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Sickle Cell Disease Implementation Care Redesign Protocol Study

INTEGRATION OF mHEALTH INTO THE CARE OF PATIENTS WITH SICKLE CELL DISEASE TO INCREASE HYDROXYUREA UTILIZATION – mESH study

Sickle Cell Disease Implementation Consortium (SCDIC)

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Revision History

Version	Date	Comments
1.0	12 November 2019	Initial Release
1.1	03 January 2020	Section 1.4: Study Design and Implementation Conceptual Framework Section 2.1: Study Setting Section 2.2: Eligibility Criteria, Section 2.4: Data Collection, Measures, and Outcomes Section 2.7: Recruitment Section 5.3: Consent or Assent Minor grammatical and formatting changes throughout.
1.2	05 June 2020	Section 2.4: Data Collection, Measures, and Outcomes

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Appendix

Acronyms List

ANOVA	analysis of variance
CCNC	Community Care of North Carolina
CMS	Centers for Medicare & Medicaid Services
CONSORT	Consolidated Standards of Reporting Trials
ED	emergency department
HbF	fetal hemoglobin
HbS	mutant haemoglobin
HbSS	People who have this form of SCD inherit two sickle cell genes (“S”), one from each parent. This is commonly called sickle cell anemia and is usually the most severe form of the disease.
HSD	hydroxysteroid dehydrogenase deficiency
LDH	lactate dehydrogenase
LMM	linear mixed model
MARS	mobile app rating scale
MCC	medical coordinating center
MCV	mean corpuscular volume
MPR	medication possession ratio
MTD	maximum tolerated dose
NC	North Carolina
NHLBI	The National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NP	nurse practitioner
NPT	Normalization Process Theory
PA	physician’s assistant
PCP	primary care physician
PDC	proportion of daily coverage
PHI	protected health information
PI	principal investigator
PROMIS	Patient-Reported Outcomes Measurement Information System
RA	research assistant
RE-AIM	Reach, Effectiveness, Adoption, Implementation and Maintenance
SCD	sickle cell disease
SCDIC	Sickle Cell Disease Implementation Consortium
SMART	Sickle Cell Disease Mobile Application to Record Symptoms via Technology
TAM	technology acceptance model

Abstract

The National Heart, Lung, and Blood Institute (NHLBI) created the Sickle Cell Disease Implementation Consortium (SCDIC) to apply implementation science methods to identify and address barriers to guideline-based care in sickle cell disease (SCD) and promote evidence-based treatment for SCD patients between ages 15 to 45 years. The SCDIC conducted a systematic literature review and a comprehensive needs assessment among the eight participating centers. A major conclusion was that care redesign to support better hydroxyurea utilization would likely improve clinical outcomes for patients with SCD. Hydroxyurea therapy has been shown to improve patient outcomes and reduce disease complications and is endorsed by the NHLBI. SCDIC now proposes to develop, test and evaluate targeted interventions to improve clinical provider prescribing of and patient adherence to hydroxyurea.

The overall purpose of this proposed project is to address barriers identified by the needs assessment to improve adherence with hydroxyurea therapy. Multiple approaches for improving adherence with pharmaceutical regimens have been studied and demonstrate a need to address barriers that both providers and patients face. This project aims, via a stepped-wedge design, to test two innovative interventions utilizing mobile health (mHealth), to address both patients' and providers' needs: 1) an mHealth application for patients (*InCharge Health* app) that includes multi-component features to address the memory, motivation, and knowledge barriers to hydroxyurea use, and 2) an mHealth toolbox application for providers (*HU Toolbox* app) that addresses the clinical knowledge barriers in prescribing and monitoring hydroxyurea use. These two interventions will be tested through the following aims:

Aim 1. Improve Patient Adherence to Hydroxyurea: Addressing Memory, Motivation, and Knowledge Barriers to Hydroxyurea Use. Primary hypothesis: We hypothesize that among adolescents and adults with SCD, the adherence to hydroxyurea, as measured by proportion of daily coverage (PDC), will increase by at least 20% at 24 weeks after receiving the *InCharge Health* app, compared to their hydroxyurea adherence at baseline.

> **Sub-Aim 1.a. To examine and assess both patient engagement and behaviors related to use of the *InCharge Health* app**, we will evaluate consistent use of the app among enrolled patients, patient satisfaction, and continued use of the app beyond the study period.
>
> **Sub-Aim 1.b. To examine the clinical influence of the use of the *InCharge Health* app** on PDC, patients' clinical outcomes, perceived health literacy, health related quality of life, and perceived self-efficacy between baseline and 24 weeks.

Aim 2. Improve Provider Hydroxyurea Awareness, Prescribing and Monitoring Behaviors. We will examine among providers using the *HU Toolbox* app if there is an increase in reported awareness of hydroxyurea benefits and risks, accurate prescribing of hydroxyurea, and perceived self-efficacy to correctly administer hydroxyurea therapy between baseline and after 9 months of using the *HU Toolbox* app.

> **Sub-Aim 2.a. To examine and assess provider engagement and behaviors related to use of the *HU Toolbox*,** we will evaluate consistent use of the app among enrolled providers, providers' satisfaction, and continued use of the app beyond the study period.

Sub-Aim 2.b. To assess the combined effects of the patient and provider mHealth interventions on hydroxyurea and health care utilization, we will examine if the changes in hydroxyurea adherence are enhanced by the use of both provider and patient interventions compared to those not exposed to one or both interventions.

Aim 3. Identify and Evaluate the Barriers and Facilitators to the use of mHealth Interventions. We will evaluate the strategies used by participating sites in supporting the implementation of mHealth interventions via a mixed-method evaluation of the facilitators and barriers in adopting and implementing the mHealth interventions from multiple stakeholder perspectives: patient, provider, and organization.

Both mHealth interventions will be tested concurrently and because we are using a stepped-wedge design, each site will enter the study at different times. Provider participants will receive the *HU Toolbox* intervention for 9 months with a lagged but overlapping introduction of the *InCharge Health* intervention patient participants for 24 weeks. The implementation evaluation will be guided by RE-AIM to assess the Reach, Effectiveness, Adoption, Implementation and Maintenance of the interventions. All sites will also complete follow-on needs assessment and medical record abstractions that will provide data to evaluate other patient and provider outcomes, barriers and enablers to hydroxyurea prescribing, use, and monitoring.

mHealth technology can be leveraged to support more effective use of hydroxyurea and eventually improved SCD clinical outcomes. If the mHealth applications tested in this study show preliminary efficacy, both apps could be scaled up within SCDIC centers and expanded to other institutions outside the SCDIC. In that case, a subsequent study may be conducted to study implementation strategies to increase its uptake and study its effectiveness, and in a larger number of patients and providers.

1. Introduction

1.1 Background and Rationale [SPIRIT 6a-6b, StaRI 3-4]

Sickle cell disease and hydroxyurea therapy

Sickle cell disease (SCD) is a chronic disorder affecting approximately 100,000 Americans,[1] many of whom are economically disadvantaged. The effects of SCD are devastating: most patients experience one or more complications, including chronic severe pain, cognitive disability, renal failure, and lung disease. Although medical advances have reduced mortality of children with SCD, most adults with SCD die before age 45.[1-3] Over 30 years of rigorous investigation has proven that hydroxyurea reduces disease complications, health care utilization, and costs for patients with SCD.[4-7] Consequently, the National Institutes of Health/National Heart, Lung, and Blood Institute (NIH/NHLBI) released a guideline recommending that hydroxyurea be offered to symptomatic adults and all children with SCD (HbSS and HbSβ^0-thal genotypes) when they are 9 months or older and consult with a hematologist if other SCD genotypes (e.g., HbSC, HbSβ^+-thal) have sufficient disease severity prompting this therapy.[8] Hydroxyurea induces fetal hemoglobin (HbF) production, thereby decreasing erythrocyte HbS polymers, hemolysis, and vaso-occlusion. In addition, hydroxyurea reduces inflammation through HbF-independent mechanisms. In uncontrolled population studies, hydroxyurea reduces hospitalizations and mortality, supporting its effectiveness outside of clinical trials.[9-14] Hydroxyurea is given as a once-daily oral dose that costs less than $1 per day in the United States. Hydroxyurea is initiated and monitored in medical settings (e.g., outpatient clinics) by health care providers (e.g., physicians, advanced care practitioners, qualified nurses, and clinical pharmacists). During hydroxyurea therapy, blood counts are monitored every 1-3 months with titrated dose escalation to reach a maximum tolerated dose (MTD) defined by mild, reversible myelosuppression.

Hydroxyurea utilization is low in SCD care

Despite overwhelming evidence for positive effects, hydroxyurea is vastly underutilized.[19,20] Given the relative ease of its administration, low cost, and safety profile, barriers to hydroxyurea utilization are primarily constrained by the health system as well as provider and patient determinants. Although we do not examine them here, system-level barriers include access to SCD-specific care and loss of health coverage. Provider-level barriers include providers' reluctance in prescribing due to lack of knowledge about the drug and appropriate dosing. Patient-level barriers include low acceptance due to insufficient knowledge or misconceptions about risks and benefits, and forgetfulness leading to poor adherence.[19-27] Negative perceptions toward hydroxyurea are strongly associated with lower adherence to this medication.[28] Forgetfulness related to daily hydroxyurea use may be exacerbated by the known cognitive dysfunction, including working memory deficits that result from brain insults from SCD.[29,30] In analyses conducted through Medicaid

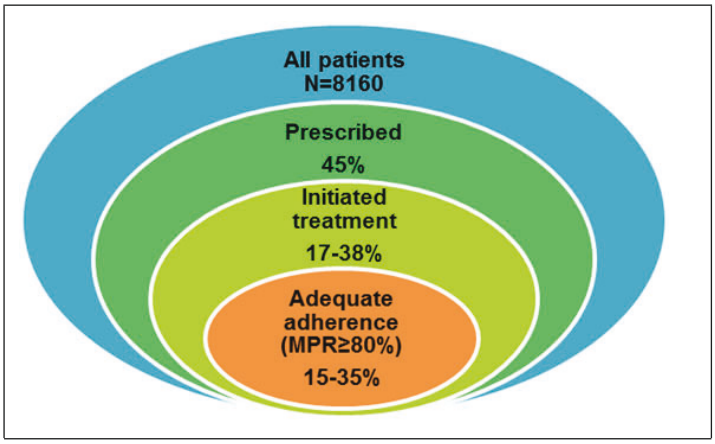


Figure 1. Hydroxyurea utilization among dults with SCD. Estimated hydroxyurea utilization in three U.S. states using Medicaid claims due from Florida, Maryland, and North Carolina and survey of adult providers.[15-18]

claims data, fewer than 50% of adults were prescribed or initiated hydroxyurea and only about 30% of those who initiated treatment achieved adequate adherence levels, as defined by medication possession ratio (MPR) ≥80% (Figure 1).[15-18] Among children, adherence was higher, but less than 50%.[21,31] Anticipation of known poor patient adherence dissuades medical providers from prescribing hydroxyurea.[18,21,32] Improving adherence to hydroxyurea would achieve higher HbF levels, fewer disease complications, and reductions in health care costs, resulting in a major improvement in overall clinical outcomes.

Mobile health (mHealth) technology and its potential for SCD care and hydroxyurea utilization

mHealth refers to the practice of medicine and public health supported by mobile devices. Short message service (SMS) text messaging (through cell phones) is a widespread means of communication, particularly among adolescents and young adults,[33,34] and an emerging intervention modality to improve medication adherence. The existing body of research provides support for mHealth interventions to improve treatment adherence across a variety of chronic conditions, including SCD.[35-38] For example, structured text message interventions have been shown to improve medication adherence by 15.3–17.8% and improved clinical outcomes in patients with HIV, hypertension, diabetes, and epilepsy.[39-42] Text message interventions also have been found to improve patient-provider relationships.[43] In the most recent and also largest systematic review of mHealth applications for outpatient cardiovascular therapies, the effectiveness of mHealth was summarized from randomized trials involving approximately 2,500 patients. All interventions aimed at increasing medication adherence and showed modest, but significant reductions in cholesterol levels and blood arterial pressure.[35] Similar benefits were observed in patients with asthma who received mHealth interventions, who experienced improved quality of life and reduced pulmonary exacerbations.[36] Among patients with SCD, approximately 84–92% own smart phones and 91% use SMS regularly for communication;[44-46] most SCD patients (87%) already accept and use this technology to monitor pain.[47,48] Since the first reports of text messaging in the SCD population, mHealth applications have been developed to increase patient engagement and symptom tracking.[38,49] Preliminary studies also suggest that mHealth interventions can specifically be used to improve hydroxyurea utilization. In one study, 14 children with SCD received text message reminders combined with a video recording to verify therapy and a financial incentive, which improved hydroxyurea adherence by 18% after 6 months.[50]

Acceptance and adherence to hydroxyurea for SCD patients is impeded by mistrust of the medical establishment and misperceptions about relative risks and benefits.[51] mHealth can address patient behavioral barriers, such as forgetfulness, and enhance communication with SCD providers who can use this intervention to educate patients on the benefits of hydroxyurea and improvement in hydroxyurea adherence. mHealth is also increasingly used to aid providers in their medical decision-making and to facilitate consultations with other providers and experts in their areas,[52,53] highlighting the broad applicability of mHealth, not only for patients, but for providers.

Why test an intervention to increase adherence to hydroxyurea within an implementation science research framework?

Enhancing the implementation of SCD evidence-based care guidelines can lead to population-wide improvements, but requires that contextually relevant findings be evaluated for future translation to diverse patients, clinics, and communities.[54,55] Current evidence about beneficial effects of hydroxyurea is based primarily on efficacy trials, where eligibility screening criteria and low participation rates may lead to narrowly selected patients and settings. This limited evidence impedes our ability to generalize findings to the full spectrum of SCD patients, leading to limited use of hydroxyurea among providers and patients—and overall suboptimal effectiveness. Expanding

evidence-based use of hydroxyurea in SCD requires a multi-level systems perspective, evaluation of generalizability, and inclusion of practical measures and participatory approaches.[55]

Hydroxyurea utilization barriers within the SCDIC

In Phase I of the needs assessment, we conducted a mixed-methods analysis of hydroxyurea barriers using surveys, interviews, and focus groups across all eight clinical sites of the SCDIC. We identified obstacles at many levels of care, with salient barriers at the patient and provider levels. In qualitative analyses, patients reported the following as barriers to hydroxyurea use: it was not recommended or offered by their provider, difficulty remembering to take the medicine, perceived lack of benefit, and side effects. Related to these barriers, patients (both adolescents and adults) expressed the need to have greater communication with the providers, access to other patients (e.g., communication forums), and information about hydroxyurea and SCD. Among providers, lack of dosing and monitoring support in the electronic medical record were all reported as barriers, while the use of mHealth was identified as a potential source of support. Consistent with qualitative findings, the survey indicated that among a sample of 165 providers, nearly 30% reported they did not prescribe hydroxyurea, 39% reported patient anticipation of side effects influenced their prescribing of hydroxyurea, while 34% said patient adherence was important in their decision to prescribe the medicine.

Logic model of change to increase hydroxyurea utilization

Our logic model combines established behavioral models, including the Health Belief Model, as a framework for understanding patient hydroxyurea utilization. The technology acceptance model (TAM)[56,57] is used to understand uptake of the mHealth apps. These behavioral models and the knowledge gained from the needs assessment phase helped conceptualize a logic model that guided the development of the interventions to positively change hydroxyurea utilization and improve provider prescribing behaviors. This logic model used Intervention Mapping methods to develop and adapt the behavioral models for testing mHealth as the intervention to increase hydroxyurea use. Intervention Mapping is a systematic framework for developing, implementing, and adapting theory- and evidence-based interventions.[58] Using the knowledge of barriers to using hydroxyurea, we mapped the determinants of hydroxyurea utilization (Figure 2). These determinants are hypothesized to drive the behaviors involved in patients' and providers' use of hydroxyurea. Furthermore, these determinants correspond to the barriers of hydroxyurea use that were identified through literature review and the results of the needs assessment analysis. Importantly, the interventions were developed and aimed at the determinants that could affect the behavior involved in taking and prescribing hydroxyurea; the ultimate goal (the behavioral outcome) is to foster greater patient adherence to hydroxyurea.

Intervention to increase hydroxyurea prescribing habits and improve patient adherence

We used Intervention Mapping to systematically develop and adapt two mHealth interventions addressing the barriers and determinants of hydroxyurea utilization: 1) a patient phone app, *InCharge Health*, and 2) a provider phone toolbox app, *HU Toolbox* app. Informed by the needs assessment analysis and patients' preferences, the *InCharge Health* app incorporates features that address each determinant of the behavior in taking hydroxyurea, including reminders (determinant: cue to action), tracking of progress (determinant: motivation), and education bank (determinant: disease and hydroxyurea knowledge and perceptions). The *InCharge Health* app went through an iterative process during its development, including extensive feedback by stakeholders in different regions (Appendix B). Informed by the providers' desire to have greater and easier access to SCD management, the *HU Toolbox* app gives providers direct access to experts (determinant: perceived

peer support), and care flowcharts (determinant: disease and hydroxyurea knowledge), among other features.

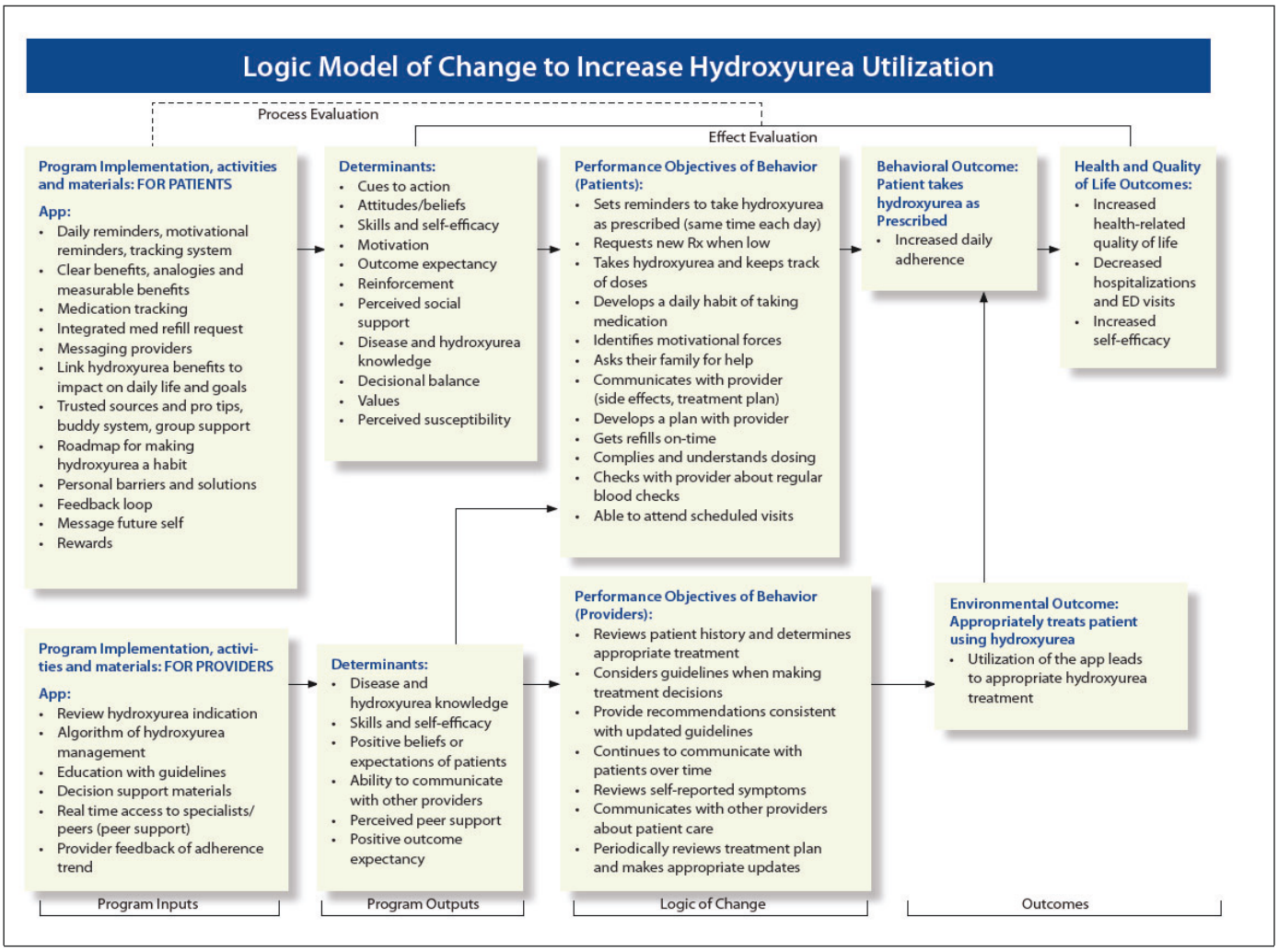


Figure 2. Logic model of change to increase hydroxyurea utilization. This logic model maps all barriers identified by literature review and needs assessment analysis, and focuses on the determinants of the behaviors in hydroxyurea use. The intervention addresses the determinants of hydroxyurea use at both the patient and provider levels. If this two-level intervention is successful, hydroxyurea utilization will increase, as reflected by increased hydroxyurea adherence, resulting in improved health-related quality of life and reduction in acute health care utilization.

Hydroxyurea adherence behaviors for patients

To guide the development of the mHealth intervention for patients, we used the Health Belief Model as the framework for the behavioral change necessary to increase hydroxyurea acceptability and use (Figure 3). The Health Belief Model is a widely used theoretical model that attempts to explain and predict health behaviors and focuses on these individuals' attitudes and beliefs. The health-related action driving the increased use of hydroxyurea include five constructs: perceived susceptibility, perceived severity, perceived benefits, perceived barriers, and self-efficacy. Individual factors including socio-demographics (including financial barriers and social support), clinical/medical status, cognitive functioning and emotional functioning, may influence these perceptions that ultimately drive the behavior of reducing the threat of disease complications by increased use of hydroxyurea. Notably, these five constructs represent modifiable factors that,

together, can be influenced to increase use of hydroxyurea. Cues to action represent prompts that trigger an individual to utilize hydroxyurea. The patient intervention focuses on these five constructs to help identify the mechanisms the patient intervention addresses to change behavior.

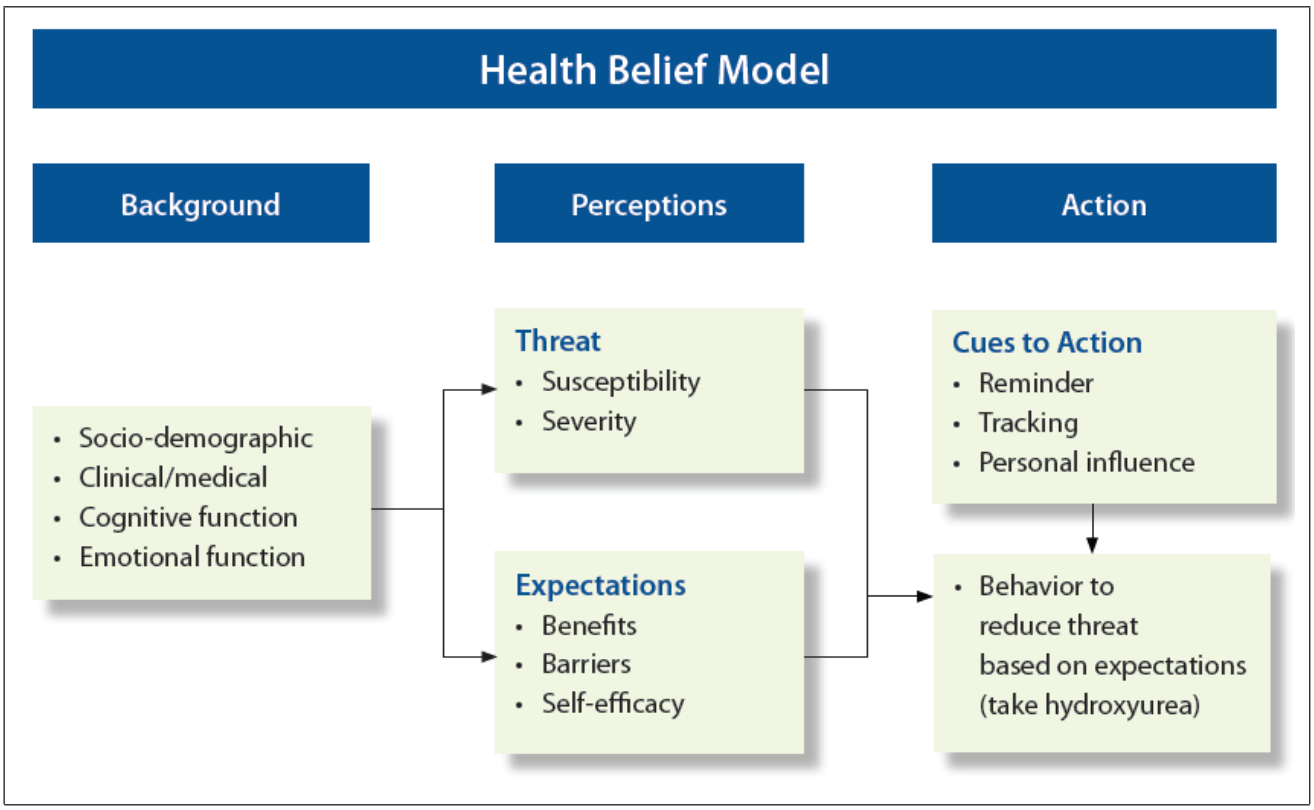


Figure 3. Health belief model as the behavioral theory for increased hydroxyurea utilization.

Behavioral model for mHealth utilization among providers

Users' acceptance of new technology, including new mHealth innovations, determines its successful adoption and, therefore, its downstream effects. TAM[56,57] is a conceptual model that explain the intent to use a new information technology (including mHealth) or information science among users, including medical providers. TAM has five constructs, but perceived ease of use and the perceived usefulness are the two dominant determinants of technology use. Mobile health care systems self-efficacy is the health care professional's perception of her or his ability to use mobile health care systems to accomplish the health care task. Mobile health care systems self-efficacy is an important construct that should also be accounted for when new technology is implemented. When combined, these two models explain 70% of the behavior of intent to use a new mobile technology: perceived usefulness, perceived ease of use, compatibility, and also mobile health care systems self-efficacy are the most important determinants of the behavior intent (Figure 4).[59] The compatibility construct was the strongest driver to directly affect the behavior intent of using mobile technology.

Developers of the mHealth intervention for the providers considered all of these drivers. The new intervention for providers accounted for:

- Perceived usefulness: SCD providers' needs to receive more information about hydroxyurea, to improve their knowledge of prescribing this medication
- Compatibility: SCD providers' prior experience in using mobile technology (i.e., the *HU Toolbox*) to acquire general SCD knowledge
- Perceived ease of use: SCD providers' perception that mobile technology can be integrated with their electronic medical record and their clinical daily routine
- Mobile health care systems self-efficacy: SCD providers' perception that mobile health could help with the task of caring for patients with SCD

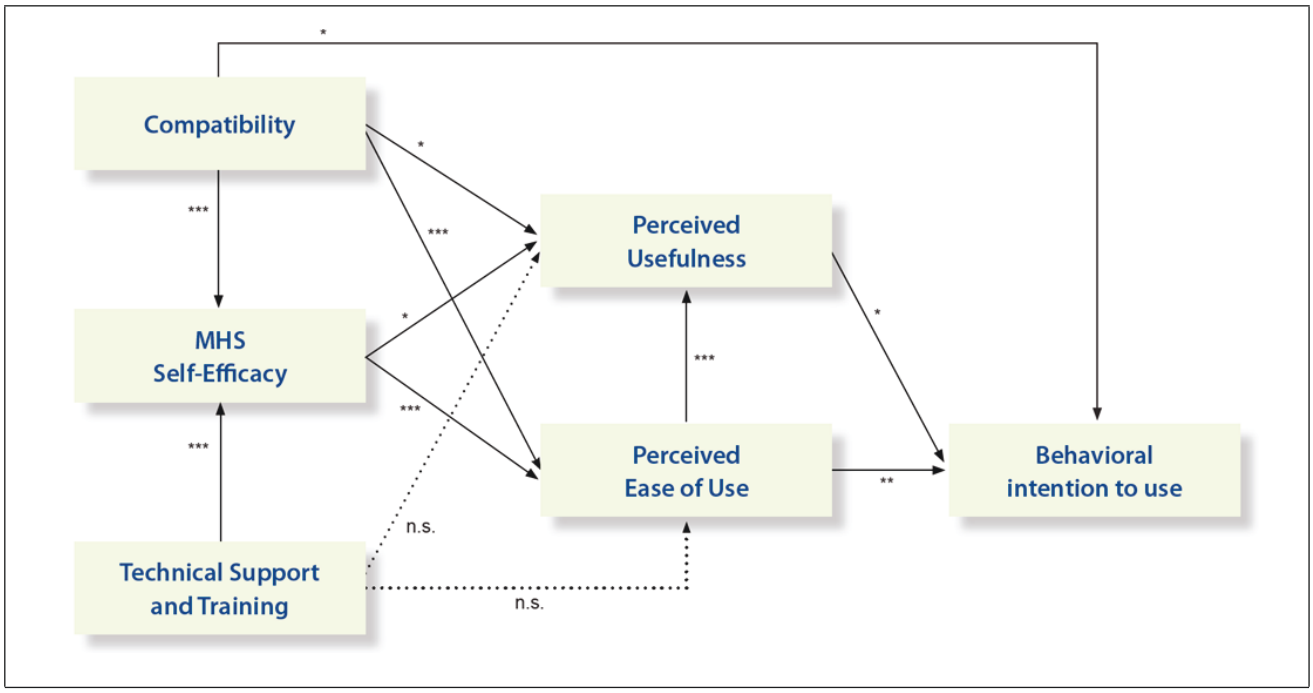


Figure 4. Conceptual model for mobile health care. Solid arrows denote direct significant effect. Dashed arrows indicate no significant direct effect. * denotes path significant at the 0.05 level, ** denotes path significant at the 0.01 level, and *** denotes path significant at the 0.001 level, and n.s. denotes nonsignificant (modified from Wu et al.[59])

Provider prescribing hydroxyurea according to guidelines

The *HU Toolbox* app will detail clinical guidelines for prescribing hydroxyurea to SCD patients, but behavioral processes will influence provider's change in practice methods. Factors such as awareness, familiarity, agreement and self-efficacy impact physicians' following guidelines and were identified in the needs assessment as potential barriers.

Preliminary data for the efficacy and process development of mHealth Interventions

mHealth for Patients with SCD

In a study conducted at St. Jude Children's Research Hospital, 81 patients with SCD and who were treated with hydroxyurea (with variable adherence levels), received a text messaging application to improved hydroxyurea adherence.[60] In this study, 97% of the population owned smart phones.

Messages were customizable for content, delivery time, frequency and duration of delivery. Children with HbSS or HbSβ^0-thalassemia age <19 who had been on hydroxyurea therapy at MTD, and who had utilized the text messaging for at least 12 months were retrospectively analyzed. Significant increases in hematological indices (HbF, MCV, Hb), and significant reduction of hemolysis markers (absolute reticulocyte count, bilirubin, and lactate dehydrogenase) were seen. These findings are proof of principle in SCD that: 1) text messages are feasible when used with the intent of enhancing hydroxyurea adherence, and 2) hydroxyurea effect can be improved with the use of text messages, denoting improved adherence. A systematic review of mHealth applications for SCD has confirmed these findings but observed that the sample size of most studies was not large, and the studies were mostly observational or retrospective.[38]

These preliminary findings served as the basis to develop a more robust and multi-component mHealth intervention to increase hydroxyurea adherence, the *InCharge Health* app. Our approach was to build on the prior experience and develop an intervention that would not only increase memory by sending text messages to patients, but that would also affect the other determinants of hydroxyurea utilization, namely motivation, knowledge and self-efficacy. This mHealth application was developed using a patient-centered design, in which the users (patients) input was obtained through an iterative process that started with a design-thinking session with adult patients and the investigators. Following the design-thinking session, 100 adolescents and adults with SCD were surveyed and 20 participated in semi-structured interviews for their interest and desire in using an mHealth application to help with hydroxyurea use. An app developer (Drawn, LLC) was hired to develop the app. Data summarizing hydroxyurea barriers, facilitators, and patients' preferences, including the results of the surveys and interviews, were analyzed in partnership with Drawn. Drawn developed the app prototype that was further refined through focus groups in 17 patients in Memphis, TN and 10 more in Chicago, IL (Appendix B) where the app was tested in patients' phones. Following the positive feedback of focus groups, Drawn finalized the app prototype adding features suggested by the patients (e.g., partner to remind of hydroxyurea doses, switch off during admissions), which is now ready to be used in this study (Appendix C).

mHealth for Providers of Patients with SCD

An earlier version of the *HU Toolbox* app, called *SCD Toolbox*, was built based on a collaborative effort by the Community Care of North Carolina (CCNC). Beginning in 2016, CCNC led efforts to develop primary care physician (PCP) directed guidelines, based on the new NHLBI guidelines for SCD. Surveys of 53 PCPs around NC found 73% were comfortable with the number of patients they had in their clinics; however, the majority did not communicate with a SCD specialist (67%) and were not aware of the 2014 NHLBI guidelines (66%). Additionally, the majority (76%) did express interest in having the guidelines provided to them and most (51%) were interested in accessing the guidelines via a mobile app.[61]

Due to need to provide PCP specific guidelines and algorithms for patients with SCD, stakeholders were brought together through CCNC. Stakeholders included pediatrician, internists, and hematologists from all academic centers in NC and members of CCNC. Guidelines were grouped by age for pediatric patients and by history, exam, and labs for adult patients. In early 2018, the newly developed *SCD Toolbox* was then provided to PCPs in NC via a paper, web-based link, and mobile app. Although dissemination efforts (through flyers, talks, and word of mouth) were only focused to NC, the *SCD Toolbox* has been downloaded over 1,000 times, in four countries (USA, Canada, China, and Brazil), and it is currently in use by dozens of providers in NC. Feedback for the use of the *SCD Toolbox* by PCPs is currently being assessed via follow up surveys and qualitative interviews. Based on feedback by the Care Redesign co-investigators, additional revisions were made to the *SCD Toolbox*.

RE-AIM as the evaluation framework for mHealth intervention impact

Key considerations to begin implementing mHealth for hydroxyurea utilization include recruitment in diverse care settings and estimating the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) of the intervention, elements that comprise the RE-AIM framework.[54] RE-AIM is used in many areas of clinical investigation,[62-64] and is a useful framework to evaluate the utility of mHealth to foster hydroxyurea utilization and to broaden the applicability of this intervention. RE-AIM will be used in this study to evaluate the overall robustness of interventions at achieving patient adherence to hydroxyurea in real-world clinical settings. Secondary objectives of the study include additional clinical outcomes and reach, adoption, implementation, and maintenance to better understand the context for implementation to facilitate the spread of the interventions. The measures of RE-AIM are outlined in Tables 5 and 6 and address the secondary implementation aims of this proposal.

In summary, we are conducting a pragmatic trial,[65] which informs a clinical or policy decision by providing evidence for adoption of the intervention into real-world clinical practice as opposed to an explanatory trial, which confirms a physiological or clinical hypothesis. The requirements for pragmatism were loosened substantially in PRECIS-2,[66] and a pragmatic extension to the CONSORT statement has been proposed.[67] We will use the PRECIS-2 as outlined by Ford and Norrie.[68]

1.2 Primary Hypotheses

Among individuals with SCD ages 15 to 45 years who initiate or already receive hydroxyurea therapy, adherence, as measured by proportion of days covered (PDC), will be increased by 20% at 24 weeks after receiving the *InCharge Health* app intervention, compared to their hydroxyurea adherence measured at baseline before the *InCharge Health* app is initiated. This analysis is a pre/post analysis of individuals receiving the patient intervention. PDC is a proxy measure of adherence and the metric used by CMS as the process measure of adherence.[69] It best reflects the "real world" setting, as opposed to the use of electronic bottles (e.g., MEMS CAP), or video-recorded daily dose ingestion (i.e., directly-observed adherence measure). A 20% increase in PDC is a clinically meaningful change, because it represents an increment of approximately 1.5 additional days of hydroxyurea use in a week's period and is associated with improved clinical outcomes.[60] Twenty-four week (6 months) is the interval were an increase in hydroxyurea adherence promote changes in clinical and laboratorial outcomes, as it takes an average of 4 to 6 months to observe full hydroxyurea effects. Furthermore, our estimated increase of 20% is conservative and based on the increase in prior studies that used text message to increase hydroxyurea adherence that observed adherence increases as high as 60%.[70]

1.3 Aims and Objectives [SPIRIT 7, StaRI 5]

Overall objective of proposed research

We propose to overcome the barriers to hydroxyurea utilization by using a two-level mHealth intervention: the *InCharge Health* app for patients, and the *HU Toolbox* app for providers. While acknowledging the multi-factorial barriers to hydroxyurea utilization, our approach will address the main barriers affecting hydroxyurea adoption and use among patients, while focusing on improving prescribing practices among providers who prescribe this treatment. This multi-prong approach will allow us to demonstrate the clinical effect of mHealth intervention to improve adherence among patients, while addressing and evaluating other barriers to optimal care among providers. Our findings will enhance subsequent implementation of mHealth into diverse settings and populations, as the participating sites are substantially different in geographical, setting (e.g., urban, suburban,

and rural) and population characteristics. The study will provide data on the efficacy of integrating mHealth into clinical care, its clinical influence, and evaluate how well this strategy is accepted, adopted, and sustained in diverse clinical settings.

Aim 1. Improve Patient Adherence to Hydroxyurea: Addressing Memory, Motivation and Knowledge Barriers to Hydroxyurea Use. Primary hypothesis: We hypothesize that among adolescents and adults with SCD, the adherence to hydroxyurea, as measured by proportion of daily coverage (PDC), will increase by least 20% after 24 weeks of use of the *InCharge Health* app, compared to their hydroxyurea adherence measured at baseline.

> **Sub-Aim 1.a.** To examine and assess both patient engagement and behaviors related to use of the *InCharge Health* app, we will evaluate consistent use of the app among enrolled patients, patient satisfaction, and continued use of the app beyond the study period. Specifically, we will assess:
>
> 1) *InCharge Health* reach (proportion of patients approached and enrolled in the study among all patients who receive treatment with hydroxyurea at each site)
>
> 2) *InCharge Health* adoption (proportion of patients who initiate the use of the app but then later discontinued or completed the study at each site)
>
> 3) *InCharge Health* implementation (consistency with which sites are able to implement the app as planned)
>
> 4) *InCharge Health* maintenance (extent to which program leaders express a desire or intent to continue providing the app to patients at the conclusion of the study)
>
> **Sub-Aim 1.b. To examine the clinical influence of the use of *InCharge Health* app** on "adequate" PDC (proportion of patients with PDC>80%), patients' clinical outcomes (e.g., differences in hematologic indices, acute healthcare utilization), perceived health literacy, health-related quality of life, and perceived self-efficacy between baseline and 24 weeks among adolescents and adults with SCD after receiving the *InCharge Health* app. Patients will also be stratified into their low and high intervention uptake groups and compared between baseline and 24 weeks on all the clinical outcomes listed above.

Aim 2. Improve Provider Hydroxyurea Awareness, Prescribing and Monitoring Behaviors. We will examine whether, among providers using the *HU Toolbox* app, reported awareness of hydroxyurea benefits and risks, accurate prescribing of hydroxyurea, and perceived self-efficacy to correctly administer hydroxyurea therapy will increase between baseline and after 9 months of using the *HU Toolbox* app.

> **Sub-Aim 2.a.** To examine and assess both provider engagement and behaviors related to use of the *HU Toolbox*, we will evaluate consistent use of the app among enrolled providers, providers' satisfaction, and continued use of the app beyond the study.
>
> Specifically, we will assess:
>
> 1) *HU Toolbox* reach (proportion of eligible providers approached and enrolled in the study among all providers at each site)
>
> 2) *HU Toolbox* adoption (characteristics of the clinics that choose to adopt the app)
>
> 3) *HU Toolbox* implementation (consistency with which sites are able to implement the app as planned)

4) *HU Toolbox* maintenance (extent to which program leaders express a desire or intent to offer or encourage the use of the app by their clinical providers at the conclusion of the study)

Sub-Aim 2.b. To assess combined effects of the patient and provider mHealth interventions on hydroxyurea and health care utilization. We will examine if the changes in hydroxyurea adherence are enhanced by greater implementation of both provider and patient interventions. We will examine patient behaviors and clinical outcomes between patients with use of the *InCharge Health* app while receiving care from a provider with use of the *HU Toolbox*.

Aim 3. Evaluate the Barriers and Facilitators of the Adoption of the mHealth Interventions. We will evaluate the strategies used by participating sites in supporting the implementation of mHealth interventions via a mixed-method evaluation of the facilitators and barriers in adopting and implementing the mHealth interventions from multiple stakeholder perspectives: patient, provider, and organization (clinic level evaluation).□

1.4 Study Design and Implementation Conceptual Framework [SPIRIT 8, StaRI 6]

The study design is a nonrandomized, closed cohort, step wedge cluster trial where the two mHealth interventions will be introduced sequentially in 8 participating clinic sites over three time periods (Figure 5), where a cohort of subjects recruited from within each site will be followed over each time period. The stepped wedge design will be used because it provides greater flexibility and is more appropriate given known barriers. The small number of sites in this trial make it unlikely that random allocation will produce a balance in baseline covariates across the three time intervals, so it was decided to order sites from the highest to the lowest adult to pediatric patient ratio then group sites with differing ratios within each time interval. The adult to pediatric patient ratio was used as the grouping variable as there are likely to be substantial differences between youth and adults in both uptake of the interventions and adherence to hydroxyurea. The unit of analysis is the patient. We are using the innovative stepped wedge design to address heterogeneity of practices and providers, the potential for limited uptake, and to reduce implementation burden across sites.

There will be 8 sites participating. Within each site, there will be one or more treating clinics. We have determined that randomization of the sites is not possible, since in this study we will be investigating the interventions' efficacy and the comparison is between baseline and at 24 weeks. Each provider within a participating clinic will receive the *HU Toolbox* intervention for 9 months while each patient participant will receive the *InCharge Health* app intervention for 24 weeks. The providers (physicians and advance care practitioners) will begin receiving the provider intervention two months before patients (at the same site) initiate use of the patient intervention. There will be a staggered eight months between sites 1 & 2 and the next cohort including sites 3, 4, and 5. The study roll-out will allow for a baseline evaluation, followed by preparation and introduction of the provider intervention (education of providers and remaining staff), followed by implementation of the interventions that will be used simultaneously for patients and providers, and evaluation post-intervention (Figure 5). The study time periods are as follows:

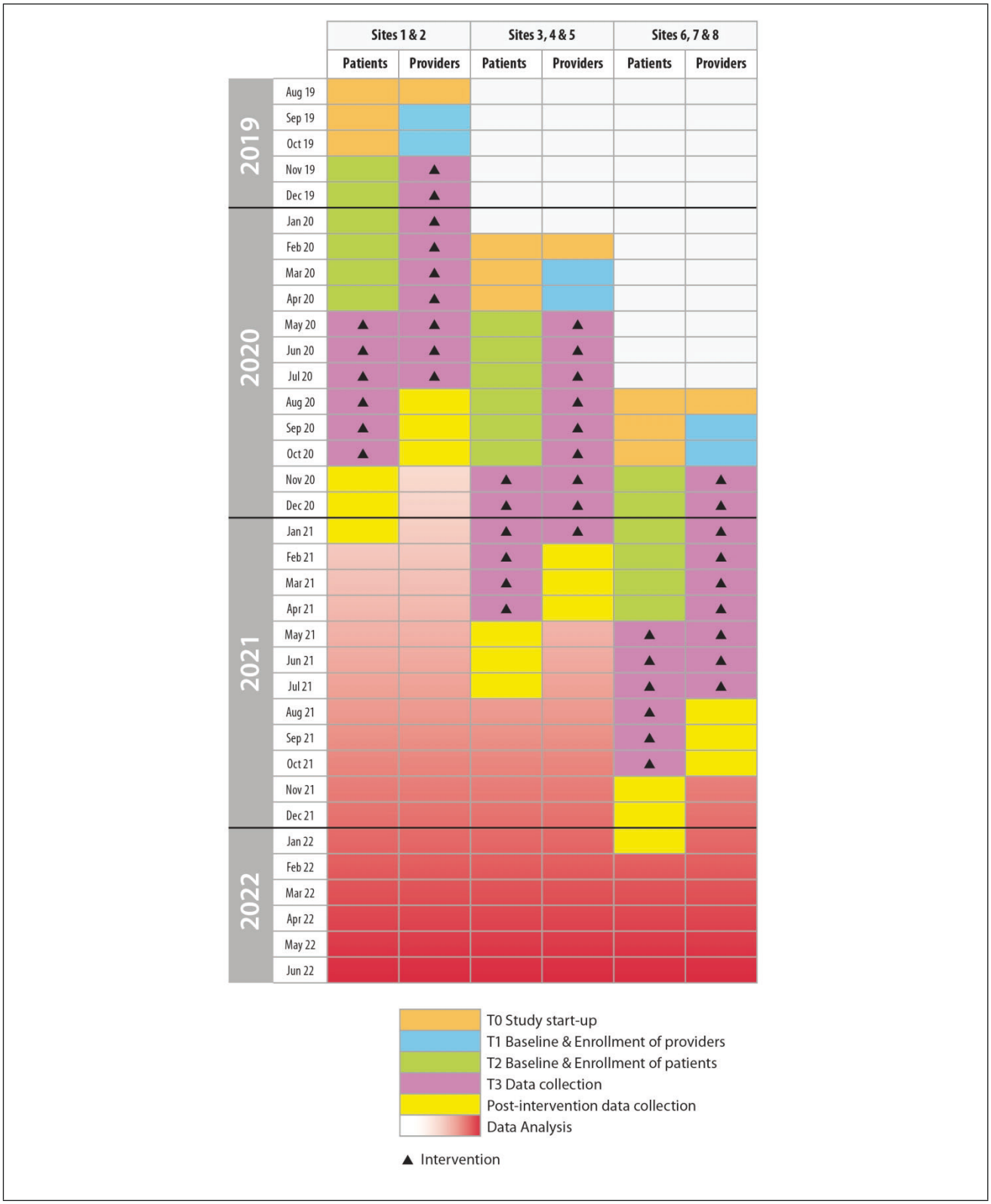


Figure 5. Study time periods and staggering of sites using the stepped-wedge design.

- **T0 baseline evaluation.** Baseline measures and observations of provider prescribing practices and overall patient adherence to hydroxyurea. Total duration of this phase is 1 month.

- **T1 enrollment of providers.** This phase includes enrolling providers and introducing the provider toolkit with education support; training staff on using the *HU Toolbox* app; and measuring (with chart audit) prescribing practices and population patient adherence. All providers will be enrolled within 60 days. Total duration of this phase is 2 months.
- **T2 enrollment of patients.** This phase includes enrolling patients and introducing the patient *InCharge Health* app with education support. All patients will be enrolled over a period of 6 months. Total duration of this phase is 6 months.
- **T3 data collection.** During this phase, all enrolled patient and provider participants are followed as active study participants. Following enrollment, each provider will be followed for 9 months and each patient for 24 weeks. Each participant receives study evaluations as outlined on the schedule of evaluations (Tables 3 and 4). Total duration of this phase is 6 months for patients and 9 months for providers.
- **Post-intervention data collection**. This phase reflects the sustainability of the interventions. We will continue to provide technical support for both patient and the provider apps and measure continued utilization of the apps and the long-term adherence to hydroxyurea. Total duration of this phase is 3 months.

By the end of the study, all sites will have received the intervention. This design offers a number of opportunities for data analysis, particularly for modeling the effect of time on the effectiveness of the interventions, and may conserve resources, as not all sites will be actively enrolling and testing participants at a time. It would not be possible to initiate the intervention at all sites simultaneously given existing resources. In addition, implementing the interventions at the first two sites will allow us to determine any challenges and adapt to ensure increased uptake and implementation for the following four sites. The order of site participation is as follows:

1. Sites 1 and 2: St. Jude and Duke University
2. Sites 3, 4, and 5: Augusta University, Mount Sinai and University of Illinois at Chicago
3. Sites 6, 7, and 8: MUSC, UCSF and Washington University

To promote uptake of both the patient and provider mHealth apps into practice, we will employ multiple implementation strategies. Sites will be provided with a list of discrete strategies (Table 1), based on the most recent compilation in the field.[71] Each principal investigator (PI) and his/her team will be able to select the strategy(ies) that best fit their context, providing a small rationale for selection based on the needs assessment, literature review, and/or feasibility of the strategy. Because we are also using a stepped-wedge design and not all sites will have access to the interventions at the same time, information and experience from previous sites will help inform the implementation of the next sites and allow sharing of local knowledge. As sites implement their strategies, centralized technical assistance, provided by St. Jude for *InCharge Health* and Duke for *HU Toolbox*, will help identify potential barriers to the use of the apps and ensure a high level of fidelity in their implementation. All new strategies that are introduced at each site will be collected and tracked.

Table 1. Example Implementation Strategies to Promote Uptake of the mHealth Apps (modified from Powell et al.[71,72])

Plan Strategies

• Conducted a local needs assessment
• Assessed for readiness and identified barriers
  ○ Surveyed providers that will test the mHealth interventions and ensured their level of interest in testing the apps was high and that they recognized the need for an intervention for both patients and providers
  ○ Consulted with patients and providers regarding relevance and interest in having mHealth interventions to improve hydroxyurea use
• Tailored strategies to overcome barriers and honored patients' preferences
• Built a coalition within the SCDIC that will implement the mHealth interventions
• Identified the providers that will test/champion the mHealth applications
• Obtained input from patients and providers regarding features of the mHealth interventions. Used this input to develop the apps
• Beta tested both the patient and the provider apps for functionality

Educate Strategies
• Distribute educational materials (both through the apps and in person) • Conduct ongoing training • Conduct regular check-ins with patients and providers regarding app functionality • Sharing of local knowledge across sites
Quality Management Strategies
• Audit and provide feedback • Deliver centralized technical assistance to identify implementation issues.   ○ St. Jude will provide technical assistance for *InCharge Health*; Duke for *HU Toolbox*.

2. Methods: Participants, Interventions, and Outcomes

2.1 Study Setting [SPIRIT 9, StaRI 7-8]

Table 2 describes the setting of each participating site, including the total population, academic or community and urban or rural settings, and the type of health professionals comprising the provider staff. The context for the program is diverse and presents an opportunity to test mHealth in different settings, with not only geographical but also structural differences using the RE-AIM evaluation framework.

Table 2. Study Site Characteristics

Site	City	Estimated Population		Type of Community Setting	Academic Setting	Number of Providers in the Practice Caring for SCD Patients	
		Pediatric (15.0-17.9yrs)	*Adults (18.0-45.0yrs)*			*Physicians*	*Advanced Practitioners*
St. Jude							
St. Jude Children's Research Hospital	Memphis	140	0	Urban	Yes	3	10
Methodist University Hospital	Memphis	0	350	Urban	No	2	1
Baptist Health Care	Memphis	0	100	Suburban	No	3	3
Duke University							
Duke Adult Sickle Cell Clinic	Durham	*0*	*450*	*Suburban*	*Yes*	*5*	*4*
Duke Pediatric Sickle Cell Clinic	Durham	*80*	*0*	*Suburban*	*Yes*	*3*	*2*
University of Illinois							
UI Hospital & Health Sciences System, Sickle Cell Center	Chicago	*0*	*600*	*Urban*	*Yes*	*6*	*3*
UI Hospital & Health Sciences System, Pediatric Department	Chicago	*20*	*0*	*Urban*	*Yes*	*2*	*1*
OSF Healthcare/Children's Hospital of Illinois	Peoria	*9*	*20*	*Rural*	*Yes*	*2*	*1*
Sinai Health System	Chicago	*14*	*141*	*Urban*	No	*3*	*3*
Lawndale Christian Health Center	Chicago	*3*	*13*	*Urban*	No	*7*	*6*
UCSF							
UCSF Benioff Children's Hospital Oakland	Oakland	*50*	*286*	*Urban*	*Yes*	*3*	*2*
Mount Sinai							
Mount Sinai Hospital	New York	*15*	*175*	*Urban*	*Yes*	*1*	*2*
Mount Sinai St. Lukes Hospital	New York	*0*	*30*	*Urban*	No	*1*	*0*
Washington University							
St. Louis Children's Hospital Pediatric	St. Louis	*55*	*20*	*Urban*	*Yes*	*4*	*2*
Barnes Jewish Hospital Hematology	St. Louis	*0*	*300*	*Urban*	*Yes*	*4*	*2*
Christian Hospital Northeast-Hematology	St. Louis	*0*	*87*	*Suburban*	*Yes*	*2*	*2*

Site	City	Estimated Population		Type of Community Setting	Academic Setting	Number of Providers in the Practice Caring for SCD Patients	
		Pediatric (15.0-17.9yrs)	*Adults (18.0-45.0yrs)*			*Physicians*	*Advanced Practitioners*
Augusta University							
Augusta University Adult Center for Blood Disorders	Augusta	*0*	*358*	*Urban*	*Academic*	*1*	*1*
AU Pediatric Hem/Onc	Augusta	*123*	*0*	*Urban*	*Academic*	*4*	*0*
AU Macon Outreach Clinic	Macon	*0*	*87*	*Rural*	*Community*	*1*	*1*
AU Sylvester Outreach Clinic	Sylvester	*0*	*137*	*Rural*	*Community*	*1*	*1*
AU Savannah Outreach Clinic	Savannah	*0*	*65*	*Urban*	*Community*	*1*	*1*
MUSC							
Adult sickle cell clinic	Charleston	*0*	*520*	*Urban*	*Academic*	*11 (both physicians and APs)*	
Pediatric sickle cell clinic	Charleston	*350*	*0*	*Urban*	*Academic*	*6 (both physicians and APs)*	

2.2 Eligibility Criteria [SPIRIT 10, StaRI 8]

Eligibility criteria for patient participants

A total of **46 patients** per site will be enrolled to allow for a 25% patient attrition (total of 368 patients enrolled in all 8 sites). Women and children will be included to the extent that they exist in the population being studied and meet eligibility criteria for study participation. In addition to parental/guardian consent, adolescent assent will be obtained from children 15–17 years old, or as determined by the Institutional Review Board (IRB). Because SCD disproportionally affects individuals of African descent in the United States, we expect enrollment to consist primarily of African American participants.

Inclusion criteria:

- Age 15 years up to and including 45 years
- Treated at or affiliated with one of the SCDIC sites
- English speaking
- Confirmed SCD diagnosis. An SCD diagnosis is defined as Hb fractionation test (e.g., high-performance liquid chromatography or another technique) that is diagnostic of one the following: Hb SS, Hb SC, Hb Sβ-thalassemia, Hb SO, Hb SD, Hb SG, Hb SE, or Hb SF.
- Willing and cognitively able to give informed consent
- Access to a cellular/mobile smart phone (either Android or iPhone are acceptable)
- Hydroxyurea therapy:
    - Already receiving hydroxyurea therapy: defined as at least one prior prescription to hydroxyurea in the past 3 months and no plans to escalate the dose by more than 5 mg/kg/day

- Initiating hydroxyurea therapy: defined as at least one prescription written at the time of study enrollment (the first prescription must be written on the same day as study enrollment)*

Exclusion criteria:

- Current pregnancy
- On a chronic transfusion program in which they receive more than 8 erythrocyte transfusions in a 12-month period. This exclusion is necessary, since transfusions will mask laboratorial changes and will contaminate clinical outcomes.
- A red blood cell transfusion in the past 60 days
- Currently using another phone application or an online-based tool (e-health tool) to increase hydroxyurea adherence

*Patients who initiate hydroxyurea on the same day of study enrollment will not contribute to the total of 46 patients target accrual for the site. A max of 30 patients who are initiating hydroxyurea can be enrolled per site.

Patients who become pregnant during the study will have discontinued hydroxyurea; therefore, we will withdraw these participants from the study. This does NOT apply to those who discontinue hydroxyurea during the study for other reasons as patients may decide to restart hydroxyurea.

Eligibility for provider participants

Inclusion criteria:

- Physician or advanced practice provider (NP or PA) who care for at least one patient with SCD for an anticipated minimum of 12 months from study enrollment
- Willing to provide informed consent
- Access to a cellular/mobile smart phone (either Android or iOS) or access to a computer with internet connectivity (a version of the *HU Toolbox* app can be accessed via internet on any device)

Exclusion criteria:

- Currently using another phone application to increase hydroxyurea adherence for patients with SCD in his/her practice

2.3 Interventions and Enrollment Strategy [SPIRIT 11a, StaRI 9-10]

Patient-level intervention

We will approach patient participants who meet inclusion and exclusion criteria. Potential participants will be approached while they are not experiencing an acute complication of the disease. The setting of patient enrollment may be the clinic or a venue outside the hospital, but with adequate patient privacy and with IRB knowledge and approval.

A member of the research team (e.g., nurse assistant, research assistant, research coordinator) will verify that the participant meets study eligibility and will approach the subjects. Alternatively, clinic staff will be trained to also approach eligible participants, and will be encouraged to do so, if clinic flow allows. Eligible participants will be asked to sign the informed consent form (or we will ask the

legally authorized caregiver, if a minor is involved). Once informed consent is signed, a clinic staff or a member of the study team (a nurse, research assistant, or other trained investigator) will help install the *InCharge Health* app on the patient's mobile phone. The study team will provide input on the settings into the app, explain how to use the app, and answer any questions. Before participants leave the clinic, patients will be asked to demonstrate their knowledge and ability to use the app. We will provide supporting material to reinforce what was discussed. In addition, a number to call with questions regarding the app or the study in general will be provided.

All features of the *InCharge Health* app were developed with patient input through surveys, interviews, and focus groups. This iterative process addressed all performance objectives identified during the process of developing the logic model for increased hydroxyurea utilization (Figure 5). To address all behavior determinants and process objectives, four main features were incorporated into the app: daily medication reminders, motivational tools, disease education, and communication tools (see Appendix C for more details about the app). The app data will be stored under the study provider's unique ID (study ID number), and the *InCharge Health* app will not collect any protected health information (PHI).

Provider-level intervention

A member of the study team will ask provider participants who care for patients with SCD to sign an informed consent form. All providers within each practice will be approached and invited to participate. All clinics will have each provider register within the app to allow provider-specific data. The app data will be stored under the study provider's unique ID (study ID number), and the *HU Toolbox* app will not collect any PHI. The following app-related data will be collected: features of the app used, frequency of each feature used, and number of times specialists are contacted via the app. We will encourage providers to use the app for all of their SCD patients for at least 9 months, however, they will have the option to keep it in their phones (or computers) for an indefinite period. All providers will be given an email address and phone number to contact should any technical problems occur related to the use of the app. Data related to technical problems related to the app will also be tracked evaluate its functionality.

The *HU Toolbox* app contains NHLBI guidelines adapted for pediatrics (guidelines/ recommendations separated by age) and for adults (guidelines/recommendations separated by organ system, laboratory, or physical exam finding) providers (Appendix C). It was developed with provider input and contains algorithms guiding the clinician on how to prescribe hydroxyurea and monitor its effect. The *HU Toolbox* also guides clinicians on how to recognize hydroxyurea side effects and how to manage them. Finally, a contact list of local SCD specialists and important contacts is included, so providers can contact SCD experts and expect an answer in 24 hours or less.

The *InCharge Health* and *HU Toolbox* apps will both comply with Health Insurance Portability and Accountability Act (HIPAA) requirements, because: (1) participants will electively enroll into the program and sign informed consent; (2) messages will contain no PHI; (3) messages will be delivered to private cellular telephones, (4) no personal information will be shared with third parties, and (5) usability data stored in secure sites (e.g., firebase or Mixed Tables software) and will contain no PHI, because all participants' data will be stored under a study number assigned upon study enrollment.

Figure 6 shows the introduction and investigation of each intervention sequentially. Four possible intervention combinations will be evaluated and compared: provider and patient use the intervention, neither provider nor patient uses the intervention, provider uses the intervention but patient does not,

and patient uses the intervention but provider does not. Comparisons within and across groups will be conducted as shown.

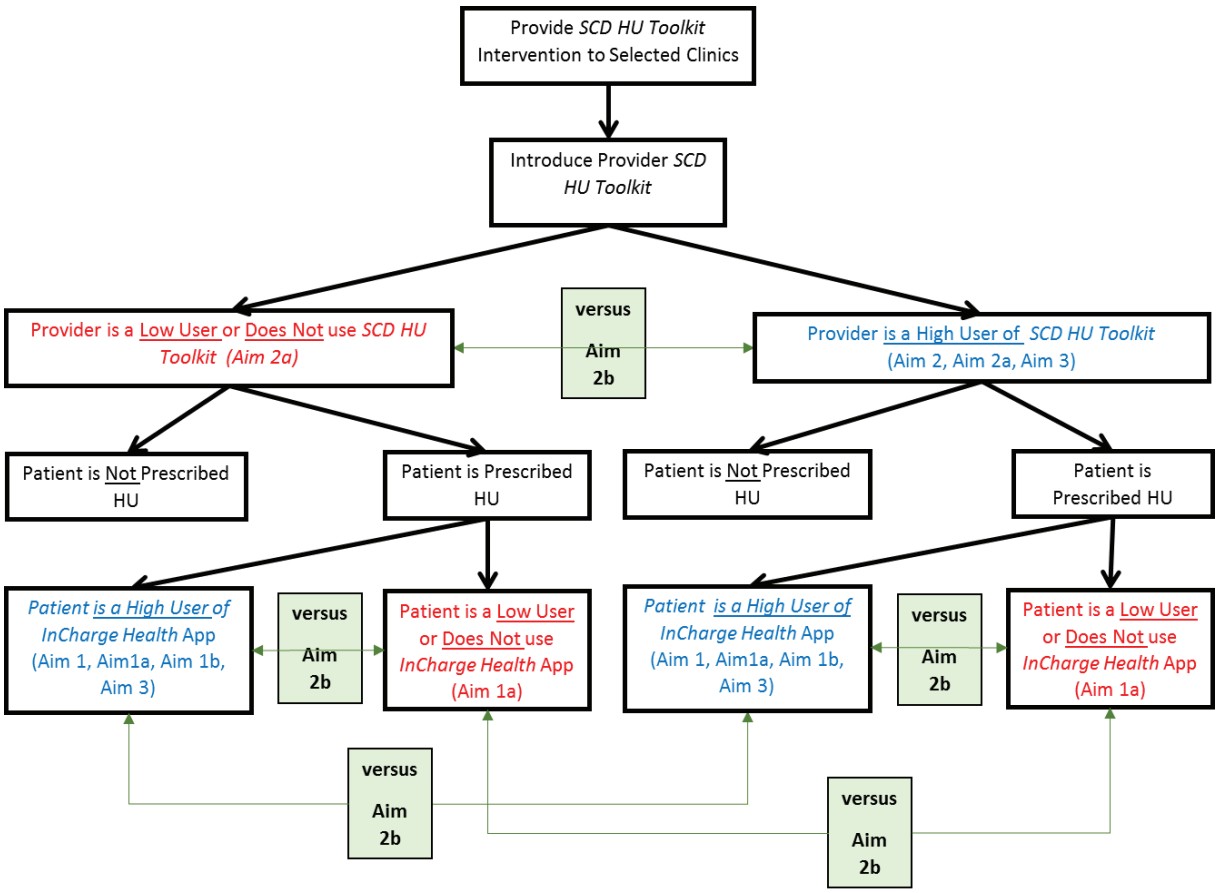


Figure 6. Study groups comparisons according to each aim.

2.4 Data Collection, Measures, and Outcomes [SPIRIT 12, 18a-18b, StaRI 11-13]

Patient participants will be enrolled while they are not experiencing an acute event. During enrollment, the patient participant will receive the instructions about app use and undergo a baseline evaluation. Patient participants will then return every 12 weeks for study visits, where study-related procedures will be conducted (Table 3). The visit window for the follow-up visits is +/- 4 weeks. Follow-up visits that occur outside the visit window will be considered a protocol deviation.

Table 3. Schedule of Evaluations for Patient Participants

Measures	Definition	Pre-Baseline (Retrospectively Collected up to 12 months prior to baseline)	Baseline	Week 12	Week 24 (Study Exit)	Week 36 (Post-Study)
Socio-demographic	Age, sex, race, ethnicity, marital status, educational attainment, health insurance type, income, occupation		x			
Informed consent			x			
Aim 1. Patient Adherence to hydroxyurea **Aim 2b. Combined effects of the patient and provider mHealth Interventions**						
Hydroxyurea adherence	Proportion of daily coverage (PDC)	x	x	x	x	x
	App daily adherence statistics and 7-day recall measure using the Brief Medication Questionnaire (BMQ)[65]		x		x	
Sub-Aim 1b. Clinical Influence of the *InCharge Health* app **Aim 2b. Combined effects of the patient and provider mHealth Interventions**						
Hydroxyurea effect	Date hydroxyurea initiated		x			
	MTD dose (mg/kg/day) and date reached		x			
	Current dose (mg/kg/day and mg/day)		x	x	x	x
	Biomarkers of hydroxyurea effect (HbF%, Hb, MCV, ANC, ARC, indirect bilirubin, LDH)	x	x	x	x	x
Health care utilization	Date and discharge diagnosis of ED visits, acute care/infusion visit hospitalizations	x	x	x	x	x
Self-efficacy and health literacy	PROMIS self-efficacy for medication short form		x		x	
	Perceived Health literacy[66]		x		x	
Health-related quality of life and pain report	ASCQ-Me Pain Impact, ASCQ-Me Pain Episode Frequency and Severity, PROMIS Pain Quality		x		x	
Sub-Aim 1a. Engagement of patients related to the use of *InCharge Health* app						
Implementation Measures	See RE-AIM tables for a full description of measures				x	
mHealth satisfaction	Perceived usability and acceptability of mHealth intervention (MARS scale)[67]			x	x	
Aim 3. Evaluation of facilitators and barriers to implementation of the mHealth app						
Barriers and facilitators to implementation	Qualitative interviews†				x	x

Notes: MTD: maximum tolerated dose, HbF: fetal hemoglobin, Hb: hemoglobin, MCV: mean corpuscular volume, ANC: absolute neutrophil count, ARC: absolute reticulocyte count, LDH: lactate dehydrogenase, ED: emergency department, ASCQ-Me: adult sickle cell quality of life measurement information system. MARS: mobile app rating scale. †Conducted at end of implementation at each study site.

Provider participants (i.e., physicians and advanced practice providers who care for individuals with SCD) will consent to use the *HU Toolbox* app and will use this tool for at least 9 months. During these 9 months, providers will provide feedback on the *HU Toolbox* app's clinical usefulness and its usability and impact on clinical care provided. (Table 4). The visit window for the follow-up visits is +/- 4 weeks. Follow-up visits that occur outside the visit window will be considered a protocol deviation.

Table 4. Schedule of Evaluations for Provider Participants

Measure	Definition	Baseline	Week 36 (Study Exit)	Week 48 (Post-Study)
Socio-demographics	Age, sex, race, ethnicity, type of professional (physician, nurse practitioner, physician assistant), years in practice	x		
Informed consent		x		
Aim 2. Improve provider hydroxyurea awareness, prescribing and monitoring behaviors				
Self-efficacy and hydroxyurea knowledge	Perceived confidence in prescribing hydroxyurea to patients with SCD, including correct daily dosing	x	x	
Sub-Aim 2.a. Engagement of providers related to the use of the *HU Toolbox* app				
Implementation and mHealth satisfaction	See RE-AIM tables for a full description of measures		x	
	Perceived usability and acceptability of mHealth intervention (MARS scale)[67].		x	
Hydroxyurea prescribing practices (clinic level measures)	Total number of patients with SCD	x	x	x
	Number of patients eligible to receive hydroxyurea therapy at provider participant's site*	x	x	x
	Number of hydroxyurea-eligible patients who are prescribed hydroxyurea (all sickle genotypes)*	x	x	x
Aim 3. Evaluation of facilitators and barriers to implementation of the mHealth app				
Barriers and facilitators to implementation	Qualitative interviews†		x	x

Notes: *Hydroxyurea eligibility will follow the 2014 NHLBI guidelines as follows: hydroxyurea should be offered to all children with HbSS/HbSβ^0-thalassemia age ≥ 9 months (regardless of clinical severity) and prescribed to all symptomatic adults with HbSS/HbSβ^0-thalassemia, i.e., >3 episodes of severe vaso-occlusion in the preceding 9 months.[8] # hydroxyurea indication according to the NHLBI guidelines. †Conducted at end of implementation at each study site.

Tables 5 and 6 summarize how the RE-AIM framework will be used to evaluate the effectiveness and implementation of the patient and provider mHealth applications. Timeline for measurement can be found in Tables 3 and 4 schedules of evaluations.

Table 5. Patient App (*InCharge Health*): RE-AIM Evaluation Measures

Domains	Measures	Data Sources	Data Collection Instrument Mapping
Reach	Socio-demographic characteristics of patients at each site	Clinic administrative data Clinic data collection forms	**Qualitative interviews with patients**

Domains	Measures	Data Sources	Data Collection Instrument Mapping
	Proportion and representativeness of patients screened for the study (numerator) among all patients who receive hydroxyurea treatment (denominator) at each site Proportion and representativeness of patients eligible for the study (numerator) among all patients who receive hydroxyurea treatment (denominator) at each site Proportion and representativeness of patients participating/enrolled in the study (numerator) among all patients who receive hydroxyurea treatment and were eligible (denominator) at each site	Screening log Qualitative interviews	**Patient Reported Outcome Form, all of Demographic Section** **Clinic Data Collection Form, all of Sections B** (patient population), **C** (patients who meet NHLBI criteria to receive HU), **G** (Patients who are prescribed HU), **E** (case mix), **Case/Screening log**
Effectiveness	<u>Primary outcome</u> >20% improvement in refill for hydroxyurea among those receiving the intervention <u>Secondary outcomes</u> Change in Quality of life, self-efficacy, perceived health literacy Change in Percentage of patients with ED visits, hospitalizations since last study visit Change in biomarkers of hydroxyurea effect (MCV, ANC, ARC, indirect bilirubin, HbF, Hb, LDH)	Prescription drug claims Surveys (ASCQ-Me, PROMIS, Perceived Health Literacy, Electronic health record Qualitative interviews	**Examine hydroxyurea Rx data from pharmacy records** **Qualitative interviews with patients** **Patient Reported Outcome Form, all of Your Pain History, Medication Self-Efficacy, Hydroxyurea History, Hydroxyurea adherence** **Patient Medical Record Abstraction Form (acute care visits)** **Patient Lab Reporting Form** (biomarkers)
Adoption Clinic-Level Provider-Level	 Proportion and description of clinics in each site agreeing to support *InCharge Health* Proportion and description of providers in each clinic agreeing to support *InCharge Health*	Institutional data to describe clinics (e.g., size, case mix, yrs. in service, regional socio-demographics of SCD patients)	**Qualitative interviews with administrators** **Clinic Data Collection Form: Sections A** (clinic name and address), **B** (patient pop), **E** (case mix), **F** (provider and clinic setting description)

Domains	Measures	Data Sources	Data Collection Instrument Mapping
Implementation	Consistency with which sites are able to implement the app as planned Qualitative assessment of any adaptations or enhancement to recruitment strategies needed to meet enrollment by clinic, by site Assess adaptation of training needed to improve *InCharge Health* implementation at each clinic Percentage, number and representativeness of patients who used *InCharge Health* app during the study period (in the entire practice) (low, medium-low, medium-high, or high use – see pg. 33) Proportion, number, and characteristics of patients who complete the study among those who initiate the use of the app but then later discontinue at each site, and by provider Percentage and characteristics of patients who reported satisfaction with the *InCharge Health* app Clinic/provider assessment of perceptions of the *InCharge Health* app for further scale-up or sustainability – ease of use, preferred features, etc.	*InCharge Health* app data use and (e.g., daily clicks) and percentage of features of the *InCharge Health* app used on a daily basis (e.g., pain score, adherence documentation). Survey (MARS scale)	**Qualitative interviews with administrators and patients** **App usage statistics** (not captured in CRF – this data will be transferred directly to RTI) **Clinic Data Collection Form, all of Sections B** (patient population), **C** (patients who meet NHLBI criteria to receive HU), **D** (Patients who meet criteria and prescribed HU), **E** (case mix) **Patient Reported Outcome Form, all of Engagement with the *InCharge Health* app Section**

Domains	Measures	Data Sources	Data Collection Instrument Mapping
Maintenance	Extent to which program leaders express a desire or intent to continue providing the app with patients at the conclusion of the research Percentage of patients who continue to use the app beyond the study period and their representativeness	*InCharge Health* app data use 3 months after end of study Clinic data collection forms Qualitative interviews Pharmacy claims data	**Qualitative interviews with patients** **App usage statistics** (not captured in CRF – this data will be transferred directly to RTI) **Patient Reported Outcome Form: Section** Engagement with the *InCharge Health* app, **4.f** (plan to continue to use app) **Patient Medical Abstraction Form Question #16-#19** (HU refills) **Clinic Data Collection Form, all of Sections B** (patient population), **C** (patients who meet NHLBI criteria to receive HU), **D** (Patients who meet criteria and prescribed HU), **E** (case mix),

Table 6. Provider App (*HU Toolbox*): RE-AIM Evaluation Measures

Domains	Measures	Data Sources	Data Collection Instrument Mapping
Adoption – Provider	Characteristics of providers at each site (e.g., specialty, yrs. in practice, socio-demographics, level of expertise) Proportion and representativeness of eligible providers approached in the study (numerator) among all providers (denominator) Proportion and representativeness of enrolled providers in the study (numerator) among all eligible providers (denominator) at each site	Survey Clinic population demographics and treatment data, study database (CRFs)	**Qualitative interviews with providers** **Provider Data Collection Form:** Demographics Section **Clinic Data Collection Form**: Section F (provider and clinic setting description) **Case/Screening log**
Effectiveness (see Table 4 for a complete listing of measures)	Number and proportion of providers demonstrating improved knowledge and self-efficacy in hydroxyurea administration Percentage of patients who were prescribed hydroxyurea per provider	Self-efficacy survey Chart audit	**Provider Data Collection Form:** HU self-efficacy, Experiences Providing Care to Patients with SCD **Patient Medical Abstraction Form: HU refills**

Domains	Measures	Data Sources	Data Collection Instrument Mapping
Adoption – Clinic	Proportion and representativeness of clinics that agree to support the *HU Toolbox* *HU Toolbox*	Institutional data to describe clinics (e.g., size, case mix, yrs. in service, regional socio-demographics of SCD patients)	**Qualitative interviews with administrators** **Clinic Data Collection Form: Sections A** (clinic name and address), **B** (patient pop), **E** (case mix), **F** (provider and clinic setting description)
Implementation	Consistency with which sites are able to implement the use of the *HU Toolbox* app as planned Engagement with the app: Percentage of participating providers that used the provider *HU Toolbox* app (in the entire practice) (low vs high use – see pg. 34) Percentage of providers who reported satisfaction with *HU Toolbox* app Percentage of patients whose provider used the *HU Toolbox* (per practice site)	*HU Toolbox* app data (e.g., monthly clicks) and features of the *HU Toolbox* app used (e.g., monthly consultations with SCD experts) Provider Survey *HU Toolbox* app data	**Qualitative interviews with administrators and providers** **App usage statistics** (not captured in CRF – this data will be transferred directly to RTI) **Provider Data Collection Form:** MARS Scale (*HU Toolbox* App Quality Ratings) **Clinic Data Collection Form: Sections A** (clinic name and address), **B** (patient pop), **E** (case mix), **F** (provider and clinic setting description) **App usage statistics** (not captured in CRF – this data will be transferred directly to RTI)
Maintenance/ Sustainability	Extent to which program leaders express a desire or intent to offer or encourage the use of the *HU Toolbox* app by their clinical providers at the conclusion of the research Percentage of providers who continue to use the provider app beyond the study period, and representativeness Percentage of providers who continue to prescribe hydroxyurea to their patients	*HU Toolbox* app data 3 months after end of the study Clinic administrative data	**Qualitative interviews** with providers **App usage statistics** (not captured in CRF – this data will be transferred directly to RTI) **Clinic Level Form: Section D** (patients who are prescribed HU)

Mixed-method evaluation of the facilitators and barriers in adopting and implementing the mHealth interventions

Sufficient understanding of the contextual factors in implementation of mHealth interventions is critical to ensuring future scale-up and translation of study findings to other institutional settings outside the SCDIC.[76] As such, for Aim 3, we will elaborate on the RE-AIM quantitative findings with qualitative inquiry at study midpoint and end of implementation at each study site to continuously identify and address barriers as the study progresses and provide an understanding of the

contextual factors at each site that may have influenced how and why results of individual RE-AIM domains occurred and variations in implementation across the sites. Qualitative methods can also help to understand disparate patterns across RE-AIM domains (e.g., high reach but low rates of adoption).[77] We will use the Normalization Process Theory (NPT) to systematically assess barriers and facilitators that affect RE-AIM domains.[78] NPT comprises four core constructs that are concerned with identifying and understanding the ways that people make sense of the work of implementing and integrating a new technology (coherence); how they engage with it (cognitive participation); enact it (collective action); and appraise its effects (reflexive monitoring). Each NPT construct has four specific components (e.g., coherence – *differentiation*, cognitive participation – *initiation*, collective action –*relational integration*, reflexive monitoring – *systematization*) that can be used to develop a detailed understanding of the data and the factors that influence the process by which mHealth interventions become integrated into practice. What we learn about barriers and facilitators under Aim 3 could also be used to develop specific implementation strategies for use in other settings.

Data would be collected and analyzed concurrently using a quantitative+qualitative approach, where qualitative data will be secondary to the quantitative assessment.[79] We will plan key-informant interviews (60–90 minutes) with multiple stakeholders at the patient-, provider-, and clinic-level. Questions will be developed using the broader RE-AIM domains and NPT constructs as a guide. For example, to further understand adoption, providers may be asked to describe what they thought when they first heard about or used the *SCD HU Toolbox* app. We will purposively sample and interview patients and providers (physicians, NPs, PAs) from each site according to mHealth intervention adoption (low uptake vs high uptake), and plan interviews with clinic administrators to gain a clinic-level perspective on factors that influenced implementation. Example topic areas are provided in Table 7.

Table 7. Sample Qualitative Evaluations

RE-AIM Domain	Potential Interview Topics	Example
Reach	• Why do patients/providers choose to participate in the app intervention?	• Interviews with patients/providers at study midpoint to understand contributors to intervention participation
Effectiveness	• Do providers find the effectiveness results meaningful? If unanticipated negative results are found, why are they observed?	• Interviews with providers at end of implementation
Adoption	• Why do different clinics—and providers within those clinics—use the app intervention or not? • What factors contribute to patients' initial app use but later discontinuing or completing the study?	• Interviews with patients/providers at study midpoint and end of implementation
Implementation	• What strategies influence implementation of the apps? • How are the app interventions modified or adapted over time?	• Interviews with patients/providers at study midpoint and end of implementation
Maintenance	• What existing infrastructure could support the ongoing use of the app interventions?	• Interviews with providers at end of implementation

2.5 Participant Timeline [SPIRIT 13]

Please see Tables 3 and 4.

2.6 Sample Size [SPIRIT 14, StaRI 14]

The linear mixed model proposed by Hussey and Hughes[80] was adapted for the Care Redesign Study. If Y_{ijt} is PDC in subject *i* at site *j* provider sites and time *t*, then the modified model is

$$Y_{jti} = \mu + \alpha_j + X_{jt}\theta + \alpha_j X_{jt}\theta + v_{ji} + \varepsilon_{jti}$$

where μ is average baseline hydroxyurea adherence, α_j is a random site effect; X_{jt} is a treatment indicator (=1 if intervention is present in site *j* at time *t* and =0 prior to implementing the intervention), θ is the fixed treatment effect, v_{ji} is a random subject effect and ε_{jti} is an error term. The interaction term $\alpha_j X_{jt}\theta$ captures the heterogeneity in treatment response across sites. It is assumed that α_j, v_{ji} and ε_{jti} are normally distributed with mean zero and zero correlation, given the model fixed effects.

Hussey and Hughes did not include the random subject effect but did include a fixed time effect in their model. Their model was intended for a study that involved repeated cross-sectional sampling of the study population. The observations at different time points were assumed to be independent. In Care Redesign Study, we will instead follow a cohort longitudinally. The random site effect was added to account for the correlations between repeated observations of the same subjects.

The time effect in the Hussy and Hughes model is not included in the model for they Care Redesign Study. The time effect accounted for background variation in adherence during a study. Accounting for this variation made sense in the context of repeated cross-sectional sampling. The Care Redesign Study involves repeated observations on the same subjects. The treatment effect is measured by within-subject changes in adherence, rather than differences in mean adherence between samples taken at different times. The interpretation of the time effect in the context of within-subject changes is less clear than it is with repeated cross-sectional sampling. In fact, with the planned study design and the model above, it is difficult or impossible to separate the time effect from the treatment effect.

A simulation study was conducted to evaluate the statistical power of a study with 8 study sites and 46 subjects per site. The first step in developing the simulations was to model the distribution of baseline values of PDC. Candrilli,[17] reported a mean of 60 and standard deviation of 30 for the MPR, with is a slightly more liberal measure of hydroxyurea adherence than PDC. Both MPR and PDC are constrained to be $\geq$0 and $\leq$100. These constraints, combined with the mean and standard deviation reported by Candrilli, point to a left skewed distribution for baseline values. Therefore, baseline PDC was modeled as PDC=100*X where X follows a beta distribution. The beta distribution has two parameters, A and B, mean A/(A+B) and variance $AB/[(A + B)^2(A + B + 1)]$. If A=1 and B=0.6667, then the distribution has mean 0.6 and standard deviation 0.3; i.e., PDC has mean 60 and standard deviation 30.

Site-to-site variation in the distribution of baseline values was expected. Therefore, a site-specific random variable r, drawn from a normal distribution with mean 0 and standard deviation 0.2, was added to A and B, converting the parameters to A+r and B+r. In a simulation study, 95% of the resulting site means were between 56 and 69. The overall baseline mean remained close to 60. Several additional assumptions were made in conducting the simulations:

1) The subjects at each site will be recruited at a constant rate over a six-month interval.
2) The 8 sites will be divided into three groups of size 2, 3 and 3. Recruitment in the second group will start 6 months after recruitment begins in the first group and recruitment in the third group will start 6 months later.

3) Adherence was expected to increase 20% as a result of the intervention so θ was set at 12% (i.e. at 20% of 60%).

4) A two-sided p-value < 0.05 is assumed for rejecting the null hypothesis.

5) Finally, the simulation assumes that about 25% of the participants will have no data at the 24-week follow-up, a conservative estimate given the interactive intervention.

To account for variation in treatment response among sites, a site-specific random variable, drawn from a normal distribution with mean zero, was added to the expected treatment difference of 12%. Missing values at the 24-week follow-up point were generated by assigning a uniform random variable U to each post-treatment observation and deleting the observations for which U<0.25. To account for the residual errors that are represented by ε_{jti} in the linear model, a separate random variable, drawn from a normal distribution with mean zero, was added to each pre-treatment and post-treatment observation. Finally, some of the values for PDC that were generated in the simulations were <0% or >100%. Values <0% were set to 0% while those >100% were set to 100%.

With these assumptions, 368 total subjects will be recruited and an average of 276 subjects will provide post-treatment values. Given the design of the study, site-to-site variation in the treatment response and residual errors in the pre- and post-treatment measurements will both contribute to the noise against which the treatment response will be measured. The power of the study was evaluated by varying the standard deviations for the error term and site-to-site variation in treatment response to determine the conditions under which the study will have power of at least 80% to reject the null hypothesis of no treatment effect in favor of a positive treatment effect. A total of 1,000 simulated data sets were generated under each set of assumed conditions. Power was estimated as the percentage of the simulations in which the null hypothesis was rejected and the estimated treatment effect indicated an increase in adherence.

Although site-to-site variation in treatment response was included in the simulated data, the interaction between site and treatment was not included in the analytical model used in the initial simulations. The goal of these simulations was to evaluate the power of the study to identify an overall treatment effect, not the power to evaluate differences in the treatment effect among sites.

It is expected that those with relatively low pre-treatment adherence will still tend to have lower post-treatment adherence than those who start with higher values. This expectation implies a moderate to strong correlation between pre- and post-treatment values for PDC. The correlation varies inversely with the variance of the observations. Thus, a higher correlation implies lower variance of the observations and higher statistical power. The simulations indicate that the study will have >90% power to reject the null hypothesis under the assumed conditions. To illustrate this, consider an extreme case in which the error variance is 2,100 (SD=45.83) and the site-to-site variance is 30 (SD=5.48). The resulting correlation between pre-treatment and post-treatment PDS is only 0.29, which is much lower than expected. Even so, the study would have 80% power to detect the treatment effect. Experience indicates that adherence in one interval is a reasonably good predictor of adherence in another interval, which leads to the expectation that the correlation will be much higher than 0.29. If this expectation is correct, then the study will have power much greater than 80% to detect the expected treatment effect. For example, cutting the error variance in half while maintaining the site-to-site variance at 30 boosts the correlation to a modest 0.48 but increases statistical power to >90%. Thus, even with conservative assumptions about the variance structure of the data, the planned sample size will provide more than adequate statistical power for the study.

2.7 Recruitment [SPIRIT 15]

Recruitment for this study will occur at each participating clinical center as well as within its respective geographic catchment area. Enrollment will be restricted to the SCDIC participating sites and affiliated institutions within each site, which are representative of academic and community centers.

All recruitment materials will be approved by the IRB, as appropriate, prior to implementation. The SCDIC Clinical Center infrastructure allows efficient access to the proposed study population. Eligible subjects may be identified and recruited in different ways. People may be contacted in person (e.g., in clinic, emergency department), by phone, or via electronic media (e.g., chat rooms, text) about enrolling in the study. Informed consent for patient-app participants only will occur in the following ways, with appropriate IRB approval:

- In person (e.g., in clinic or hospital, at SCD community events)
- Telephone

The SCDIC participating Centers will enroll both patient and providers. For the provider app, all centers will request a waiver of consent since these participants will all be adult clinical providers and downloading the app will imply consent to participate. **All providers within a clinic will be approached**. **Patients treated by these providers will be approached**, that is, at least 46 eligible participants per Center who meet inclusion criteria for this study. A participant will be considered enrolled when consent is obtained, and inclusion criteria have been confirmed. The SCDIC enrolling Center will maintain a local log of consented participants and will also confirm enrollment status in the data management system (DMS). SCDIC clinic staff will identify eligible patients using the eligibility criteria developed and approved by the Steering Committee. The research team will both screen their current patient population as well as identify new patients that attend the clinic. Eligible patients will be solicited during clinic visits according to the protocol approved by the IRB. Depending on the geographic area covered by the SCDIC, patients may also be recruited during outreach visits to outlying areas or through other outreach efforts within the community. This flexibility on the part of the SCDIC will insure inclusion of the greatest number of eligible patients for the study.

Designated study staff will screen, approach, consent, and verify eligibility of potential study participants. If the patient (and parent/guardian of minors) agrees, the designated study staff will meet with the patient for a more comprehensive explanation of the study. If there is continued agreement, the designated study staff will proceed with the consent and enrollment process. Signed informed consent will be obtained prior to uploading application on participants' phones and any data collection. Patients will receive a hard copy of the completed and signed consent form to keep. Patients will be able to ask questions at any time. The consenting patient or parent/guardian must be literate in English. Adolescent assent will be obtained from children 15–17 years old, or as determined by the IRB. If a minor becomes a legal adult during the 6-month study participation, an age of majority consent will be obtained from the participant. All participants must also sign a HIPAA Research Authorization form.

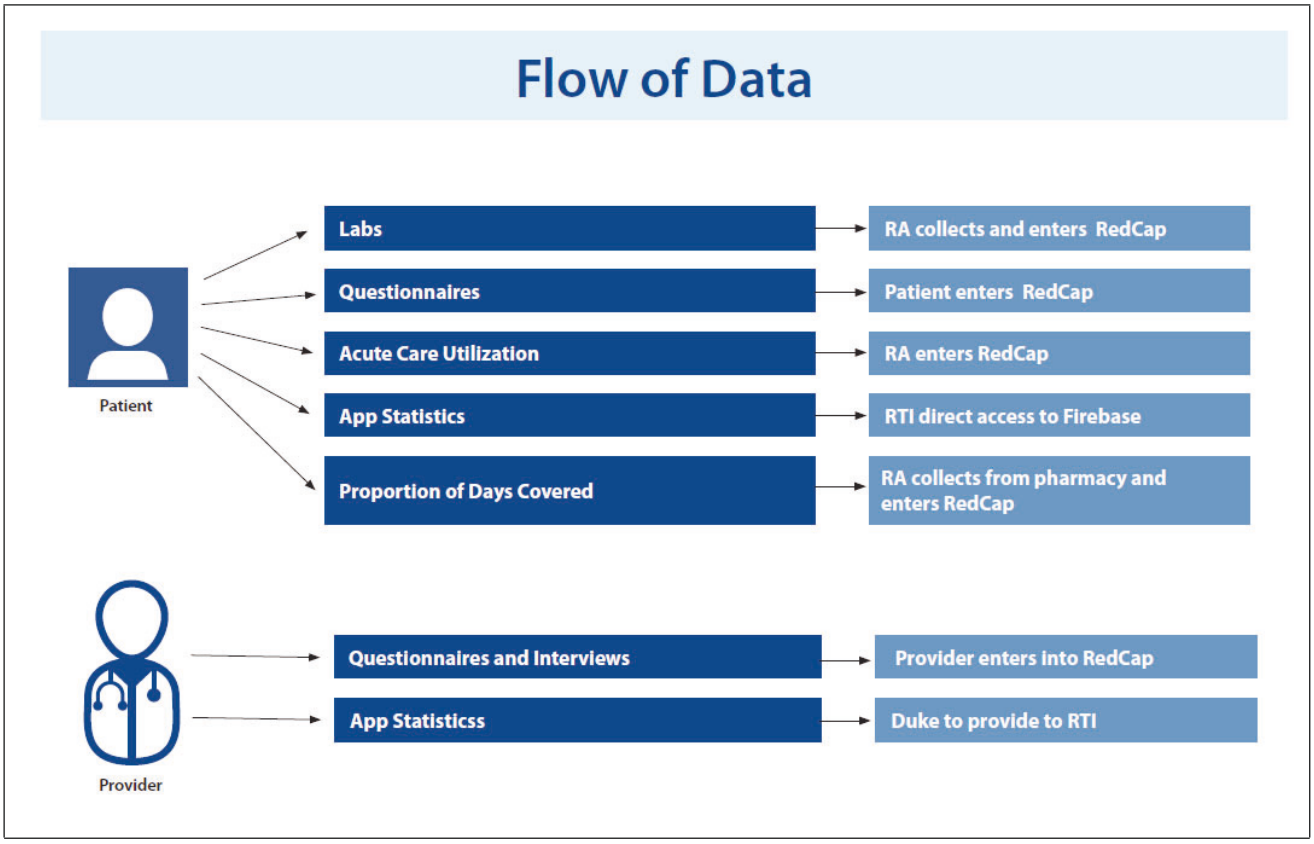
All sites will compensate $25 to each patient participant upon each study visit completed (max $75) and $25 to each participant upon completion of an interview.

3. Methods: Data Management and Analysis

3.1 Data Management [SPIRIT 19]

RTI will develop an electronic data capture (EDC) system for this study. eCase Report Forms will reflect the data elements to be collected at each visit. Data will be entered into the EDC and stored in the study database in REDCap. A research assistant at each site will collect study data and enter it into the EDC. Different data sources will be used, such as pharmacy records for PDC, laboratory results from local electronic medical records and patient-reported outcomes that can be completed in electronic format (e.g., tablets) or paper. Figure 7 depicts the flow of data from multiple sources.

Figure 7. Flow of data from patients and providers (participants) into study database.



*RA denotes research assistant

3.2 Methods of Analysis [SPIRIT 20a-20b, StaRI 15-16]

Aim 1. Improve Patient Adherence to hydroxyurea: Addressing Memory, Motivation, and Knowledge Barriers to Hydroxyurea Use.

Characterization of study patients: A characterization of the study's patients by their demographic characteristics, baseline hydroxyurea adherence, hydroxyurea dosage, laboratory values, measures of self-efficacy, health literacy and quality of life, as detailed in Table 3, will be provided for all patients combined and across sites.

Primary outcome: The primary outcome is the proportion of days covered (PDC) of hydroxyurea change from baseline (prior the intervention) to week 24. For the PDC, the pharmacy that fills the most prescription claims within the target therapeutic category for a specific patient within the calendar range will be assigned responsibility for the patient. The pharmacy where hydroxyurea is

filled will be verified by the research coordinators at each study visit and refill information will be obtained from this(es) pharmacy(ies). All prescription drug claims, regardless of dispensing pharmacy, will be counted towards the patient's PDC threshold.

PDC is calculated as follows:

1) Determine the number of days in each individual's treatment period.
2) Within the treatment period, count the days each individual was covered by hydroxyurea based on the prescription fill dates and days of supply of each prescription.
    a. If multiple prescriptions for hydroxyurea are dispensed on the same day, count the number of days covered using the prescription with the longest days of supply.
    b. If multiple prescriptions for hydroxyurea are dispensed on different days with overlapping days of supply, count each day covered by the medication only once within the treatment period. For example, if a prescription A and a prescription B are filled 5 days apart and each has a 30-day supply, then the total days covered are 35.
    c. If multiple prescriptions for hydroxyurea are dispensed on the same day or different days where the days of supply overlap, adjust the prescription start date to be the day after the previous fill has ended. For example, if three prescriptions for hydroxyurea are dispensed on the same day, each with a 30-day supply, then a total of 90 days are covered.
    d. Any days of supply that extend beyond the end of the measurement period are not included when calculating the total number of days covered.
3) Calculate PDC: Divide the number of covered days found in Step 2 by the number of days found in Step 1 and multiply this number by 100 to obtain the PDC (as a percentage) for each individual.

As noted in the power calculations, the assumed data generating process is considered a linear mixed model (LMM) as expressed in the equation in section 2.6, where the primary outcome of PDC is a continuous outcome denoted Y_{ijt} and is measured in i individuals located in j provider sites at t time periods. Given the normality and independence assumptions of the variance components α_j, v_{ji} and ε_{jti}, the impact of the intervention on the primary outcome ($X_i\theta$), controlling for variation across sites (α_j) and time periods (β_t), can be estimated using standard statistical software for mixed effects models such as PROC MIXED in SAS. A LMM model with a random effect parameter for subject nested within site, a fixed intervention effect parameter, a fixed effect for time interval, a fixed effect interacting the intervention effect with time ($\beta_t X_{jt}\theta$), and five fixed effect dummy parameters (for all but one site) will be specified and interacted with the intervention parameter ($\alpha_j X_{jt}\theta$).

The fixed effect intervention parameter (θ) specified in the LMM model will test the primary hypothesis by estimating the change in hydroxyurea adherence, as measured with PDC, at 24 weeks after introduction to the *InCharge Health* app compared to their measured adherence at baseline. The fixed effect parameter $\beta_t X_{jt}\theta$ will test the hypothesis that the intervention effect changes over time as implementation of the intervention may improve over time periods. The fixed effect parameter will test the hypothesis that the intervention effect differs across sites. The initial LMM will include all fixed effects listed above and if either of the two interaction terms have p-values greater than 0.2, they will be removed to create a parsimonious LMM that will be compared to the full model with a likelihood ratio test to test the null hypothesis that the parsimonious model fit to the data is not different than the full model. If the null hypothesis holds (p-value ≥ 0.05) in the parsimonious model will be used.

After 40 patients are enrolled, the Care Redesign workgroup will verify their baseline PDC to ensure that there is diversity in the PDC distribution. The DCC (i.e., RTI) will provide this data and report it to the workgroup for review. If after this initial review, if >80% of the patients have PDC of 85% or higher, we will amend the protocol to restrict participants with PDC of 80% or lower.

Sub-Aim 1.a. To measure implementation of the *InCharge Health* app among adolescents and adults with SCD. The assessment of implementation of the *InCharge Health* app among patients after 24 weeks will be assessed using the measures listed in Table 5 (i.e., use of the apps features measured by daily clicks, symptom and adherence tracker app outputs, satisfaction with the MARS scale, use after 24 weeks, measured by clicks in the app). Counts and scores of these measures will be graphed with box plots by month. Using the box plots from the last month, patients will be classified into four levels of app implementation: “low” (<25% of the days use of the app), “medium-low” (25 to 49% of the days use of the app), “medium-high” (50 to 74% of the days use of the app) or “high” (75 to 100% days use of the app) by initially using quartiles of the implementation measures, then examining the box plots of the measures and adjusting as needed to create four clinically meaningful groupings of app users. As no specific hypothesis regarding app implementation has been specified a priori, no statistical tests will be conducted. App uptake will be computed at the end of the study at each site.

Sub-Aim 1.b. To examine the clinical influence of the use of the *InCharge Health* app, the clinical influence outcomes listed below will be compared in patients at baseline and 24 weeks for all subjects together and stratifying by the four levels of implementation as defined in sub-aim 1.a.

Definition of the clinical influence outcomes

- Daily recorded adherence on the app
- Proportion of patients with PDC ≥80%
- Hematologic indices (blood tests) MCV, HbF, Hb, Absolute reticulocyte count, ANC, Bilirubin (indirect), LDH (this will be calculated separately for those on previous and newly started hydroxyurea therapy, and stratified by genotype)
- Health care utilization—incidence of hospitalizations and ED visit rates
- Quality of life—pain score and pain interference as measured by PROMIS and ASCQ-Me
- Health literacy scores with one question perceived health literacy
- PROMIS medication self-efficacy short form (for patient participants only)

The continuous clinical influence outcomes measured at baseline and 24 weeks, including MCV, HbF, Hb, Absolute reticulocyte count, Bilirubin (total and indirect), LDH, quality of life, pain and pain interference, health literacy, self-efficacy, and satisfaction with care scores will also be analyzed using the LMM analysis listed above. The LMM will initially include the dichotomous variable X_i to test intervention effects as was done for the primary outcome, but a second analysis that uses a categorical parameter labeled Z_i, denoting the level of app uptake, will replace X_i to determine if there is a change in the effect of the intervention on the clinical influence outcomes at different levels of *InCharge Health* app usage. The parameter is found to have a p-value less than 0.05, pairwise comparisons among groups will be using Tukey’s HSD test control for potential type I error.

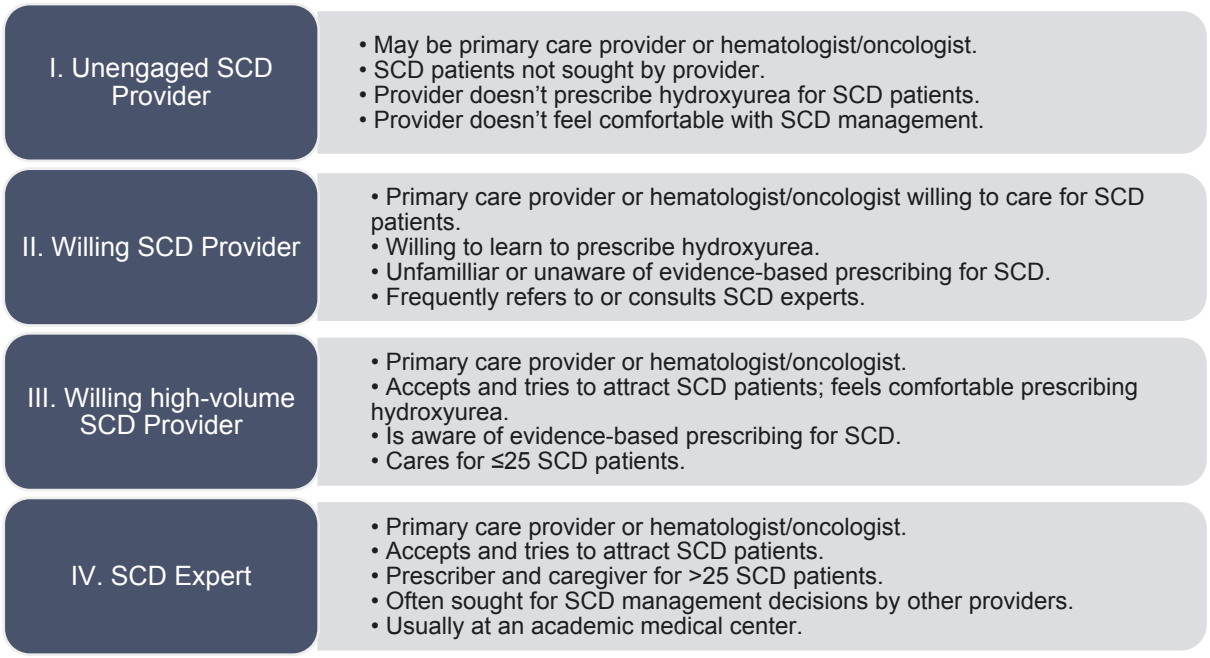
For the laboratory outcomes of MCV, MCV, HbF, Hb, Absolute reticulocyte count, bilirubin (total and indirect) and LDH, the LMM analysis will be conducted as stated above but will include variables to control for variation in when hydroxyurea was initiated and sickle cell phenotype. Models including site level characteristics of urban versus rural and academic versus community will also be created to determine if heterogeneity in the site characteristics impact intervention effectiveness.

The categorical clinical influence outcomes measured at baseline and 24 weeks include daily recorded adherence, the proportion of patients with PDC adherence above 80%, whether patients are prescribed and initiate hydroxyurea and if the patient experiences an ED visit. For these outcomes, generalized linear mixed models (GLMM) will be used, where the outcome is specified as a dichotomous variable modeled with a logit function as indicated.[81] The GLMM models would follow the same format as linear mixed model above with fixed effects for time, intervention/app use and random effects subjects within sites. Such models can be fit with standard statistical software like PROC GLMMIX.

Aim 2. Improve Provider Hydroxyurea Awareness, Prescribing and Monitoring Behaviors. The analysis specified below for Aim 2 seeks to understand how providers utilize the *HU Toolbox* app, whether the app improves providers' provision of hydroxyurea therapy to SCD patients, and their perceived self-efficacy to correctly administer hydroxyurea therapy between baseline and after 9 months of using the *HU Toolbox* app. Given the limited number of providers expected to enroll in the study (**no more than 40 per site**) many the analysis conducted below are simplified and do not account for the across site and across time complexities of the study design. As such, the results should be considered exploratory.

Using baseline data, providers will be classified into 4 categories, according to the level of comfort and expertise in caring for patients with SCD (Figure 8). In the analysis specified below, we will attempt to evaluate the implementation and effectiveness outcomes stratified by this provider categorization to better understand how expertise impacts the implementation and effectiveness of the *HU Toolbox* app.

Figure 8. Categorization of providers according to expertise level.



Characterization of the study providers: Using the socio-demographic, self-efficacy and patient hydroxyurea therapy characteristics listed in Table 4, characteristics of the study providers will be presented overall and by expertise level. This characterization will be done upon study entry. Dichotomization of provider classification can be done at the end of the study to simplify the analysis, as follows: category IV versus collapsed categories I to III.

After the first 5 providers in each site are enrolled, the Care Redesign workgroup will verify if their level of expertise is diverse based on the Figure 8 classification. The DCC (i.e., RTI) will provide this data and report it to the workgroup for review. If after this initial review >80% of the providers are level IV, we will amend the protocol to encourage participation of providers levels I, II, and III by restricting the total number of level IV provider participants.

Sub-Aim 2.a. To measure the implementation of the *HU Toolbox* app among providers serving adolescents and adults with SCD. Uptake of the *HU Toolbox* app by providers after nine months will be assessed using the implementation measures identified in Table 6 (proportion of providers that use the *HU Toolbox* app at least once a week based on monthly clicks, satisfaction with the *HU Toolbox* app with the MARS scale, use of features of the *HU Toolbox* app measured in clicks, documentation of provider consultations with experts measured in clicks, *HU Toolbox* app utilization after nine months measured in clicks) will be assessed after nine months using box plots for each measure, for all participants combined and stratifying by expertise level. One-way ANOVA or Kruskal-Wallis tests will be used to test the hypothesis that there is a significant difference in the uptake of the *HU Toolbox* app across expertise levels. If the null hypothesis is rejected, then Dunn's test will be employed for multiple comparisons. If an experience level has fewer than five providers, it will be combined with the closest lower experience level. The results of these analysis will be used to identify clinically meaningful "low" and "high" *HU Toolbox* app uptake groups for Sub-Aim 2.b.

Sub-Aim 2.b. To assess combined effects of the patient and provider mHealth interventions on hydroxyurea and health care utilization. This analysis seeks to identify the impact of both the patient and provider interventions on hydroxyurea adherence, as measured by healthcare utilization as measured by the count of ED visits and hospitalizations per patient at baseline and at nine months. For each of the outcomes a GLMM will be employed as the outcomes are not likely to be linear, normally distributed variables. The GLMM will assume these parameters are have a Poisson distribution with a log link function, with a 0/1 indicator variable for baseline versus nine months, a categorical indicator parameter for four levels of *InCharge Health* app uptake defined in Sub-Aim 1.a, an indicator parameter for low (less than 1 day per month use of the app in a 9-month period) versus high provider (1 or more days per month use of the app in a 9-month period) *HU Toolbox* app uptake, an interaction parameter for the combined effect of both patient and provider uptake, and a random effect parameter to account for clustering of baseline and nine month measures within providers. If the patient, provider, or interaction parameters are found to have a p-value less than 0.05, pairwise comparisons among groups will be using Tukey's HSD test control for potential type I error. App uptake will be computed at the end of the study at each site.

Aim 3. Evaluate the Barriers and Facilitators of the Adoption of the mHealth Interventions. We will evaluate the strategies used by participating sites in supporting the implementation of mHealth interventions via a mixed-method evaluation of the facilitators and barriers in adopting and implementing the mHealth interventions from multiple stakeholder perspectives: patient, provider, and organization (clinic level evaluation). □

The Normalization Process Theory (NPT) will be combined with RE-AIM to guide the coding structure for the qualitative analysis. A common codebook will be used for the deductive coding of the interviews, and further expanded and refined once the interviewing begins. Using this deductive approach, the codebook will create an initial list of codes to be used in the analysis and include operationalized examples on how to apply the code. We will revise the codebook as necessary to hone definitions to increase consistency in coding across the research teams. We will use qualitative software to code the transcripts and identify emergent patterns and themes in the data. Any discrepancies in coding and analysis will be identified and resolved. Interview data will be analyzed by different stakeholder groups both within and across the study sites. Data integration will occur by embedding the qualitative data within the quantitative outcomes data (for example, using a matrix where sites are organized from low to high levels of adoption) to understand why and how outcomes were obtained and contextual factors related to the mHealth interventions.

4. Methods: Monitoring

4.1 Data Monitoring and Quality [SPIRIT 21a-21b]

The RTI International Data Coordinating Center (DCC) will manage a central web-based EDC of all data collected by SCDIC Care Redesign research sites. RTI will monitor the ratio of enrolled patients throughout the duration of recruitment. In this way we will ensure a final enrollment ratio at the desired target.

4.2 Harms [SPIRIT 22] (Adverse Event, Unanticipated Problem Reporting)

This study does not involve a drug intervention, device intervention, or highly invasive data collection procedure. However, recognizing that unanticipated events can occur during any study, even a minimal risk study, the following reporting protocols will apply. The site principal investigator (PI) or designee will assess the event to evaluate whether it is unanticipated (i.e., unexpected), related to the study, places the participant or others at risk, and/or is serious to determine whether it should be reported to the IRB and DCC.

Adverse events and unanticipated problems

This study will collect the following information:

- unanticipated (i.e., unexpected) and related adverse events (possibly related, probably related, or definitely related to study participation), and
- unanticipated problems that may involve risk to participants or study staff, but do not necessarily result in an adverse event (i.e., harm).

Unanticipated adverse events are new or greater than previously known events in terms of nature, severity, frequency, or occurrence, as documented in the protocol, consent, or other study documents approved by the IRB.

An example of an unanticipated problem that may not result in an adverse event (i.e., harm) is misplacement of a participant's research record containing PII such that the risk of loss of confidentiality is introduced. This event is reportable regardless of whether the confidentiality is breached or not breached. If the PI or designee identifies the adverse event or unanticipated problem as meeting the following criteria, it will be reported to the IRB within 5 business days and to DCC within 10 business days:

- involves substantive harm (or genuine risk of substantive harm) to the safety, rights, or welfare of the site's research participants, research staff, or others

Otherwise, the site will report the events to the IRB and Steering Committee (if applicable) on an annual basis at the time of continuing review. It is expected that patient participants will have acute disease complications (e.g., pain crises). Acute events will be treated as per each site's standard of care. If they lead to a visit to the clinic/hospital, they will be captured in the study dataset.

4.3 Auditing [SPIRIT 23]

Clinical research monitors will review up to 10% of the study participants annually for appropriateness of the informed consent process, eligibility, serious adverse event reporting and patient protocol status. Additional information may be monitored at the request of the NHLBI, the IRB, or other institutional administration. The monitor will generate a formal report, which is shared with the PI, study team, and the NHLBI.

Continuing reviews by the IRB will occur at least annually. In addition, SAE reports in are reviewed in a timely manner by the IRB and NHLBI. Monitoring of this protocol is considered to be in the “low risk” risk category.

5. Ethics and Dissemination

5.1 Research Ethics Approval [SPIRIT 24]

No data collection activities will begin at an individual SCDIC participating clinical center until approvals from the IRB have been granted. The IRB will focus on data security (receipt, storage, sharing, protection of breach) and defer to the Center IRBs for procedures related to direct patient interaction and those conducted locally. All participating SCDIC clinical centers and RTI have a Federal Wide Assurance issued through the U.S. Office of Human Research Protections which assures that the organizations are complying with all Federal regulations to protect research subjects.

Risks and benefits

The data collected for this study may come from medical record abstraction, self-reported information, and application intervention. The patient surveys are not considered greater than minimal risk but may trigger uncomfortable feelings about one's lifestyle, quality of life, or personal or family history of disease. Some patients may benefit from participating in the study through improved understanding of hydroxyurea and/or increased adherence to hydroxyurea and the associated health benefits. Some patients may benefit from knowing that they are helping to advance knowledge for future patients with their condition.

Unbiased recruitment

All eligible participants will be recruited without bias. Adolescents, women, and minorities will be included as they represent the patient population of each Center.

5.2 Protocol Amendments [SPIRIT 25]

Modifications to the protocol or consent form that impact eligibility criteria, outcomes, or analyses will be submitted to the RTI and IRB for approval prior to implementation. Protocol modifications and consent form changes will be submitted to the appropriate oversight committees according to the timetables set forth by those committees.

5.3 Consent or Assent [SPIRIT 26a-26b]

Participants will be recruited by local clinical staff from all eight participating Centers (University of Illinois at Chicago in collaboration with Sinai Health System, Washington University School of Medicine, Augusta University, St. Jude Children's Research Hospital, Duke University Medical Center, University of California Benioff Children's Hospital Oakland, Medical University of South Carolina), who will consent participants at the community clinic sites. If a minor is involved in this study, the minor's guardian will be approached during regular clinic visits and invited to have his/her child participate in the study. If a participant is eligible, the family will be informed and given detailed information about the study, including the risks and benefits of study participation. An informed consent session will take place in which patients and guardians will have the opportunity to ask questions regarding participation in the study, as well as to learn the risks and benefits of participation.

After detailed discussion of the protocol, participants will be given a copy of the informed consent document for review. Participation will be voluntary, and patients may withdraw from the study at any time. Families will receive a set amount for reimbursement per study visit to help offset the costs for parking, food, and travel. Subjects and families will be informed of any information that becomes available during the study that might impact their continued participation.

There will be a consent form specific to the protocol:

- Study consent
    - To recruit 368 participants, 15-45 years old, diagnosed with SCD
    - Adult participants (ages 18 and older) will sign informed consent, adolescents ages 15 to 17 will sign informed assent and their legal guardians will sign the informed consent

5.4 Confidentiality [SPIRIT 27]

All study data will be collected by local study coordinators with the supervision of the local study leaders and sent via EDC to the study database, which RTI manages. Full names and other identifying information, excluding date of birth, will be retained only by the Centers. Participants' data will be labeled and stored with coded identification numbers that can be linked to names only by the corresponding Center. Access to the database will be restricted to the local study leaders, PIs, and designated research staff and will be password-protected. Each study participant will have a study identification (ID) number to protect patient identity. App data will be collected and stored under this subject ID. RTI will receive data coded with subject ID numbers for tracking and linkage only with no identifying information. Once data collection is complete, an analysis file will be provided to begin analysis. Data will be encrypted to protect against loss of confidentiality. Study coordinators will maintain a list to allow linkage to subject identity; this list will be restricted to designated study staff (PIs and research coordinators) and to entities that may need access to verify accuracy and completeness of data (IRB and study monitors). All collected data will be kept confidential to the extent permitted by law. The DCC will not be able to link an individual to their identifying information.

5.5 Access to Data [SPIRIT 29]

Data will be entered into a password-protected, secure web-based data management (DMS) system. Within this system, the DCC will build in edit, range, and validity checks on the data as they are entered. In addition to data entry, the DMS will allow SCDIC staff to produce data management reports to monitor their performance. The DCC will train Center staff in data collection and management in accordance with the protocol and manual of operations.

To monitor enrollment, data flow, delinquent data, and data quality, the DCC project managers will run reports that monitor the performance of the individual Centers. These reports will also be distributed and reviewed regularly by the Center staff and the Executive and Steering Committees. The reports will show the number of patients enrolled, the number and type of forms submitted through the DMS, the number of incomplete and delinquent forms, and the number of unresolved data edits. The DCC will collaborate with the Center staff to design reports that are helpful in monitoring the conduct of the study and producing high-quality data for analysis.

5.6 Dissemination Policy [SPIRIT 31a-31c]

The primary goal of the SCDIC Care Redesign study is to increase the appropriate use of hydroxyurea among patients and providers. Data collected from this study will be shared with SCDIC investigators and qualified researchers outside of SCDIC interested in studying additional aspects of SCD that are not being addressed by this protocol. Results will be published in peer-reviewed journals and presented at national and international conferences, community and professional meetings. De-identified patient-level data will be made available to researchers outside the SCDIC through an application and approval process as part of the SCDIC's Ancillary Studies Policy and Data Dissemination Plan. To protect the confidentiality and privacy of the subjects, investigators

granted access to the limited access data and biologic specimens must adhere to strict requirements incorporated into a standard Data Use Agreement. In accordance with NHLBI policy, outside researchers will also be required to submit an approval from their IRB. Dissemination of the app will be done upon a larger-scale study, upon completion of the current study.

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Appendix A
Informed Consent Materials

Please refer to documents entitled informed consents.

Appendix B
Patient Feedback on *InCharge Health* App

ISAAC

Chicago SCDIC site community and patient engagement learnings

WHO WE TALKED TO...

Community Advisory Board (CAB) meeting - 9/11/18
2 study coordinators
1 SCDIC PI
1 community health worker
4 patient representatives

Patient workshop - 10/05/18
4 patients with sickle cell
1 patient with sickle cell trait

WHAT WE SHOWED THEM....

Both groups saw screens and prototypes of:

1. Care Redesign HU app for patients, screens and live prototype
2. Pain plan in patient portal, UIC version and pathway

WHAT IS IN THIS WRITE-UP...

HU APP

Patients and community members were excited about...

... using the app to find new resources.
Participants were impressed with the 'connect' section of the app. Many of them did not know about the patient portal or SCD One Voice.

★ *Could the app get updates with links to new resources, conferences or events for sickle cell patients?*

... the mood tracking feature.
One participant said, "With my health, the emotional or psychological staff is as bad as physical". All participants appreciated that tracking moods was an option.

... weekly reports and reminders.
Some patients found the tracking the most helpful aspect of the app, saying it was 'proof' of what was working. Others said the reminder was the most helpful.

... learning more about sickle cell through videos.
Participants were excited about learning more about sickle cell from videos in the HU app. Some participants pointed out that sounds can be triggers for pain during a crisis.

... connecting with other sickle cell patients through social media and posting videos.
Social support videos were cited as important for addressing isolation felt by our participants.

To successfully use the HU app, patients wanted...

... the app to be free.
Participants in the workshop were unanimous that the app should be free.

... a tutorial on how to use the app and on-going support for troubleshooting.
When asked if they would use the app, patients emphasised that they would like to be trained on the app and have support if they ran into problems.

... to be able to share their weekly progress report with their doctor.
Some participants said they would like to be able to share their weekly progress reports with their doctor remotely (through email or text).

... specific tips and tricks for staying on top of their HU routine.
During the session, patients exchanged tips on how to say on top of HU. Tips included: always having your medication on your person, use a pill case attached to your keys, have a pill case in your purse or bag,

A patient shows the group the pill case she keeps in her bag with her HU and pain medication.

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HU APP CONT.

In context of HU, patients and community members also talked about...

... concerns about fertility.
Patients commented that fertility and family plans were a big concern for them while taking HU.

★ *Could the education section of the HU app include links about fertility and planning to have a family?*

... taking HU was often a reminder of traumatic events, like pain crises and the impact of sickle cell on their lives.
Patients mentioned that taking medication reminded them of traumatic events, like pain crises.

★ *When introducing the app to patients, can we recommend they use the customization features of the app to remind them of their personal reason for staying healthy - 'for my grandchildren' or 'for our anniversary trip'.*

We ask patients to write down what habits they have to manage SC at home and how the HU app might support developing habits around HU.

... they had concerns about the special precautions for handling HU medications.
One patient was concerned about the extra measures needed when handling HU. She talked about washing her hands after touching the medication bottle and washing the carpet three times if the medication spilled. Based on this, she worried about what HU would do to her body.

★ *Could we provide patients with an overview of the medication and medication safety?*

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Appendix C
App Descriptions

InCharge Health app

The *InCharge Health* app features include several features to increase patient engagement and motivation. Below is a detailed description of the app features.

- Daily reminders will be sent to the participants' phone. These daily messages will involve a customized push notification with medication reminder (Figure C1A).
- The ability to customize the content of the message and time of the day when the message comes (Figure C1B).
- Symptom tracker to monitor daily pain and mood (Figure C1C).
- 7-day streak that tracks daily adherence (Figure C1D).
- Graphing adherence against pain symptoms (Figure C1D).
- Communication feature that allows the patient to connect to the clinic and to a "health partner" (Figure C1E).
- Link to discussion forum where communication to other patients can occur (Figure C1E).
- Education bank that provides information about SCD and hydroxyurea (Figure C1F).

Participants will be encouraged to use the app daily by documenting when they take hydroxyurea once the push notification arrives. On any given day, participants will have the option to delay the daily push notification; however, the notification will occur again between 1 and 12 hours later (the participant chooses, that timing when the app is set up). This feature accommodates the scenario when a participant is occupied with other activities but wishes to be reminded once activity is completed (e.g., delay message while driving). In addition, if they are hospitalized, participants may stop push notifications. Participants will be encouraged to visit other components of the app. A special feature of the app, optional for the participant, is to set up an "health partner" who will follow the participant's progress. The participant may choose a person from his/her contact list (e.g., family member, friend) who will receive notifications if it had been <4 hours since not documenting the use of hydroxyurea. The "app accountability partner" will be encouraged to message the participant to remind him/her to take the medication, if he/she received the message of "participant failed to take medication today". The accountability partner will not have access to the data the patient inputted in the app, however he/she will receive a notification if the patient was hospitalized.

Use statistics of the *InCharge Health* app will be collected and stored in the Mixed Tables software in an Enterprise account housed at St. Jude and then transferred to RTI for analysis. The use statistics (app usability data) will be stored under the study participant's number, and the *InCharge Health* app will **not** collect any protected health information (PHI). The following app-related data will be collected: features of the app used, frequency of each feature used, daily adherence, daily pain scores, daily mood scores. We will encourage each participant to use the *InCharge Health* app for the duration of the individual patient participation, i.e., 24 weeks. At each study visit (12 and 24 weeks), the participant will meet with a study member who will review the app use, functionality, encourage him/her to continue using it, and answer any questions related to its use. Upon study enrollment, participants will be given an email address and phone number to call should any technical problems occur related to the use of the *InCharge Health* app. They will receive a local

number in addition to a central number from the study sponsor for any technical difficulty during the study. Data related to technical problems related to the app will also be tracked to evaluate its functionality.

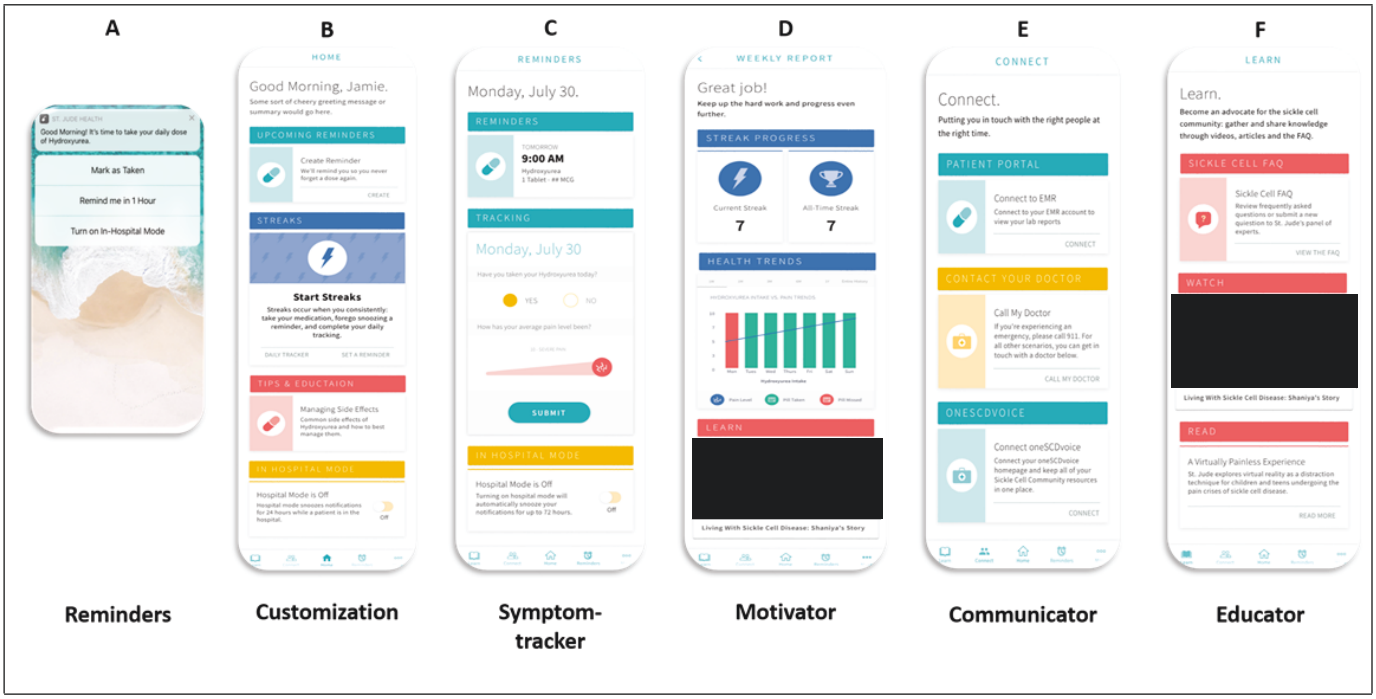

Figure C1. Features of the *InCharge Health* app for patients. A) Push notifications will come daily and will prompt the patient participant to mark if dose was taken, not taken, or be reminded later, B) customization of the push notification messages, time of the day, choice of "app buddy" are available featuers, C) daily pain and mood tracker are available and will capture pain level and mood changes, D) graphing of pain level versus mood and pain is available for the past 7 days or longer, E) a link to the patient porter (EMR), clinic numbers, and patient-led discusson forums are available, and F) a large resource bank is available with links to vetted educational websites, educational material, and educational videos and is included.

HU Toolbox app

The *HU Toolbox* app is an updated version of the *SCD Toolbox* mobile application released approximately 1 year ago. It has been modified to emphasize algorithms (Figure C2, C3, and C4) for appropriate hydroxyurea use and is ready for immediate use on Apple and Android operating systems (i.e., iPhones and Android phones). In addition, it has the NHLBI guidelines adapted for pediatrics (guidelines/recommendations separated by age) and for adults (guidelines/ recommendations separated by organ system, laboratory, or physical exam finding) (Figure C2). The guidelines and algorithms are the consensus of U01 medical providers as adapted versions of the NHLBI guidelines. The *HU Toolbox* app includes the ability to search guidelines for key words and add notes. Algorithms are also included as PDF documents that can be printed out or emailed. Finally, a contact list of local SCD specialists and important contacts is included, so providers can easily contact SCD experts and expect an answer in 24 hours or less. The *HU Toolbox* app is easily updated with all data and resources stored on a cloud-based server that can provide instant up-to-date information to those using the app. All updates and maintenance of the *HU Toolbox* app will be provided by SickleSoft, LLC, which developed the mobile app and has agreed to continue its support of this effort.

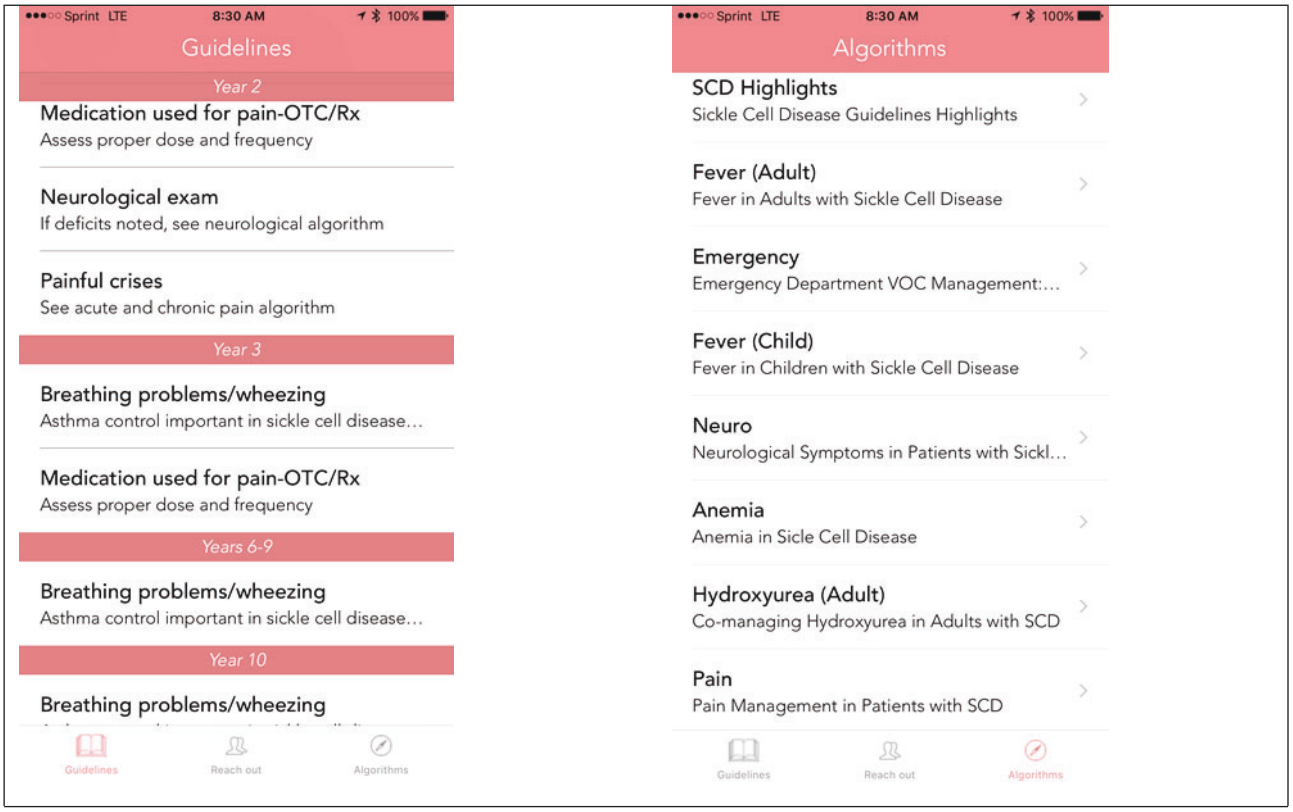

Figure C2. Features of the *SCD Toolbox* app for providers. NHLBI guidelines and associated algorithms are presented in simplified and ready-for-consumption format.

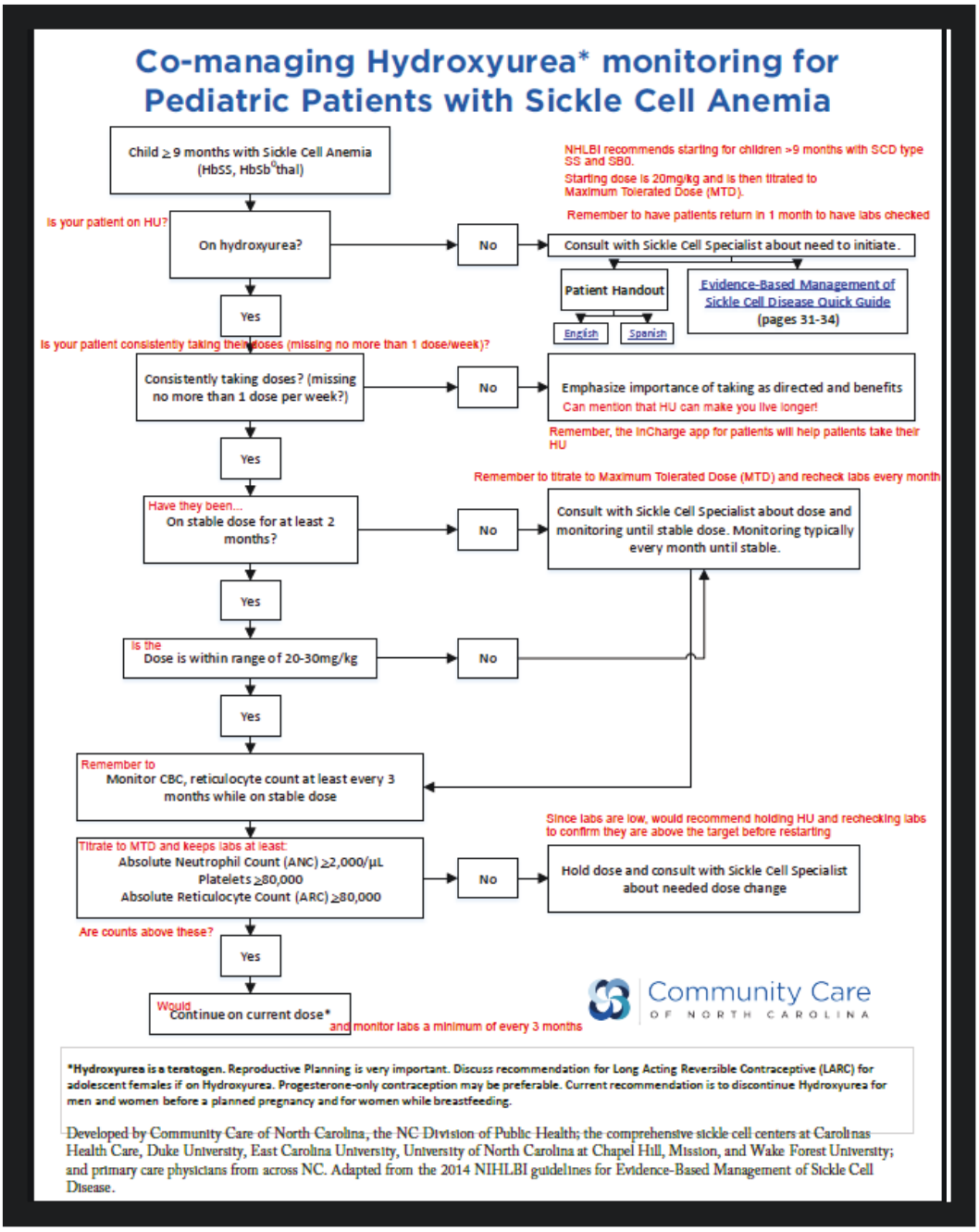

Figure C3. Algorithm for managing hydroxyurea therapy in children with sickle cell disease.

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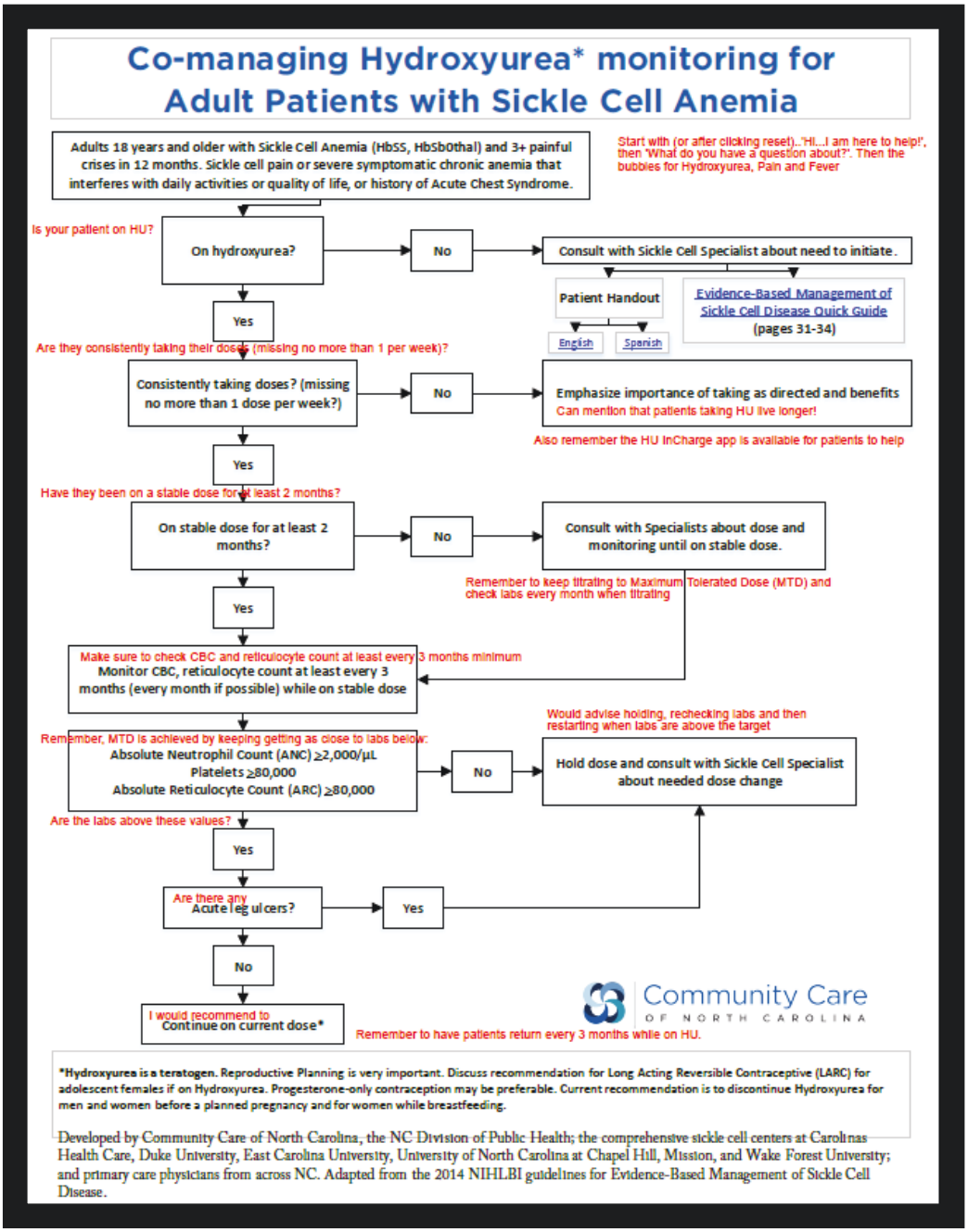

Figure C4. Algorithm for managing hydroxyurea therapy in adults with sickle cell disease.

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