and institutional review board (IRB) administration and compliance. CCHMC will not serve as a study site.

We are proposing to use a Single (Central) IRB model to administer this project. Under this model, an ENGAGE HU site has the option to rely exclusively on the full review conducted by the CCHMC IRB provided a reliance agreement is in place. The Site’s local IRB will not be involved in the approval of annual reviews and in any of the amendments to the study. However, local sites and their IRB teams will be updated on study progress and amendments by the ENGAGE HU CC team.

Design

This study will be a stepped wedge cluster randomized controlled trial (RCT). In a stepped wedge design, each clinic begins to enroll patients using the usual care dissemination method. Then, each cluster, one-by-one, crosses over to using the H-SDM toolkit dissemination method (one cluster will crossover every 6 months). Training for the H-SDM toolkit will begin during the last month of the Usual Care period for each cluster. Each cluster will enroll approximately 7-9 participants per time period. Enrollment will end 27 months after study initiation.

A total of 260 participants (parents of young children with SCD) will be enrolled and complete measures at baseline, and 4-6 months later in-person or online via REDCap. Data on clinician offering of hydroxyurea, hydroxyurea uptake and healthcare utilization will be collected throughout the study. Fidelity will be assessed using a checklist and by reviewing audio recordings of clinic visits (20% of visits).
Study Flow - Chart:

Prior to Enrollment

Total 260: Obtain informed consent. Screen potential subjects by inclusion and exclusion criteria; obtain history, document.

Baseline & Intervention

Baseline assessments and administer study intervention (SCD quality of life, ages & stages, health literacy, demographics, decisional conflict scale, dyadic option, hydroxyurea knowledge, satisfaction with decision making)

Final Visit (6 months later)

Final visit assessments of outcome measures and safety (SCD quality of life, ages & stages, medication adherence, adverse events, use of decision aids)

31-36 months Study Closeout

Maintenance Assessment

Site follow-up survey
Specific Aim 1: Evaluate the effectiveness of the usual care dissemination method (clinician pocket guide) and the H-SDM toolkit dissemination method on: 1) parent report of decisional uncertainty for hydroxyurea (primary outcome chosen by parents of children with SCD - Effectiveness); and 2) parent report of experiencing shared decision making when talking with their clinician about hydroxyurea (Effectiveness), in a sample of children (0-5 years of age).

Hypothesis 1: Compared to usual care (clinician pocket guide), the H-SDM toolkit dissemination method will result in an increase in the use of a shared decision making process for hydroxyurea, and parents feeling less uncertain in their decision about hydroxyurea.

Specific Aim 2: Evaluate the effectiveness of the usual care dissemination method (clinician pocket guide) and the H-SDM toolkit dissemination method on: 1) parent knowledge of hydroxyurea (Effectiveness); 2) children offered hydroxyurea (Reach); 3) children with an active hydroxyurea prescription (uptake – Effectiveness); and 4) child health outcomes: pain, neurocognitive functioning, sickle cell related quality of life and healthcare utilization (Effectiveness).

Hypothesis 2: Compared to usual care (clinician pocket guide), the H-SDM toolkit dissemination method will result in parents of children with SCD 0-5 years of age knowing more about hydroxyurea, more children offered and receiving hydroxyurea, and these children experiencing positive health outcomes.

Interventions

Usual Care: In this condition, sites will provide current guidelines for offering hydroxyurea and use the American Society of Hematology (ASH) pocket guide as a reference. ASH developed ‘The Hydroxyurea and Transfusion Therapy for the Treatment of Sickle Cell Disease’ clinician pocket guide based on the National Heart, Lung, and Blood Institute’s Evidence Based Management of Sickle Cell Disease: Expert Panel Report, 2014.’ The pocket guide recommends use of shared decision making.

Hydroxyurea shared decision making toolkit (H-SDM toolkit): During the H-SDM toolkit condition, sites will develop methods for identifying Eligible Patients & Monitoring Progress, have the opportunity to use Implementation Tools, and will use the Visit Decision Aids. The H-SDM toolkit has four visit decision aids to support parents in their decision about hydroxyurea: pre-visit brochure, in-visit issue card, after-visit booklet and video narratives (videos of parents telling their story about how they made a decision about hydroxyurea).

5. DURATION:

The project will begin in December 2017 and will last until November 2020. Each participant will be enrolled in the study for 4-6 months. Enrollment will be completed 27 months after the study begins. The final data report will be submitted for peer review to PCORI in February 2021.

6. SELECTION AND RECRUITMENT OF PARTICIPANTS:

260 children diagnosed with sickle cell disease, 0-5 years of age, and their parents who receive care in one of the IRB-approved sickle cell sites will be enrolled in the study.

Inclusion Criteria
1. Diagnosis: sickle cell disease
2. Age: birth-5 years, inclusive
3. Eligible for hydroxyurea (genotype SS, Sβ0Thal or other genotype + clinical complications)
4. Child’s parent, legal guardian, or designated decision maker (caregiver) must participate in both study visits
5. Child’s parent, legal guardian, or designated decision maker (caregiver) must able to read, understand, and speak English

Exclusion Criteria
1. Parent/legal guardian has previously been approached OR made a decision about whether to initiate Hydroxyurea.
2. Any and all other diagnoses or conditions which, in the opinion of the site investigator or hematologist, would prevent the patient from being a suitable candidate for the study.

Recruitment

Successful recruitment and retention of parents is essential to this study. To ensure successful recruitment, the Stakeholder Advisory Council will review and provide feedback on the recruitment/retention plan.

We will consecutively enroll eligible young children with SCD who have been identified by provider referral or EMR review. Provider referral and EMR will be used to identify potentially eligible study participants (see informed consent section about partial waiver of authorization). The research team will approach the child’s provider to obtain approval before contacting the potential participant.

Eligible patients will receive a letter and flyer by mail. A research coordinator with experience recruiting patients with SCD will then either follow up by phone or approach families in clinic. Interested families will be consented in clinic or by phone (e-consent) and the baseline assessments scheduled. Study visits will be scheduled at the family’s convenience (before/after clinic visits, evenings, and SCD events). If a parent/caregiver fails to complete baseline assessments within 30 days of consent, then the parent/caregiver may be rescreened, re-consented and asked to complete baseline assessments again. A participant may only be rescreened and re-consented one time.

Retention

Retention strategies will include: 1) scheduling visits at times convenient for the family (during clinic visits); 2) “reminder” phone calls for visits or to complete assessments; 3) allowing questionnaires to be completed online. In addition, the rationale for two visits and the importance of follow-up will be reviewed with each family at baseline to engage them as partners in the research process. To prevent loss to follow up, we will also collect patient permission to contact two close family members or friends if the participant’s family is difficult to reach.

7. PROCESS OF OBTAINING CONSENT:

The protocol includes a waiver of informed consent and a waiver of documentation of consent for clinicians participating in the trial. The protocol this protocol is eligible for waiver or alteration of required elements of the informed consent process for clinicians because the protocol meets all of the following criteria: 1) the research presents no more than “minimal risk” of harm to clinicians, 2) the
waiver or alteration will not adversely affect the rights and welfare of clinicians, 3) it is not practical to obtain consent from all clinicians at all sites as this would impede the research, 4) clinicians will be provided with additional pertinent information after their participation (e.g. information on their individual performance and the performance of their site and other sites in the trial), 5) the research is not subject to FDA regulation, and 6) the research involves no procedures for which written consent is normally required outside of the research context.

This protocol also includes a partial waiver of authorization for recruitment purposes. The purpose of this waiver is to allow the ongoing review of PHI for the purpose of identifying patients who need to be approached to obtain consent/authorization for research. This review will include all patients from birth to age 5 diagnosed with SCD receiving clinical care at the performance sites.

This protocol also includes a short parent consent form as 1) the research presents no more than “minimal risk” of harm to the child/parent, 2) the waiver or alteration will not adversely affect the rights and welfare of the child/parent (caregiver), 3) since the goal is to consent by phone or in clinic, it would not be practical to use a long consent form (a long consent form can be used if a local IRB requires it), 4) parents/caregivers may be provided with additional pertinent information after their participation (e.g. clinicians will discuss adherence to hydroxyurea with child/parent as part of routine clinical practice), 5) the research is not subject to FDA regulation, and 6) the research involves no procedures for which written consent is normally required outside of the research context (i.e. parents/caregivers may complete measures during clinic visits or at home as part of routine clinical practice).

All parents/caregivers will receive a study information sheet and participate in an informed consent process. Sites may use the study information sheet or full consent form as the study information sheet. The informed consent process will be initiated prior to the parent/caregiver agreeing to participate in the study and will continue throughout study participation. Discussion of risks and possible benefits of study participation will be provided to participants. An IRB-approved short consent form describing the study procedures and risks will be given to participants (some sites may use the IRB-approved full consent form). Participants are required to read and review the document or have the document read to her or him. Research staff will explain the research study to the participant and answer any questions that may arise. The parent/caregiver will sign or electronically sign the informed consent document prior to any study-related assessments. Parents/caregivers will be given the opportunity to discuss the study with family members or friends and think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to parents/caregivers for their records. The rights and welfare of the family will be protected by emphasizing to parents/caregivers that the quality of their child’s clinical care will not be adversely affected if they decline to participate in this study. The consent process will be documented in the research and/or clinical record.

8. STUDY PROCEDURES:

Clinics will either use the pocket guide or the H-SDM toolkit. The goal is to change care at the clinic level. In this way, all eligible patients will receive care consistent with the condition (usual care or intervention) regardless of whether they enroll in the study or not. Clinical teams will use tools from the dissemination methods during previsit planning, during the clinic visit where clinicians ask the parent to make a decision about initiating hydroxyurea, and afterwards to monitor progress (e.g., offering HU, documentation of parent decision, HU prescription, HU labs).

8a. Study Schedule
### Day -28 to -1 - Screening
- Total N=260 (n = 1-2 patients per month per site)
- Obtain informed consent
- Screen potential subjects by inclusion and exclusion criteria
- Obtain history, document

### Day 0 ± 14 - Baseline period/Study intervention visit
- Measures may be completed online before or after visit if participant requests
- Administer study intervention

### ± 7 days – Intervention visit follow-up
- Mail reminder for 6 mo visit (and to text pictures if have a hydroxyurea prescription)

### 5.5 months ± 7 days – Final Visit reminder telephone call
- Reminder call for 6 mo visit

### 6 months ± 8 weeks – Final Visit
- Follow-up assessments of study endpoints and safety

### 33 months ± 2 weeks after study ends – Site follow-up telephone call
- Site staff complete follow-up survey with coordinating center

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8b. For the usual care condition:

All sites receive printed copies, the link to download copies, and the link to the app for the pocket guide to distribute to their clinicians. Site clinicians view a live or recorded didactic presentation reviewing the NHLBI guidelines for hydroxyurea. Sites will then develop or update their site-specific care guidelines for hydroxyurea, and a plan for implementing them. A printed copy of the pocket guide will be made available in the clinic for reference. Research staff will approach eligible patients/families prior to their clinic visit, provide informed consent (in-person or e-consent), and administer baseline assessments (15-30 minutes). If parents/caregivers prefer, some baseline assessments can be completed online. Clinicians discuss hydroxyurea. Research staff administer remaining baseline assessments at end of the clinic visit (15-30 minutes) but parents/caregivers can complete these online if they prefer. After the baseline assessments are complete, clinicians/research staff document hydroxyurea offered and use of usual care (i.e. site-specific guidelines). The goal is to schedule the final visit to coincide with a routine clinic visit (4-6 months later); however, final visit assessments can be completed online (10-20 minutes).

8c. For the H-SDM toolkit condition:

All sites develop a systematic way of identifying eligible patients and documenting offering hydroxyurea. All sites receive didactic presentation on toolkit and virtual practice. Clinicians are trained on implementing visit decision aids and develop a process for systematically implementing them with eligible patients. Research staff will approach eligible patients prior to their clinic visit, provide informed consent (in-person or e-consent), and administer baseline assessments (15-30 minutes). If parents/caregivers prefer, some baseline assessments can be completed online. Research/clinical staff
give parents/caregivers previsit brochure and access to parent video narratives. Clinicians use in-visit and after visit booklet with eligible patients/families (10-20 minutes). Research staff administer remaining baseline assessments at end of the clinic visit (15-30 minutes) but parents/caregivers can complete these online if they prefer. After the baseline assessments are complete, clinicians/research staff document hydroxyurea offered and use of usual care (site-specific guidelines). The goal is to schedule the final visit to coincide with a routine clinic visit (4-6 months later); however, final visit assessments can be completed online (10-20 minutes).

8d. Baseline and Final Assessments

The following data will be collected from participants/families or clinical/research staff:

<table>
<thead>
<tr>
<th>Construct</th>
<th>Measure</th>
<th>Baseline</th>
<th>6 mo (Final Visit)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcomes</strong></td>
<td></td>
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<tr>
<td>Parent reported decisional uncertainty</td>
<td>Decisional Conflict Scale (DCS)(O’Connor) – E*</td>
<td>X</td>
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<td></td>
<td>Measures uncertainty experienced when feeling uninformed about options, unclear about personal values, or unsupported in making a choice. Cronbach’s alpha of 0.96.</td>
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<tr>
<td>Parent reported perception of shared decision-making</td>
<td>Dyadic OPTION(Melbourne, Sinclair, Durand, Légaré, &amp; Elwyn, 2010) – E*</td>
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<td>Describes clinician behaviors to involve a patient/parent in decision-making. A total score is calculated which ranges from 0 (no involvement) to 100 (maximal involvement). Dyadic OPTION scores correlate well with OPTION scale(Melbourne et al., 2011); 1 item &quot;My doctor and I made the decision together&quot;(Légaré et al., 2010) -</td>
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<td><strong>Secondary Outcomes</strong></td>
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<tr>
<td>Parent reported satisfaction with decision making</td>
<td>6 item survey – E*</td>
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<td>3 items adapted from the empirical research related to the concept of procedural justice and 3 items assessing influence of faith on decision making.(Allen &amp; Marshall, 2010; Cascardi, Poythress, &amp; Hall, 2000) If the Cronbach’s alpha for these items is acceptable (≥ .70), ratings will be summed to obtain a total score; otherwise, items will be analyzed separately.</td>
<td>X</td>
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<tr>
<td>Parent reported Hydroxyurea knowledge</td>
<td>8 item survey – E*</td>
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<td>Hydroxyurea knowledge survey (8 items): developed based on the existing literature, the Ottawa Knowledge User Manual, parent and clinician stakeholders and used in our pilot work.(Walton et al., April 2016) If the Cronbach’s alpha for these items is acceptable (≥ .70), items will be summed to obtain a total score; otherwise, items will be analyzed separately.</td>
<td>X</td>
<td></td>
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<tr>
<td>Hydroxyurea offered</td>
<td>1 item reported by research coordinator – R*</td>
<td>X</td>
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<td>1 of 3 responses – completed by the research coordinator based on review of EMR data: hydroxyurea was not offered, offered, or previously prescribed. If not offered, coordinators will choose a reason why (i.e. not eligible because patient is on transfusions, not eligible because patient has comorbid condition, no time to offer, clinician forgot, ill visit, or an open field to enter another reason). This will be verified for recorded encounters using the audio files.</td>
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<tr>
<td>Hydroxyurea uptake</td>
<td>Active hydroxyurea prescription –E*</td>
<td>X</td>
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<td></td>
<td>1 item reported by the research coordinator. They will report whether patients enrolled in the study have an active prescription for hydroxyurea using the EMR (prescription in the last 6 months).</td>
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<tr>
<td>Hydroxyurea adherence</td>
<td>Lab values &amp; pharmacy refill records –E*</td>
<td>X</td>
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<td></td>
<td>Labs reported by the research coordinator based on the EMR: 1) fetal hemoglobin (HbF) level – fetal hemoglobin increases when taking hydroxyurea as prescribed; 2) absolute neutrophil</td>
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**Assessment Strategy**

<table>
<thead>
<tr>
<th>Construct</th>
<th>Measure</th>
<th>Brief Description/ Psychometrics (GM-4)</th>
<th>Baseline</th>
<th>6 mo (Final Visit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent report of Hydroxyurea adherence</td>
<td>Medical Adherence Measure (MAM) Subscale: Medication Adherence (Zelikovsky et al., 2008) – E*</td>
<td>9 item survey measuring adherence problems, extent of non-adherence in pediatric populations. Nonadherence and late adherence are calculated as a percent (0% to 100%).</td>
<td>X</td>
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<tr>
<td>Parent report of SCD-specific quality of life and pain</td>
<td>Peds-QL SCD Module(Panepinto et al., 2013) – E*</td>
<td>Measures several domains of health-related quality of life including pain impact, fatigue, pain management, emotions, communication and treatment adherence; Total Score; α = .95.</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Parent report of neurocognitive functioning</td>
<td>Ages &amp; Stages Questionnaire(Squires, Bricker, &amp; Potter, 1997) – E*</td>
<td>Reliable, accurate developmental and social-emotional screener for children between birth and age 6. Cronbach’s alpha ranges from .60 to .85.</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Healthcare utilization</td>
<td>Hospitalizations, emergency room visits, ill visits – E*</td>
<td>EMR data on the number of hospitalizations, ill visits, and emergency room visits in the 6 months prior to enrollment (if possible, some participants may be 9 months of age) and the 6 months after enrollment.</td>
<td>X</td>
<td>X</td>
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</table>

**Covariates**

| Demographics | Demographics survey | 10 item survey assessing family demographics including patient and parent age, gender, race and ethnicity, socioeconomic status, insurance (public vs. private), and parent highest level of education completed. | X |
| Health Literacy | Newest Vital Sign(Weiss et al., 2005) | Newest Vital Sign (3 minutes): tests literacy skills for both numbers and words and has been highly correlated with the REALM.(Osborn et al., 2007) Cronbach’s alpha = >.76 | X |

**Fidelity**

| Parent involvement in decision-making | Observed OPTION scale(Elwyn et al., 2005) – I* | Observer quantifies clinician behaviors to involve a parent in decision-making. A total score is calculated which ranges from 0 (no involvement) to 100 (maximal involvement). OPTION scores are reliable and valid(Elwyn et al., 2005). Each audi-taped clinic visit will be independently coded by two research coordinators to ensure high reliability [inter-observer agreement = 0.82 in Dr. Brinkman’s recent trial.(William B Brinkman et al., 2013)] | X |
| Intervention fidelity | H-SDM toolkit fidelity – I* | Checklist to assess which components of the H-SDM toolkit used and to what extent. | X |
| Continued use of intervention | Follow-up survey - M | Survey to assess continued implementation of the guidelines and clinical characteristics of the sites to understand barriers and facilitators to maintaining implementation. | 3 mo. after enrollment ends |

*RE-AIM Model: R = Reach; E= Effectiveness, A = Adoption; I= Implementation; M = Maintenance

9. DATA/ANALYSIS METHODS:

The data will be analyzed based on the intent-to-treat principle. All patients will remain in the arm of the study to which they were randomized, regardless of whether or not they receive the assigned dissemination method.

9a. Randomization
This study will be a stepped wedge cluster randomized controlled trial (RCT). In a stepped wedge design, each clinic begins to enroll patients using the usual care dissemination method. Then, each cluster, one-by-one, crosses over to using the H-SDM toolkit dissemination method (one cluster will crossover every 7 months) (Légaré et al., 2010). The order in which the clusters crossover is random (i.e., the cluster is the unit of randomization; see Figure 3) and will be managed by the study statisticians. Sites will be randomly assigned to 3 clusters (3 sites per cluster). The randomization will guarantee that each cluster has a site considered large, medium and small (<270 patients = small; >270 – 500 = medium; >501 = large). Training for the H-SDM toolkit will begin during the last month of the Usual Care period for each cluster. Each cluster will enroll approximately 7-9 participants per time period.

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Timeline</th>
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<tr>
<td></td>
<td>0-3 Months</td>
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<tr>
<td><strong>Cluster 1</strong></td>
<td></td>
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<tr>
<td>Sites 4, 7, 3</td>
<td>IRB, Training, Study Prep</td>
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<tr>
<td><strong>Cluster 2</strong></td>
<td></td>
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<tr>
<td>Sites 1, 8, 5</td>
<td>IRB, Training, Study Prep</td>
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<tr>
<td><strong>Cluster 3</strong></td>
<td></td>
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<tr>
<td>Sites 9, 6, 2</td>
<td>IRB, Training, Study Prep</td>
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</tbody>
</table>

9b. Missing Data

Missing data will be handled using multiple group multiple imputation (with M = 100 imputed datasets) (Cox, Smith, Brown, & Fitzpatrick, 2009) consistent with currently accepted methodological practice. (Godin, Bélanger-Gravel, Eccles, & Grimshaw, 2008).

9c. Aim 1

Data from all participants at all time-points will be aggregated within treatment group assignment and analyzed as such. Intervention groups will be compared on baseline characteristics, including demographics and laboratory measurements, using descriptive statistics. Specifically, for Aim 1, each of the M = 100 imputed data sets will be analyzed testing for significant DCS and Dyadic Option mean differences between Toolkit and Usual care groups using two specific a-priori analytic techniques: 1.) All predictor and both response variables will be group-mean centered (using the site-specific mean) prior to analysis to address nesting (non-independence) within site by reducing each variable’s ICC to zero, and 2.) parameter estimate constraints in multiple-group SEM will ensure that the assumption of homogeneity of covariate regression slopes is met when controlling for the influence of parent age, parent health literacy, participant gender, participant age, disease severity, and SES on DCS and Dyadic Option means between groups.

9d. Aim 2
The secondary outcomes of hydroxyurea knowledge and child reported health outcomes will be evaluated using similar methods to eliminate site level variance prior to data analysis. Specifically, we will analyze response variables (hydroxyurea offered, hydroxyurea uptake) as binary categorical and convert parameter estimates to odd ratios for interpretation. Specifically, for part one of Aim 2, simple logistic regression analyses will be performed on each of the \( M = 100 \) imputed datasets to determine significant differences between Toolkit and Usual Care after controlling for the covariates listed in Aim 1. For part 2 of Aim 2, multiple-group SEM with covariates, as outlined in Aim 1 above, will be used to test for significant group differences in hydroxyurea knowledge, PEDS-QL sickle cell disease (SCD), Ages & Stages, Health Literacy, fetal hemoglobin levels and ANC.

9e. Exploratory Analyses

For the third part of Aim 2, healthcare utilization variables (number of hospitalizations, ill visits, and emergency room visits) will be analyzed as count variables and examined in exploratory analyses. ER visits, hospitalizations, and ill visits count differences will be assessed with count variable analyses that first determine whether Poisson or negative binomial count distribution analyses are needed prior to testing for significant Toolkit versus Usual Care mean rate differences.

9f. Process Improvement

During the H-SDM toolkit period, data will be tracked on a monthly run charts (percent offered/percent eligible, percent with active prescription/percent eligible, and percent lab values in range, if H-SDM toolkit components were implemented). Run charts provide a graphic display of process performance over time to motivate and inform practice changes. We will convert run chart data to \( p \)-charts or control charts to determine if the process of offering hydroxyurea is under control (minimal variation in the data) and any special cause changes (i.e. factors that change the process significantly). Upper and lower control limits will be calculated as 3 sigma from the mean (e.g. standard Shewhart chart method)(Langley et al., 2009). Any data point outside the control limits will be considered variation from a special cause.

9g. Sensitivity Analyses

To better describe the study population and the effectiveness of the dissemination methods, the performance of the following subgroups will be compared with respect to outcome variables:

1. Characteristics of participants who decide to enroll versus those who decline (Reach)
2. Characteristics of drop-outs versus completers (Reach)
3. Characteristics of clinicians who adopt shared decision-making versus those who do not (Adoption)
4. Characteristics of sites who adopt the full H-SDM toolkit versus the core components (CRC will audit via a fidelity checklist. This will be a reported as a range [e.g. 2-3 components]) (Adoption)
5. Characteristics of settings that continue to implement guidelines versus those who do not as measured by the offering hydroxyurea measure (Maintenance)

In addition to the control covariates mentioned previously, we will examine whether certain characteristics affect the likelihood of treatment benefit (i.e., testing the interaction between subgroup variable and H-SDM toolkit group) using baseline subgroup variables that we believe may affect treatment outcomes. Primary subgroup variables will be selected based on evidence suggesting a moderating effect of these variables in the SDM literature (e.g., parent education, socioeconomic status) (W. B. Brinkman et al., 2011; Cox, Smith, Brown, & Fitzpatrick, 2009) or because we feel due to
the nature of the H-SDM toolkit that these variables will impact effectiveness (e.g., parent health literacy, child health status). The outcomes assessed with HTE analyses will be the same as those assessed in the trial (e.g., decisional uncertainty etc.) (HT-4).

Subgroup data will also be examined using advanced implementation science statistical approaches. We will use a combination of funnel charts, X-bar and S-charts to understand the implementation process and characteristics that may shift the process and to determine the relationship of these characteristics to outcomes. This will help us test and generate hypotheses that will inform future dissemination and implementation of the toolkit. For example, we will assess time to hydroxyurea prescription and possible predictors.

9h. Fidelity Analysis

Fidelity checklist data will be analyzed via descriptive statistics. The criterion will be 80% meaning if a clinician or site does not complete 80% of the components required to implement the intervention, this indicates that the clinician or site needs to be retrained. A video conference call will be set up within one week of the determination (less than 80%) and members of the CC training team will meet with the clinician or site for up to 1 hour of training. The next 3 encounters will be reviewed for fidelity to make sure the clinician or site is now implementing 80% of the required components. Data from the site survey will also be summarized with descriptive statistics specifically, a description of which sites continue to use which intervention components and any differences between those sites/clinicians continuing to implement the intervention and those who do not.

10. FACILITIES AND PERFORMANCE SITES:

The Performance centers will be added to the IRB protocol once the site has been determined as feasible for study participation. Performance sites will obtain Central or local IRB before any study activities are initiated. The Coordinating Center will be located at CCHMC.

11. POTENTIAL BENEFITS:

There is the potential for participants to receive a benefit from study involvement. First, parental knowledge about hydroxyurea may increase. Second, parents reviewing the video narratives may learn from other parents’ experiences and insights. Third, there is the potential for participants to feel more supported in the decision making process thereby improving their relationship with their health care providers.

There is also the potential for this study to impact future sickle cell clinical care and research. Due to the study design, all eligible patients at the sites will receive some level of intervention and this could be beneficial. It is also possible that information learned in this study may be used to promote shared decision making for other SCD treatments.

12. POTENTIAL RISKS, DISCOMFORTS, INCONVENIENCES AND PRECAUTIONS:

Risks for participation in the study are minimal; however, a Data Safety and Monitoring Board (DSMB) will be convened to provide oversight of study conduct, study progress, and adverse event reports by the PI and/or site PIs. Participants might be slightly inconvenienced by participating in the study over 6 months. Questionnaires used in the protocol represent minimal risk to enrolled participants; however, participants will be advised that they can skip any items or stop at any time. Also, parents may
not want to be audiotaped and can refuse participation in this part of the study, but remain enrolled in the larger study.

There is a minimal risk from inadvertent and unauthorized release of PHI to individuals outside the research team. Unanticipated problems will be documented and reported according to IRB and PCORI guidelines/standards. Unanticipated problems will be recorded in the data collection system throughout the study.

An adverse event (AE) for the current study is an unfavorable medical occurrence in a participant (parent or child) temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research. A serious adverse event (SAE) may or may not result in death, be life threatening, or require hospitalization. The Medical Monitor and the Study PI will be responsible for determining whether an AE or SAE is expected or unexpected. AE and SAE events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation will be reported according to IRB and PCORI guidelines. Research staff will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

13. RISK/BENEFIT ANALYSIS:

This study will subject participants to minimal risk, a risk level that is no greater than that encountered in a routine behavioral assessment and clinical care. The interventions and questionnaires have been used in research without any reported negative effects. Knowledge gained in this study has the potential to improve treatment of SCD by enhancing shared decision making and hydroxyurea uptake that, consequently, would improve treatment outcomes in this population.

14. DATA AND SAFETY MONITORING:

In addition to the PI’s responsibility for oversight, study oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of members with expertise in shared decision making, hematology, a behavioral psychologist, biostatistician, parent of a young child with SCD and an adult patient living with SCD. The DSMB will meet two times per year to assess safety and efficacy data (if applicable), study progress, and data integrity for the study. If safety concerns arise, more frequent meetings may be held. The DSMB will operate under the rules of a PCORI-approved charter that will be approved at the organizational meeting of the DSMB. At this time, most data elements that the DSMB needs to assess will be clearly defined. The DSMB will provide recommendations to PCORI and the PI.

Interim Analyses and Stopping Rules

Given that this is a three year study using a stepped wedge design with new sites coming on throughout the three years, the primary concern for the interim analysis is futility or worsening of decisional outcomes. The statistician will conduct an interim analysis of futility once data on approximately \( n = 32 \) participants per arm (Toolkit vs. Usual Care) is available (given proper missing data handling). The O’Brien and Fleming (1979) group sequential method, as operationalized in SAS (version 9.2) PROC SEQDESIGN (SAS Institute, Inc., 2009) was used to calculate the standardized (Wald Z) test statistic values that quantify futility. The O’Brien-Fleming procedure was conducted.
assuming: 1) a mean DCS score difference between the Toolkit and Usual Care arms of 14-points quantifies a clinically meaningful difference (O’Connor, A.M., 1993, p.6), 2) based on previous research (O’Connor, 1995, p. 28) a DCS total score standard deviation of 5.6 is anticipated in both arms, 3) data would be analyzed at two stages: midpoint and final analysis (i.e., nstages = 2), and 4) a two-sided test with (α = 0.05 & β = 0.10 [power = 0.90]) was appropriate for O’Brien-Fleming boundary calculations. Results showed the boundary for the mid-point interim analysis will be $Z = \pm 2.79651$ with $p = .0026$ (2-tail), and the boundary for the final analysis will be $Z = 1.97743$ with $p = .024$ (2-tail). If statistical evidence exists that the treatment group’s decision-making according to the DCS is significantly worse than the control condition at the interim assessment, a second informal assessment of futility using the same boundary value ($Z = \pm 2.79651$) will be undertaken. Specifically, assuming at the interim analysis, a mean DCS difference between Toolkit and Usual Care: 1) of 14 points or greater, 2) with a Z test statistic > 2.79651, and 3) indicating the Usual Care group shows greater decision certainty and less delay, a second futility analysis will examine differences between the Toolkit and Usual Care groups on a binary indicator of receipt of a prescription for hydroxyurea (1=yes, 0=no). Results from both the psychological (DCS score differences) and behavioral (binary receipt of a hydroxyurea prescription) futility analyses, both using a boundary value of ($Z \geq 2.79651$) for rejecting the $H_0$: of no group differences, will be reported to the Data Safety Monitoring Board (DSMB) who will recommend either that the trial continue or be terminated early due to both the psychological and behavioral futility criteria having been met.

15. PRIVACY AND CONFIDENTIALITY:

Privacy

The informed consent process will address various aspects of participant privacy including the level of control over the circumstances and extent of sharing one’s personal information. As stated above, participants will only be approached by study personnel after permission from their provider. The nature of the intervention (e.g. clinic-based) leads to a loss of privacy as research and other clinical staff may know that they discussed hydroxyurea treatment with their provider. During the informed consent process, the study personnel will explain these risks. At that time, the potential participant may 1) decline to participate or 2) agree to participate with the understanding that they may withdraw at any time. This will give the participant control over the circumstances of sharing their personal information. Study personnel will screen all questionnaires for completeness; participants are allowed to skip any survey questions they do not wish to answer, thereby providing additional control over the extent of sharing personal information.

Confidentiality

Individual data will not be available to anyone not directly associated with the study. All study personnel have been trained in data safety and monitoring, privacy and confidentiality, minimizing risks related to loss of privacy and confidentiality. The performance of research personnel will be monitored to ensure the strictest standards.

15.1 Data De-Identification

All data files will use unique study assigned identifier codes. Electronic data files (e.g. REDCap data) will be password protected with access limited to study personnel.

15.2 Data Storage

Informed consent documents and case report forms will be maintained in locked storage cabinets within the PI’s locked office space at each site. Consent and permission forms will be kept
separate from participant’s data. Only the study staff will have access to the keys to the cabinets. Medical chart data will be collected by trained study staff under the supervision of the site PI. The full study database will be maintained on CCHMC’s web-based server.

15.3 Data Quality

Source documents in this study will consist of Case Report Forms, parent measures (pdf or RedCap electronic data capture system, audio recordings of interventions, and Case Report Forms - CRFs). All parent data not collected directly from the parent in REDCap completed via pdf will be entered by trained research coordinators. Specific data structure routines will be utilized including double entry. Data quality will be monitored by random inspection by the CC independent monitor for the first 3-5 participants at each site and then quarterly. Inter-rater reliability among research coordinators will be computed for patient chart review. Any problems with reliability will be addressed with further training for the research coordinators. Discrepancies will be resolved by checking source data (pdf of measure or case report form) and if necessary, by returning to patient charts to correct any inaccuracies.

16. COST OF PARTICIPATION

There are no costs for participants or third party payers for this study.

17. PAYMENT FOR PARTICIPATION

17a. Baseline Assessments

If parents/caregivers choose to complete some measures prior to the baseline visit, a ClinCard will be mailed to them with $20. The remainder of the compensation ($20) will be loaded onto their ClinCard after completion of the baseline visit.

Parents/caregivers completing all measures at the baseline visit will receive $40 compensation for their time and participation.

17b. Sending text messages/emails of prescription refills

Parents/caregivers will receive $5 compensation for sending pictures via text message or email of their prescription refills to a cell phone or an email address assigned to the study and managed by the Coordinating Center.

17c. Final Visit Assessments

Parents/caregivers will receive $40 compensation for their time and participation for completing measures during the final visit (in-person or online).

17d. Transportation Hardship

In instances where parents/caregivers report financial hardship interfering with the ability to attend the Final visit (greater than 25 miles from the site, no bus route available, no insurance-related transportation available), the site CRC upon consultation with the Coordinating Center may make a
determination to provide additional compensation to cover transportation to the study visit (e.g. cover the cost of a cab/Uber).

All compensation will be in the form of a ClinCard – a reloadable debit Master Card. The Coordinating Center will send clinical sites ClinCards with no money loaded. Site research staff will collect ClinCard paperwork and scan it to CCHMC. CCHMC will register all participants in the ClinCard system and be responsible for selecting visit payments to be loaded onto ClinCards and approving all payments.
18. References


