Hydroxyurea Adherence for Personal Best in Sickle Cell Disease (HABIT): Efficacy Trial

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SPECIFIC AIMS

Sickle cell disease (SCD) is a major chronic illness affecting approximately 100,000 Americans of African descent, including Caribbean Latinos and other underserved ethnicities.[1,2] An inherited blood disease, SCD is characterized by fatigue, painful crises, organ damage, reduced quality of life (QOL) and high health care costs and shortened lifespan.[3-6] The sole FDA-approved drug for SCD therapy is hydroxyurea (HU); its use is recommended as standard practice.[7] HU markedly reduces symptoms, morbidity and mortality, improves QOL, decreases health care cost, and may protect against cumulative disease burden.[7] HU induces a dose-dependent increase in fetal hemoglobin (HbF), an effect that is largely responsible for its impact.[8,9] Despite benefits of HU, adherence in adolescents and young adults is often poor.[10-15] Barriers to adherence, especially among underserved populations, include cultural misalignment with medical staff,[16-18] incomplete knowledge of drug benefit,[19-21] logistic impediments to prescription refill.[22] Poor adherence is linked to inadequate integration of adherence into a daily medication habit.[23] Barriers to medication adherence are common in youth with chronic illness[24-28] and a source of racial/ethnic disparities in underserved communities.[29,30] **The goal of this multi-site study is to assess the efficacy of our recently piloted intervention, HABIT, which was designed to improve self-managed adherence to HU therapy while developing a daily medication habit in youth with SCD.**

The scientific premise and experience for the proposed study is based on our 2-site randomized feasibility trial of "HABIT" (R21NR013745), a 6-month intervention delivered by community health workers (CHWs), augmented by tailored text messages sent to subjects.[31] A multi-ethnic sample of 28 youth-parent dyads (youth ages 10-18 years) participated in this study. Eligible youth had ≥20% decrease from maximum HU-induced HbF levels, "Personal Best." The intervention was both feasible and acceptable, and sufficiently effective on our primary outcome of medication adherence - operationalized by two objective measures. Building on these promising results and partnering with three additional clinical sites, we propose a larger 5 site randomized controlled trial of 104 youth-parent dyads to test the efficacy of the HABIT intervention.

Study aims are to:

Aim 1: Improve daily HU adherence, the primary outcome operationalized two ways: biomarker (approach or exceed a historical Personal best HbF) and pharmacy refill (proportion of days covered).
Hypothesis 1: Compared to the control group, youth-parent dyads randomized to the intervention will improve medication adherence at 6 months, with sustained improvement at 12 months.

Aim 2: Improve quality of life and self-management responsibility measured by three *secondary outcomes*: generic and disease-specific QOL and parent/youth concordance regarding delegation of self-management responsibility. *Hypothesis 2: Compared to the control group, dyads randomized to the intervention will report improved quality of life and self-management responsibility concordance at 6 months, with sustained improvement at 12 months.*

Aim 3: Improve health status measured by two *secondary outcomes:* acute hospital use (12 month hospital length of stay, admissions and emergency room visits) and self-reported disease symptoms (fatigue, pain interference and intensity). *Hypothesis 3.1: Compared to the control group, youth-parent dyads randomized to the intervention group will demonstrate decreased acute hospital use at 6 months, with sustained improvement at 12 months. Hypothesis 3.2: Compared to the control group, dyads randomized to the intervention group will report decreased disease symptoms at 6 months, with sustained improvement at 12 months.*

Aim 4: Qualitatively describe impact and sustainability of the intervention on developing a daily medication HU habit from the perspectives of the community health workers (CHWs) and youth-parent-dyads using focus group and individual interviews (*exploratory aim*).

Impact: Adherence to daily medications is a challenge for most youth with chronic health conditions and poor adherence is common.[24] Identifying successful ways to improve adherence to HU through developmentally appropriate self-management not only has the potential to improve the health of youth with SCD, the intervention may be transferable to underserved youth with other chronic conditions. Further, this research is consistent with NINR's strategic theme of "Self-Management: Improving Quality of Life for Individuals with Chronic Illness,"[32] as well as the U.S. Healthy People 2020 goals of optimizing health across the lifespan and reducing health disparities[33] for SCD and other conditions.

RESEARCH STRATEGY

A. SIGNIFICANCE This proposal directly responds to **PA-14-029**, "Chronic Condition Self-Management in Children and Adolescents. The proposed multi-site randomized intervention trial is the next logical step from our successful feasibility trial (R21NR013745). The trial proposed here will test a replicable and scalable model for self-managing HU adherence in SCD to decrease disease morbidity and improve QOL. It could also be applied to other chronic conditions affecting underserved youth to address health disparities. Specifically:

1. Poor medication adherence is a widespread challenge to optimizing health outcomes in chronic disease,[34] rendering treatments less beneficial or even ineffective. Adherence problems are especially pronounced in underserved communities,[29,30] adding to existing health disparities, increased health cost expenditures[34,35] and decreased QOL[10,36] This problem is common among youth with chronic illness, especially those with social, economic, linguistic and cultural barriers.[16-18,20] Mismatches between providers and communities served are known risk factors for reduced adherence.[20,37,38] Barriers to adherence include incomplete understanding of disease and benefits to medication use,[11,19,39] access to medication[22] and poor family adaptation to chronic illness.[40] Adolescents with chronic medical conditions have especially high rates of poor adherence,[24,26,41] especially those from under-resourced communities.[41] Moreover, problems with self-management during adolescence interferes with successful transition to young adulthood.[40,42]

2. SCD is a major chronic multi-organ illness, affecting approximately 100,000 African American, Hispanic and other traditionally underserved communities in the U.S.[1,7,43] SCD frequently affects underserved groups in the U.S.: 1:365 of African-American births and 1:16,300 of Hispanic-American births.[1] SCD is associated with high medical expenditures,[44] early mortality, poor QOL and low rates of high school completion.[4] Reflecting the importance of SCD to population health and reducing health disparities the federal Healthy People 2020 (HP 2020) program of goals for national health-promotion and disease prevention includes target goals for SCD.[45]

3. Youth and young adults with SCD derive considerable health benefit from HU treatment,[8,9,46] **but poor adherence common**,[10-14,39] often reflecting poor self-management.[39] HU benefits include reduced symptoms,[7,47] health care expenditures[10] and improved health QOL for the common sickle subtypes (HbSS and HbS-B^0 thalassemia).[48] Increased well-being often begins within the first months of HU,[8] along with increased HbF levels. Optimum therapeutic effect is reached at maximum HbF response, which we refer to as "Personal best HbF levels".[15] Rarely is HU therapy ineffective in childhood, and is usually attributable to poor adherence.[8,11,46] Young adults with SCD utilize health care at the highest levels of all age groups,[3] including hospitalization and re-admission, and have high rates of poor adherence.[10-15] Adult HU use is associated with improved outcomes[49,50] and longevity,[51,52] In total, these findings demonstrate the impact of HU *across the lifespan*, underscoring the imperative of establishing self-management of HU during childhood and adolescence. Consistent with NINR's strategic theme of "Self-Management Improving Quality of Life for Individuals with Chronic Illness," HP 2020 public health goals for SCD include the increased use of disease-modifying therapies, of which HU is the most widely available effective treatment.[7,47]

4. If demonstrated as efficacious, our HABIT intervention could be adapted to address poor medication adherence across other chronic pediatric conditions in underserved communities. Our approach built upon Columbia's local pediatric asthma study for underserved communities in Washington Heights and Harlem.[53] CHW-based approaches are recommended to improve treatment outcomes for chronic pediatric conditions in underserved communities,[54] and need successful models for implementation.

B. INNOVATION. To develop a self-managed adherence habit[23] for HU for youth with SCD, the proposed multi-site randomized HABIT trial will continue to employ several innovative aspects:

1. Individualized Personal Best HbF target. No standard previously existed to assess HU adherence[9,11,13,39,55] We have used and validated the highest historical HU-induced HbF as an innovative minimum target for an individualized Personal Best self-management goal.[15,31] Long-term pediatric clinical HU trials demonstrated stable HbF levels over time.[56-58] The personalized biomarker of Personal best HbF adds to other adherence measures employed and serves as a customized motivational aid. In the HABIT feasibility trial, coaching by CHWs on the historical Personal best HbF helped create a concrete attainable goal and was useful and acceptable to youth-parent dyad participants. We validated the utility of Personal best as a biomarker for tracking adherence in a retrospective sample of 75 youth on HU therapy[15] (see **Preliminary studies C2**).

2. Focus on underserved parent-youth dyads and developmentally appropriate delegation of responsibility for adherence. Chronic disease management often deteriorates during adolescence as youth assume greater self-management responsibility.[20,59-62] Shared responsibility in youth-parent partnerships for self-management supports adolescents by a gradual transition to self-management.[41,63-65] To our knowledge,

the HABIT trial is the only CHW intervention to engage youth-parent dyads.

3. Community Health Worker (CHW) support augmented by tailored text messaging. Our approach combines two successful research strategies for a novel multi-component approach for improved cue-based medication adherence. Culturally aligned CHWs are an accepted mode of by community-based support for improving health in underserved communities.[53,66-68] CHWs share responsibility for patient education, support and social services with clinical staff, and have been successful in engaging and sustaining adherence among adolescents. CHWs are highly effective at promoting adherence to chronic disease management regimens through regular, structured interactions.[53] Currently, CHWs are being tested a multi-state, federally funded program to improve access to care for adults with SCD (LOS **Banks**). In the HABIT feasibility trial, CHWs established a trusting relationship with families and focused on helping the youth-parent dyad work together to address their particular barriers to medication adherence.

Texting health messages is effective for professional-to-parent short-term reminders,[69] and are widely acceptable and effective for parents and adolescents.[69,70] Text-based reminders to improve adherence in chronic pediatric illnesses may improve a biomarker but have not documented changes in health status or sustainability.[71] Other types of electronic communication were less popular in our community for connecting youth and their parents.[72] During the feasibility study, HABIT dyads worked collaboratively with the CHWs to personalize automated, cue-based text messaging to reinforce the HU habit. This approach builds on work demonstrating the importance of tailored communication messages.[70,73] **To our knowledge, this combined intervention has not previously been studied for improving medication adherence**.

C. RESEARCH STRATEGY

1. Scientific Premise and Overall Strategy. Poor medication adherence is highly prevalent among children[24] and in adults[74] with chronic health conditions. Poor adherence poses considerable risk for exacerbating health burden, cost and health disparities. Rigorous multi-level tracking of treatment adherence and its impact includes health care utilization, treatment success rates, family functioning and school/work missed, bioassays and symptoms.[75] For SCD, widespread poor adherence for therapeutic HU for SCD has been documented by pharmacy refill databases[10,13,76] and by reduction from peak HbF levels,[13,15] the most sensitive biomarker for dose-dependent HU use. Systematic reviews and meta-analyses of randomized trials to improve adherence among youth with chronic illness support the importance of multi-modal approaches,[77,78] some of which include community-based support.[53] Trials to improve HU adherence are limited, and to date have focused on immediate outcomes rather than broader patient-reported outcomes, and have not used strategies for developing longer-term self-management[71,79,80] that are sensitive to socio-cultural patient and family needs. Using individualized biomarker and pharmacy data, we propose a rigorously designed and implemented multi-site randomized controlled trial to test the efficacy and sustainability of the intervention.

2. Preliminary Studies. Our multidisciplinary team has complementary expertise, which ensures our ability to fulfill study goals. The studies that directly inform the scientific premise of this application are described below.

a. Expertise of the Inter-disciplinary Research Team: The majority of the research team (**Smaldone, Green, Jia, Findley, Manwani**) and consultants (**Matos, Stennett**) collaborated on our successful HABIT 2-site feasibility trial. **Bruzzese**, with extensive experience in developing evidence-based asthma interventions to youth and their caregivers in school settings,[81-84] and **Stockwell**, nationally recognized for her work in text messaging interventions to improve pediatric vaccination,[69,70,85] bring their expertise to the research team. Our new site PIs **Smith-Whitely,** and **Aygun** are experienced in conducting clinical research trials, community based outreach, patient/family support and assessing patient-oriented outcomes.[24,86-88]

Table 1. Study Team and Relevant Expertise Co-I = Co-investigator

	Role	Discipline	SCD	Self-mgmt	Adolesc Transition	Community Intervention	Technology in Health	Clinical Trials	Qual. Analysis
Green	PIs	Pediatric Sickle Cell	+	+		+	+	+	
Smaldone	PIs	Nursing, Pediatrics		+	+	+	+	+	+
Bruzzese	Co-I	Psychology		+	+	+		+	
Jia	Co-I	Biostatistics						+	
Findley	Co-I	Public health		+		+		+	+
Stockwell	Co-I	eHealth, texting					+	+	
Smith-Whitely	Site PI	Pediatric Sickle Cell	+			+		+	
Aygun	Site PI	Pediatric Sickle Cell	+					+	
Manwani	Site PI	Pediatric Sickle Cell	+			+		+	

Matos	Consultant	CHW training				+			
Stennett	Consultant	Community services				+			

b. HABIT feasibility trial: This study (R21NR013745) tested the feasibility and acceptability of the 6-month intervention to improve adherence to HU therapy in a sample of youth-parent dyads and estimated effect size[31]. The intervention was highly structured to assure fidelity while also tailored for individual youth-parent dyad needs. During months 1- 6, CHWs had monthly face-to-face interactions at the subject's home or other location where privacy was assured. CHWs also met dyads at one clinic visit. To support relationship building, additional contact between dyad members and CHWs was maintained, as needed, by phone or text message by dyad member preference. CHWs communicated HbF results to the dyad soon after each test, discussed challenges to reducing barriers to HU adherence, and progress made to achieve Personal Best HbF. The structured assessment for each CHW visit is found in Appendix 6.

Tailored interactive text message reminders were collaboratively developed with each dyad member to support linking a daily cue to form a HU adherence behavior. This was initiated in month 3 to allow time for establishing the relationship with CHWs. Subjects lacking a mobile phone or sufficient cell phone plan were provided a simple cell phone or were compensated to upgrade plans to accommodate texts. Text messages were programmed to appear as sent by the CHW. Texts sent and received were tracked by the MIR3 texting system (Appendix 7).

Of 74 youth screened at 2 study sites, 48 met all inclusion/exclusion criteria and 28 dyads (58% acceptance) participated in the study. Subject attrition was 10.7%. Reasons for dyad attrition were incarceration, illicit drug activity (1 youth each) and burdensome study procedures (1 parent). On average, youth were 14.3±2.6 years, 43% female and 50% Hispanic. The majority of parents were single and/or separated from a spouse, had a high school education or less, and were employed full or part time. Spanish language surveys were used by 42% of parents and 25% of youth subjects. The 2:1 enrollment scheme allowed for more feedback about the HABIT intervention.

Feasibility and acceptability. Monthly CHW visits were feasible, although more frequent visits were not. Text messages were delivered as planned, once the logistical barrier of a blocked phone number was addressed.

The majority of parents and youth reported that they found meeting time with the CHW convenient, found the study's educational materials helpful, and learned new information about SCD and HU. Intervention subjects reported that they felt the CHWs valued their opinion, were easy to talk to about their disease, and helped the dyad to improve their collaboration in managing SCD. Subjects did not find the text messaging burdensome. The majority of parents (81.3%) and youth (75.1%) reported that linking the text message to the time of an activity made it easier to remember to take HU. When asked what they liked about working with the CHWs, a dyad stated "it seemed like family talking to everyone" (parent) and "it gave me a better mindset" (youth). Of 18 dyads who participated in the intervention, 10 (56%) required referrals made by CHWs. The most frequent referrals were for mental health services (n=5) and housing (n=5). CHWs met with nearly all of the dyads at their home; visits lasted 60-90 minutes. CHW visits consisted of conversations with both dyad members present, and dyads reported making progress in working together as a team. CHWs felt that a relationship was established with the majority (68%) of parents at the first visit, with most youth (81%) by the second visit and with all by the third visit.

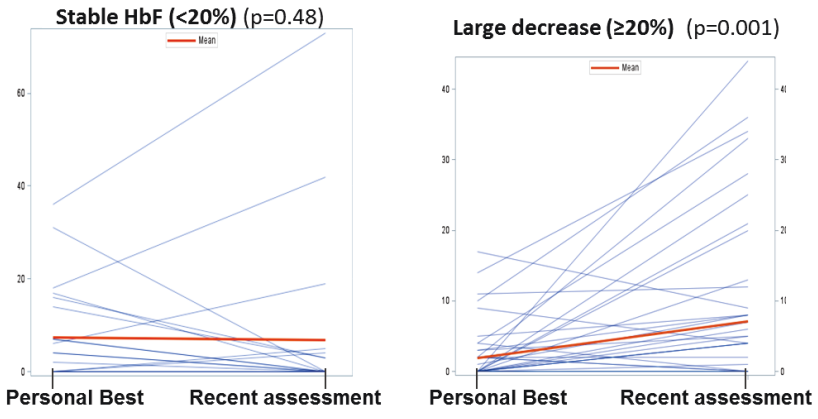
Primary outcome: improved HU adherence. At baseline, decrease of ≥20% from Personal Best HbF (Personal best) was higher in the control group compared to the intervention group (-42.6±21.3 vs -18.1±23.6). Controlling for study month the intervention group progressed to Personal best by 2.3% per month during months 0 to 4 (p=0.31). Some subjects in the invention group even exceeded their Personal Best goal, likely due to previously inadequate HU adherence. We used improvement toward Personal Best HbF as the basis for the power analysis of the proposed multi-site trial. Results were similar when we measured adherence by Proportion of Days covered by medication (PDC) using pharmacy refill data. The intervention group improved PDC from 64.6% (year pre-enrollment) to 79.4% at month 6, an increase of 14.8%. In contrast, the control group had a smaller change of 6.5% (79.4% pre-enrollment to 85.9% at month 6).

Secondary outcomes: QOL and dyad concordance regarding self-management responsibility. From 0-6 months, both generic and disease specific QOL improved for intervention youth (generic +6.3±12.6, p=0.01; disease specific 6.1±17.3, p=0.33) but not for controls (-2.4±9.1, p=0.57; -1.2±17.5, p=1.0). Controlling for month and group assignment, youth in the intervention group improved generic quality of life scores by 1.6 points/month during months 0 to 6 (p=0.02). From enrollment to 3 months, dyad self-management concordance improved for intervention dyads (+1.3±2.1, p=0.03) but not controls (0.2±1.6, p=0.80).

Value of booster session during the sustainability phase of proposed study. Parents (9 of 18) who participated in the intervention group during our HABIT feasibility trial were interviewed by telephone regarding their opinion of the value of an additional "booster" visit by the CHW. All felt that the extra CHW visit would be well accepted. The majority (89%) identified the 8 month visit as the best timing for the visit with the preferred location either at home (78%) or clinic (89%). All stated that weekly phone calls with CHWs would be accepted by parents but were not sure about weekly contact with youth.

c. Larger decline from Personal Best HbF is associated with higher urgent hospital use. To validate the concept of Personal best as a measure of HU adherence, we conducted a retrospective review of 75 youth ages 10-18 years with SCD prescribed HU at the two centers which participated in our HABIT feasibility trial.[15] HbF was examined pre-HU initiation, at Personal Best (HbF at maximum HU dose), and recent assessment. Decrease from Personal best HbF of ≥20% at recent assessment was considered a marker of suboptimal HU adherence. In contrast, a decrease of <20% was considered stable. In all, 70% of youth (n=53) met criterion for suboptimal adherence with average decrease from Personal Best HbF 40.1±17.5% significantly higher compared to 11.7±5.3% in the stable group, p<0.001). Those with greater decline from Personal Best HbF differed from those with more stable HbF in terms of longer time to achieve Personal Best (p=0.01), higher HU dose at Personal Best (p=0.02) and higher recent HU dose (p=0.03). Resource use was measured over two 1-year periods: at Personal Best HbF (6 months pre to post Personal Best) and at recent HbF assessment (6 months pre to post assessment). Comparing the periods for each group, urgent hospital visits and total hospital length of stay (LOS) (**Figure 1**) remained stable at recent assessment for youth with low decline from Personal Best (hospital use -0.05; p=0.52; -0.6; p=0.48). However, both increased for youth with larger decline from Personal Best (hospital use +1.2; p=0.01; LOS +5.2, p=0.001). A sensitivity analysis, conducted using cutoffs of 25% and 15%, tested the robustness of study findings and yielded similar results. These data support Aim 3 of the proposed study.

Figure 1. Length of total hospital stay (LOS) over two 1-year periods: at Personal Best HbF compared to a recent assessment. Increased LOS was found only for patients with large decrease from Personal best.



d. Translation and linguistic validation of PedsQL SCD module. The PedsQL Sickle Cell disease module[89] became available to researchers in 2013. Due to its alignment with HABIT outcomes, we added it into the battery of survey instruments used in our feasibility study. The instrument was only available in English. Assisted by a PhD student at Columbia's School of Nursing, the 8-12 year and 13-18 year versions of the instrument underwent a forward and backward translation process. Twenty subjects (10 parents, 10 youth with SCD, half in each age group) participated in the final phase of validation. Each subject first completed the translated questionnaire and then participated in a cognitive interview to determine whether questionnaire directions, questions and response choices were clear, relevant, appropriate, and easily understood. The translated survey was well received and required no changes. The long term goal is to make the instrument available to researchers to allow participation of Spanish speaking youth with SCD and their parents. A report of the process of translation and a summary of the cognitive interviews was submitted to MAPI Institute.

Proposed HABIT Intervention Study:

3. Theoretical Frameworks. The Self and Family Management Framework[90] guides the study design for Aims 1-3. Designed to better understand and improve self- and family self-management of chronic conditions, the framework addresses key youth and family risk and protective factors for youth and family. These factors include health status, individual and family factors, environmental context and developmental aspects. Recently updated, the revised framework[91] highlights processes such as activation of resources to promote self-management of chronic illness and differentiates proximal from distal outcomes. In this study we examine the efficacy and sustainability of a community intervention employing CHWs (process) on proximal (adherence behaviors and symptom management) and distal (quality of life, self-management responsibility concordance and health status) outcomes. Subjects ages 10-18 years are targeted for the HABIT intervention because transition of responsibility for self-management occurs *throughout this* time[59,92,93]. The PRECEDE portion of the PRECEDE-PROCEED Model of health program planning and evaluation[38] guides the qualitative interviews

and analysis of Aim 4. The model has been widely used in evaluation of health interventions such as physical activity[94] and obesity prevention.[95,96] In the proposed study, we use PRECEDE to gain better understanding of the effect of the HABIT intervention and its sustainability from the perspectives of the dyads who received the intervention and the CHWs who delivered it. These perspectives will provide context for interpretation of the quantitative findings and potential for broader dissemination of the HABIT intervention.

4. Setting. Parent youth dyads will be recruited from 4 pediatric Sickle Cell Centers (Columbia University Medical Center, NY, NY; Montefiore Hospital, Bronx, NY; Cohen Children's Medical Center at Northwell Health, Queens, NY; Children's Hospital of Philadelphia, Philadelphia, PA). Each provides comprehensive multi-disciplinary care to youth with SCD. Considerable diversity in patient population exists within and among sites, including African American, African, West Indian and Latino families, as well as geographic and urban/rural location diversity. PIs at all participating sites have strong histories of successful recruiting and retaining of pediatric SCD patients for randomized trials,[88,97-99] despite potential barriers to trial enrollment.[100-104] While the volume of patients at each center varies (see **Resources**), we are confident that each site has sufficient youth who will both meet eligibility criteria and be interested in study participation (see **Enrollment Feasibility**) and will be successful in hiring experienced CHWs to deliver the intervention (see **C6**). While Cohen-Northwell has not worked directly with CHWs, they are experienced in working with the Sickle Cell-Thalassemia Patient Network, New York City's most established SCD patient group. Each site has wireless Internet in their clinic to allow use of iPad technology for direct entry of survey data into the HABIT RedCap database. All study visits will take place in the SCD outpatient clinic setting.

5. Study Participants. To achieve **Aims 1-3**, a total of 104 youth-parent dyads meeting eligibility criteria (**Table 2**) will be recruited. Clinic rosters of youth ages 10-18 years and on HU therapy will be assessed for eligibility. Potentially eligible patients will be assessed for large decrease (≥20%) from Personal best HbF over the preceding 12 months. Those passing the initial screening will be telephoned for invitation to study participation. Of those interested, eligible dyads will be confirmed for full eligibility at their clinic visit. Those who meet all eligibility criteria will be offered enrollment until full enrollment is reached. Numbers and reasons for declining participation will be tracked at each site and cumulatively.

Table 2. Subject Eligibility and Exclusion Criteria

INCLUSION CRITERIA - YOUTH	EXCLUSION CRITERIA - YOUTH
1. Sickle type HbSS or HbS-B^0 thalassemia	1. Youth not prescribed HU
2. Age 10 through18 years (inclusive)	2. <3 HbF assessments over past 12 months
3. Currently prescribed HU ≥18 months (for identifying historical Personal best HbF)	3. Transfusion within 3 months preceding enrollment
4. Current HU dose is within 5% of dose at Personal Best HbF. For youth whose dose at Personal Best was ≥30mg/kg and whose current dose does not meet the 5% entry criterion, the dose of HU may be increased based on youth's current body weight not to exceed 30mg/kg. If subject meets all other entry criterion, subject may be recruited 3 months after dose adjustment	4. Final screen HbF (visit 0) of ≤15% decrease below Personal best HbF
5. Pre-enrollment HbF ≥15% below historical Personal best, based on mean of ≥2 HbF assessments over preceding 12 months	5. Sexually active female ≥10 years and not using reliable contraception (due to HU teratogenic risk)
6. Youth able to speak/read English or Spanish	6. Pregnancy
	7. Cognitive impairment (>2 levels below expected grade)
	8. Youth not residing with parent/legal guardian
	9. Sibling of a youth enrolled in this study
INCLUSION CRITERIA - PARENT	
1. Parent/guardian speaks/reads English or Spanish	
2. Parent/ legal guardian willing to participate	**EXCLUSION CRITERIA – PARENT**
3. Family expects to reside in community for ≥ 1.5 years	1. Parent/legal guardian does not reside with youth

For **Aim 4**, we will recruit two independent purposive samples of approximately 10 youth-parent dyads randomized to the HABIT intervention at each of 2 time points during their study experience: 6 months (perceived intervention impact) and 12 months (sustainability). The sample will represent dyads who make good progress to Personal Best HbF as well as those who continue to struggle with HU adherence.

6. Study Implementation Procedures

Randomization. A 1:1 randomization plan will be generated using computerized random number generator. A randomization plan will be generated for each site to achieve balanced randomization and will be maintained centrally at Columbia University Medical Center. Assignments to group will be placed in sequentially numbered

sealed envelopes stratified by site. Following subject consent and final screening, the site coordinator will contact Columbia PI for dyad assignment and study ID number.

Recruitment and retention

Subject enrollment. Prior to study enrollment, parent/legal guardian consent and youth assent will be obtained by site coordinators for: study participation, release of pharmacy refill information for the year prior to study entry and for the duration of study participation, and (intervention arm only) for communication of HbF results and urgent clinical events to the CHW by study staff. A final screening will ensure that current HbF is consistent with levels over the past year. This screening will require the month 0 HbF level to be ≥15% below Personal best HbF (exclusion criterion 4). Randomization will await determination of this final eligibility criterion.

Enrollment feasibility. Full enrollment of 104 dyads (52 per study group) is expected based on excess number of eligible subjects (**Table 3**) and our HABIT enrollment experience during our feasibility trial. Three sites (CHOP, Cohen-Northwell and Montefiore) have capacity to enroll additional subjects in case of insufficient enrollment elsewhere. Despite compelling evidence of the value of HU therapy for youth with SCD, research has not translated into universal uptake.[7,19] Therefore trials like HABIT require multiple sites. **Table 3** provides detail regarding enrollment expectations from each site using data from our 2-site retrospective analysis[15] to estimate the proportion of subjects who will meet the criterion of ±20% greater decrease from Personal best (i.e., 70%), and data from our feasibility trial to estimate the proportion of eligible children expected to consent (i.e., 58% of eligible subjects). With these sites we will achieve a sample size of 104 dyads, sufficiently powered to achieve the aims, while allowing for 20% subject attrition and/or receipt of blood transfusions (that alter HbF).[105] Bi-monthly study visits is within the range of usual care frequency for patients on HU at each site.

Table 3. Estimation of target recruitment from each study site

Site	# 10-18 yrs on HU	# ≥20% below Personal best	# Estimated to consent	**Target enrollment**	CHW or related experience
Columbia	48	33	19	**16**	HABIT study
Montefiore	69	48	28	**24**	HABIT study
Cohen-Northwell	90	63	36	**24**	No
CHOP	200	140	81	**40**	SCDAA
TOTAL	**461**	**322**	**186**	**104**	

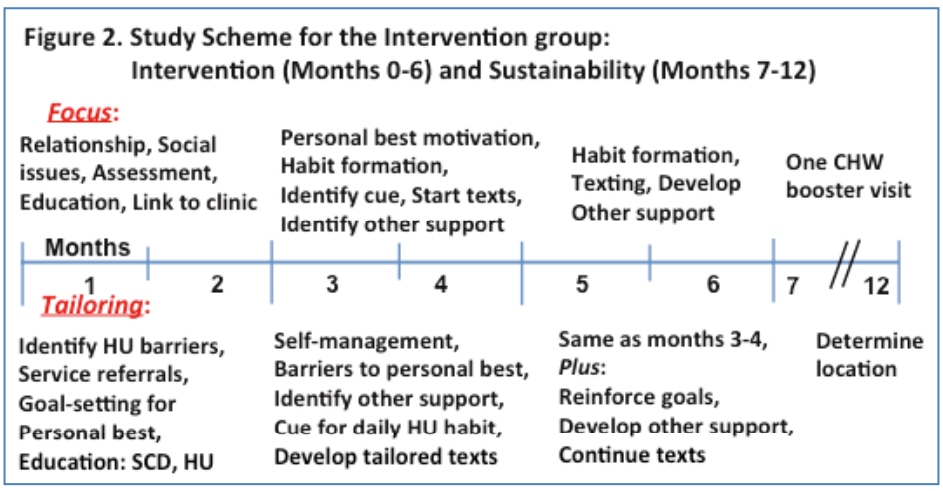
CHOP- Children's Hospital of Philadelphia; SCDAA –Sickle Cell Disease Association of America through their federally funded CHW program

Retention We expect high dyad retention based on low attrition (10.7%) during our HABIT feasibility trial; patients' long-term care at each SCD center; excellent enrollment and retention in previous SCD clinical trials under the PIs at each site; coordination of study visits with regular appointments; acceptability of text messaging for health interventions; and subject incentives weighted to study completion for extra time completing questionnaires (see Human Subjects). *Additionally, our planned 20% over-enrollment provides a cushion for subject attrition.*

Study Groups Youth-parent dyads will be randomized to the HABIT intervention or the control group. They will be blinded to specific study hypotheses, even though they cannot be blinded to the assigned group. Both groups will have bi-monthly clinic visits over the 12 month study. In addition, intervention subjects will have visits with the CHWs as detailed below.

Data regarding laboratory assessment, hydroxyurea dosing and urgent hospital use will be collected at each visit by the study coordinator or his/her designee.

Control Group. Dyads randomized to the control group will continue usual bi-monthly clinic-based care, including monitoring and review of HbF levels, and similar SCD team staff. They will receive the same educational materials (Appendix 5), complete the same questionnaires (Appendices 3, 4) and laboratory assessments as the Intervention group. They will



not receive CHW support or text messages.

Intervention group. The feasibility trial is now replicated in the proposed intervention trial (**Figure 2**) with the following additions: a) Dyad coaching on developing additional social support to enhance sustainability; b) More study sites (5 versus 2) and subjects (28 versus 104 dyads); and c) 6-month sustainability phase. CHW training and supervision are described below. The structured assessment for each CHW visit is found in Appendix 6.

MONTHS 1-2: Month 1: One CHW visit at the home or other private location will initiate relationships between the CHW and youth-parent, individually and as a dyad to assess social, educational and self-management needs and identify barriers to HU adherence. CHWs will help dyads prioritize adherence barriers, address knowledge gaps about HU benefits/risks, and help dyads establish a shared plan for attaining HU adherence goals. Referrals for social services or other needs such as job training will be made to either the site's social services, community-based organization and/or other social service agencies in the community. Results of each bimonthly HbF testing months 0 through 8 and progress to personal best will be reviewed with the dyad by the CHW.

Month 2: CHW and dyad will jointly attend a SCD clinic visit to strengthen linkage with the SCD clinical service, and aid the dyad in reviewing plans to reduce adherence barriers. In addition, CHWs will meet with the dyad at home to focus on addressing adherence barriers, HU education and self-management strategies using a problem-solving approach. Additional service referrals will be made, as needed. Goals for youth self-management responsibility will be mutually agreed upon by the dyad, based on his/her age and capabilities, and regularly reviewed by the CHW.

MONTHS 3-4: CHWs will continue to support dyads on their roles and steps toward coordinated self-management, facilitate problem-solving to address barriers to a daily HU habit, and identify additional sources of personalized support for each dyad member (e.g. a relative or neighbor). Interim goals and progress toward goal achievement will be reviewed at each visit. Self-management issues will be addressed, depending on youth's age and developmental stage.

Month 3: The established CHW relationship will facilitate the CHW in coaching each dyad member to develop a text message reminder about taking HU: identify a daily cue-based habit to link to HU use, personalize text language, time of day and options of responses. Texts developed by dyads in the feasibility trial will serve as examples to help dyads develop a text message tailored to language, daily habit on which the cue is based and time of day preferences. CHW will clarify that messages are not their direct communication, but that they will receive timely information about texts from study staff. Contact with CHWs, if desired, can be made directly with CHWs via cell phone or text message.

Month 4: Begin daily text message reminders to parents and youth. Automated personalized text messages, delivered through MIR3 Notification solution, are intended to augment habit-forming behavior and extend on-going support for a cue-based HU habit. The MIR3 system was used successfully during our HABIT feasibility trial and has been useful for Columbia faculty to automate communication with community-based research subjects[69,70,106,107].

Text messages will link HU reminders to the cue determined by each CHW-dyad, and will encourage a response such as "1" (taken) or "2" (not taken) or "3" (will take later), along with an option for sending free text, such as how they are feeling, problems with the medication, etc. Study staff will review text responses 2 times weekly and share them with the CHWs.

MONTHS 5-6: Continued CHW focus on self-management, adherence and coaching to personal best HbF. Monthly CHW visits will continue. Using dyad text message response data from MIR3, weekly phone contact will be initiated in month 5 and continued through month 6 to provide positive reinforcement of HU adherence or to problem solve regarding why adherence has been a problem. To avoid habituation to text messages, the frequency of text messages will be negotiated based on preference of each dyad member at the end of month 5.

MONTHS 7-12: During the sustainability phase one CHW visit during month 9 will be scheduled to "boost"[108] the effect of the intervention. This visit will be scheduled at the home or clinic, based on dyad preference. CHW focus will be limited to providing support by addressing questions or concerns that the dyad may have about issues related to adherence. During the sustainability phase, subjects will continue usual bi-monthly clinic visits, HbF and other laboratory assessment, and complete study questionnaires. We will track all dyad contact with the CHW during the sustainability phase.

Due to the COVID-19 pandemic and its implications for mental health distress, maladaptive behaviors (e.g. drinking, domestic violence), and food insecurity particularly in vulnerable populations, we will survey former and current parents and youth HABIT study participants using survey questions from the COVID-19 and mental health measurement working group at Johns Hopkins Bloomberg School of Public Health. All items are taken from valid survey instruments such as the CES-D (depression), GAD-7 (anxiety). We added 2 additional

items regarding food insecurity from the American Academy of Pediatrics recommended Hunger Vital Sign. The parent survey contains 18 items and the youth survey contains 15 items (an English and Spanish version of the parent and youth surveys are attached). Both surveys were translated to Spanish by our study team.

We propose to distribute the survey by either email or cell phone message that will provide a unique link to a REDCap survey. Using a script, the research coordinator at each site will contact both former and current study dyads of the HABIT Efficacy trial to describe the survey, participation is voluntary and that if a question makes them uncomfortable, they do not need to answer it. Current HABIT dyads will be contacted via telephone using a script; former HABIT dyads will be reconsented for participation by telephone using an information sheet. Participants will respond to the survey using their language of choice (English or Spanish). We propose to distribute the survey using the same platform, REDCap, as all other surveys administered as part of the HABIT study as soon as IRB approvals are obtained at each of the 4 study sites and again 2-4 months later to see the effect over time. Because of the sensitive nature of survey questions, research coordinator at each study site will monitor all survey responses as soon as possible and refer any "red flag" issues (e.g. domestic violence) to the social worker at the respective clinical site so that the patient may be referred for mental health services.

Qualitative Interviews with Dyad members. A purposive sample of parent-youth dyads from each clinical site will participate in individual interviews at 2 time points: after completing the 6-month study visit and at study completion (12 months). Interviews will be conducted by the coordinator at each site either face to face at the clinic or by telephone using uniform interview guides informed by the predisposing, enabling, and reinforcing constructs in Evaluate (PRECEDE) portion of the PRECEDE-PROCEED Model of health program planning and evaluation.[38] Interviews for parents and youth will be conducted separately and each is expected to last approximately 20-30 minutes. Subjects will be compensated $20 for their time. The interview guide for the 6 month interview will be directed to intervention impact. Interview guide questions for the 12 month interview will be geared toward the sustainability of the habit from the perspective of youth and parents. All interviews will be conducted in English, audiotaped, and transcribed for analysis. Based on clinic demographics at each site, most subjects will be fluent in English.

Sample questions will include:

- Tell me about the habit that you (your child) developed to make it easier to remember to take hydroxyurea every day? (reinforcing factor)
- What are some of the ways that you think your (your child's) health will improve through maintaining a hydroxyurea habit? (reinforcing factor)
- What do you perceive as barriers to maintaining a hydroxyurea habit? (predisposing factor); What are your ideas for how to maintain the habit that you (your child) have established? (enabling factor).

Focus groups with Community Health Workers: We will conduct 2 focus groups with all of the study CHWs at two time points: study mid-point (18 months) and end-point (36 months). Both focus groups will be conducted in English by webinar. CHWs will have become familiar with virtual meetings during monthly group supervision meetings as described below. Focus groups will be conducted in English, last approximately 60 minutes and will be led by Mr. **Matos**. The focus group interview guide questions will focus on the CHWs experiences with the dyads regarding the predisposing, enabling and reinforcing factors and their relationship to intervention impact and sustainability. Focus groups will be audiotaped and transcribed for analysis.

Intervention Training and Supervision

Training and Supervision. A study orientation meeting of all site PIs and coordinators will be held at Columbia early in year 1 prior to subject enrollment. At that meeting, **Green** and **Smaldone** will present the study's main goals and strategies, including lessons learned from our feasibility trial, review the study protocol and address issues at any of the sites.

CHW Training. Two CHWs with prior CHW experience will be hired for the HABIT study at each site. The Co-PIs and site PIs will discuss leading candidates and will review the vetting process to ensure quality of CHWs and their prior training. Following hiring, CHWs from all sites will participate in a 4-day training session at Columbia led by **Matos[66]** (see LOS). Training will use the structured training curriculum from the HABIT feasibility study.[31] The first 2 days will serve as a "refresher" regarding CHW core concepts such as role and responsibility, engagement with families, and role boundaries. Days 3 and 4 of training will provide project-specific training, to include goals, rationale and approach by the HABIT study, schedule and goal of each CHW visit, information about SCD and HU (**Smaldone** and **Green** with **Matos**). Project specific skills, e.g., establishing relationships with dyads, helping dyads to work together to address barriers to HU and identify established daily patterns on which to build a HU habit, communication with the medical team will be

addressed through discussion and role playing. **Stennett** will discuss the importance of community support and resources for families faced with chronic illness (see LOS). **Bruzzese** will work with the group regarding motivational interviewing skills and self-management expectations for youth at varying age levels. The added benefit of group training is for the CHWs form a group allied for sharing experiences during supervision sessions over the course of the project. For any "red flag" issues (truancy, depression, drug use, potential violence), CHWs will be directed to immediately inform their site coordinator for referral to the clinic's social services.

Supervision. CHWs will have weekly ongoing supervision sessions to ensure high quality support to families, study fidelity, CHW progress with dyads and challenges to adherence, and detection of any barriers to progress towards an HU habit. Supervision schedule will include: a) bi-weekly site meetings with their coordinator to problem-solve for logistics of visits and the relationships with dyads, discuss on-going barriers to progress and reinforce the communication of HbF levels to dyads. b) Monthly site meetings jointly with their PI and coordinator will review additional study information and other social or medical issues; c) **Matos** (with **Smaldone** and **Green**) will lead monthly CHW group supervision sessions delivered via webinar for all CHWs to reinforce training components and ongoing case supervision; and d) At quarterly sessions, additional input to the CHWs on community-based intervention will be provided by **Stennett**. CHWs will share their experiences in delivering the intervention and will learn from the collective experiences.

If youth-parent dyads display unresolved conflict regarding self-management or other youth-parent relationship issues, **Matos** and **Bruzzese** will guide the approach of the staff and CHWs. Each site PI will meet with their respective CHWs a minimum of once per month with site coordinators the remaining weeks for CHW caseload updates, communicate with CHWs regarding subject HbF progress, information that may trigger clinical or social worker contact (e.g. turmoil in the home, missed school due to recurring disease symptoms or truancy), and to review all CHW visit forms and automated text messaging reports.

Treatment Fidelity will be assured through a structured intervention protocol (**Figure 2** and Appendix 6), ongoing CHW supervision and monthly communication with site PIs and study coordinators. The HABIT operations manual contains: CHW encounter forms to structure and document the content of each scheduled encounter, monthly schedules and objectives to guide family discussion, key messages to promote HU adherence and youth-parent self-management partnership, exemplars of cues for text messaging reminders, and information for families on SCD and HU to be reviewed with dyads. CHW delivery of intervention and completed visit forms will be reviewed weekly during supervision. Feedback and guidance will be provided to CHWs for each dyad. Monthly conference calls will be held each for coordinators and for site PIs to oversee enrollment schedules, scheduling and logistics of home visits, obtaining pharmacy refill data, and study procedures and to problem-solving, as needed. To assure validity of HbF values, the subject's transfusion history will be reviewed during each coordinator call. Levels will be discarded if the subject had been transfused within the preceding 90 days, per standard HU protocols.[105]

Variables and Operational Definitions: Table 4 overviews the variables including HbF levels and standard blood work for clinical monitoring, their relationship within the revised Self and Family Management

Table 4. Study Measurement and Tools

Concept/Variable	Operational Definition/ *Source document*	P	Y	Month
Facilitators and Barriers				
Health Status				
Personal best HbF	Highest historical HbF; *Medical record*		•	0
Pre study HbF	Mean Preceding 12 month average of ≥3 HbF±standard deviation; *Medical record*		•	0
Decrease from personal best	% difference between personal best and Pre HbF; *Medical record*		•	0
Past year's urgent medical service use	Hospitalization, ER visits, total hospital length of stay and transfusions for past 12 months: *Medical record*		•	0
Past year's HU adherence	Pharmacy refill (proportion of days covered) for past 12 months		•	0
Health and HU monitoring				
HbF			•	0, 2, 4, 6, 9, 12
CBC with reticulocyte count	Hb, MCV, platelet and absolute retic count, WBC, ANC		•	0, 2, 4, 6, 9, 12
Liver and renal function tests	Total and indirect bilirubin, AST, ALT, creatinine, BUN		•	0, 6, 12
Personal/Lifestyle				
Age; Gender	Years; Male/female; *Demographic survey*	•	•	0
Race/ethnicity	African American; Hispanic; *Demographic survey*	•	•	0
Grade level (youth)	1 through 12; *Demographic survey*		•	0
Parental education	<high school (HS); HS graduate; college; etc. *Demographic survey*	•		0
Barriers to HU use	25-125; higher score = more barriers; *Medication Barriers scale*	•	•	0, 6, 12

Proximal Outcomes				
Behaviors				
Self-management responsibility	1-50; higher score = greater responsibility; *SCD Family Responsibility*	•	•	0, 2, 4, 6, 9, , 12
Personal best HbF progress	HbF change; *Medical record*		•	0, 2, 4, 6, 9, 12
Adherence	Progress to Personal best HbF (biomarker)		•	0, 2, 4, 6, 9, 12
	Pharmacy refill (proportion of days covered) *Pharmacy records*		•	0, 2, 4, 6, 9, 12
Symptoms	Pain interference	•	•	0, 2, 4, 6, 9, 12
	Pain intensity	•	•	0, 2, 4, 6, 9, 12
	Fatigue	•	•	0, 2, 4, 6, 9, 12
	Depressive symptoms		•	0. 6, 12
	Emotional distress - Depression	•		0. 6, 12
Distal Outcomes				
Family				
Parent productivity				
Work related	1-10; higher score = greater lost productivity; *RUQ*	•		0, 2, 4, 6, 9, 12
Non work related	1-10; higher score = greater lost productivity; *RUQ*	•		0, 2, 4, 6, 9, 12
Individual/Family Outcomes				
Quality of life	Generic 0-100; higher score = greater quality of life; *PedsQL generic core scale*	•	•	0, 4, 9, 12
	Disease specific 0-100; higher score = greater quality of life; *PedsQL Sickle Cell Disease Module*	•	•	0, 4, 9, 12
Self-management concordance	Self-management areas with consensus of responsibility; 0-10 with higher score=better communication; SCD Family Responsibility	•	•	0, 2, 4, 6, 9, 12
School attendance	Less missed school (days/past 2 months); *RUQ*	•	•	0, 2, 4, 6, 9, 12
Health Care Use				
Emergency room	Number ER visits in past 2 months; *RUQ; Medical record*	•		0, 2, 4, 6, 9, 12
Hospitalization	Hospitalizations in past 2 months; *RUQ; Medical record*	•		0, 2, 4, 6, 9, 12
Hospital length of stay (LOS)	Total LOS in past 2 months; *RUQ; Medical record*			
Urgent visits	Urgent outpatient visits/past 2 months ; *RUQ; Medical*	•		0, 2, 4, 6, 9, 12
Subject satisfaction				
Participant feedback	Evaluation survey	•	•	12

Abbreviations: HbF = Hemoglobin F; HU = Hydroxyurea; P = Parent; Y = Youth; 0 = enrollment; 2 = 2 months; 4 = 4 months; 6 = 6 months; 9 = 9 months; 12 = 12 months; PedsQL = Pediatric Quality of Life; RUQ = Resource Use Questionnaire;

framework,[91] operational definitions, data sources and timing of data collection. All self-report instruments are found in Appendices 3 and 4. All measures piloted in the R21-funded feasibility study were valuable and will be used again. The exception is the Morisky scale of self-report medication adherence. This scale was found to be inconsistent with more objective biomarker and pharmacy refill. To address this, we have added 3 pediatric Patient Reported Outcomes Measurement Information System (PROMIS) measures (pain interference[109], pain intensity and fatigue) to capture self-report of fatigue[110] and impact of pain from a youth and parent perspective[111]. PROMIS measures have been validated across multiple disease types for children[112], have been validated in youth with SCD with scores responsive to hospitalization for sickle pain and subsequent recovery.[87] All survey data will be added directly into RedCap by the study participants with the exception of the demographic survey. Since that survey contains name, address and other identifying information, parent subjects will complete this survey via paper. The coordinator at each site will transcribe de-identified responses into RedCap. The paper survey will be stored in a locked cabinet in the PIs office together with the consent and assent.

Demographic questionnaire: 29 item questionnaire obtains youth-parent demographic information, medication profile and12 month prior resource use.

Medication Barriers scales: 25 (parent) and 26 item (youth) 5 point Likert scales with established content, construct, and internal consistency[17]. Notably, the scale has established criterion validity with medication adherence[17]. Parent and adolescent scales were modified by adding 9 HU specific items[19].

Sickle cell Family Responsibility Scale: 10 items; adapted from the Diabetes Family Responsibility Questionnaire (DFRQ)[63]; measures youth-parent perceptions of who takes responsibility for self-management tasks, division of responsibility[65,113], dyadic agreement[63,114]; established internal consistency and concurrent validity (English, Spanish)[115]. DFRQ was adapted for use in asthma[116], inflammatory bowel disease[117], HIV[59].

Resource Use Questionnaire: 11 items; adapted for SCD from the Resource Utilization Questionnaire for Type 1 diabetes (RUQ-T1DM)[118] with established content and criterion validity; uses a societal perspective.

PedsQL Generic Core Scale: 23 item 5 point Likert scale; 2 versions for youth (ages 8-12; 13-18 years) with parallel parent proxy version. High internal consistency for instrument (α=0.91) and subscales (α=0.81-0.89)[119] and has been validated in youth with SCD[120-123]; validated in Spanish.

PedsQL Sickle Cell Disease Module: 43 item 5 point Likert scale; 2 versions for youth (ages 8-12; 13-18 years) with parallel parent proxy version. High internal consistency for instrument (α=0.95) and subscales (α=0.69-90)[89]; validated in Spanish (see **Preliminary Studies C2**).

Pain Interference – Short Form: 8 item 5 point Likert scale; developed as part of the *PROMIS* initiative; *T*-score scale with mean = 50 and standard deviation = 10[109]; youth and parent proxy versions; available in Spanish.

Pain Intensity – 1 item visual analogue scale; scores range from 1-10; developed as part of the *PROMIS* initiative; examines perception of intensity of pain for the past 7 days; youth and parent proxy versions; available in Spanish.

Fatigue – Short Form: 10 item 5 point Likert scale; developed as part of the PROMIS initiative; *T*-score scale with mean = 50 and standard deviation = 10[110]; youth and parent proxy versions; available in Spanish.

Depressive symptoms (youth): 8 item 5 point Likert scale; developed as part of the PROMIS initiative; *T*-score scale with mean = 50 and standard deviation = 10, available in Spanish. Youth with depressive symptom T scores greater than 2 standard deviations above the mean will be referred for mental health counseling.

Emotional distress – depression: 4 item 5 point Likert scale; developed as part of the PROMIS initiative; *T*-score scale with mean = 50 and standard deviation = 10, available in Spanish. Parents with emotional distress T scores greater than 2 standard deviations above the mean will be referred for mental health conseling.

Evaluation survey: 26 item (for intervention group; 8 items for control group) investigator developed survey; 5 point Likert scale to assess impact on self-management, usefulness of materials, quality of CHW interaction, text messaging, cue-based medication reminders, outcomes, projected long-term study impact on disease self-management; 4 open ended items.

COVID-19 survey: 18 item (parent) and 15 item (youth) survey to measure mental health, maladaptive behaviors and food insecurity experienced by participant during the COVID-19 pandemic. All items taken from previously validated surveys.

D Analytic Plan

Power and sample size analysis: We estimated the statistical power to compare score changes from the baseline to the follow-up times (for testing both improvement and sustainability) between the intervention and the control groups using the mixed model described below. All power analyses were based on the mixed model with 2-sided test and $\alpha < 0.05$. We assume that the outcome measure had a high correlation coefficient of 0.7 at different times and the clustering with each site was low with an intra-cluster coefficient (ICC) of 0.1. We also assume that this study will have 4 sites and each site has 16 to 40 subjects (total 104 subjects at the start of study). In each site, subjects will be 1 to 1 randomly assigned to the intervention and the control group with 20% attrition rate by the 12th month. For the DID analysis, we will have 83.2% power to detect a medium effect size of 0.6. We also estimated the statistical power to compare the trend of score changes from the baseline to the end of follow-up between the intervention and the control groups for outcomes that will be measured every 2 months from month 0 to month 12 visit. We will have 85.6% power to detect a small effect size of 0.25.

Data analytic plan by Study Aim

Aims 1-3:

Aim 1: Improve daily hydroxyurea (HU) adherence measured by two *primary outcomes*: biomarker (approach or exceed a historical Personal best HbF) and pharmacy refill (proportion of days covered). *Hypothesis 1: Compared to the control group, dyads randomized to the intervention will improve medication adherence at 6 months, with sustained improvement at 12 months.*

Aim 2: Improve quality of life and self-management responsibility measured by three *secondary outcomes*: generic and disease-specific QOL and parent/youth concordance regarding delegation of self-management responsibility. *Hypothesis 2: Compared to the control group, dyads randomized to the intervention will report improved quality of life and self-management responsibility concordance at 6 months, with sustained improvement at 12 months.*

Aim 3: Improve health status measured by two *secondary outcomes:* acute hospital use (12 month hospital length of stay, admissions and emergency room visits) and self-reported disease symptoms (fatigue, pain interference and intensity). *Hypothesis 3.1: Compared to the control group, dyads randomized to the intervention group will demonstrate decreased acute hospital use at 6 months, with sustained improvement at 12 months. Hypothesis 3.2: Compared to the control group, dyads randomized to the intervention group will report decreased disease symptoms at 6 months, with sustained improvement at 12 months.*

COVID-19 survey - Data will be analyzed using descriptive statistics. "Red flag" responses (e.g. domestic violence) will be referred to clinic social worker for management. Parent and youth responses will be compared.

Data analysis will be led by **Jia**. Analyses are based on intention to treat. All randomized subjects will be included in the analyses regardless of whether they adhered to the intervention protocol. Descriptive statistics will be used to profile outcome measures at each data collection point for the intervention and control groups. Distributions of all outcome variables will be made at the observational level instead of at the subject level. Medication adherence and quality of life assessments will be made at the 0, 6, and 12 month visit. Some outcomes (HbF, parent/youth concordance) will be assessed every 2 months from 0 to 12 month visit. We will compare hospital length of stay, emergency room visits, and hospitalizations during 3 time periods: 0-6 to the year prior, months 0-6, and months 7-12. The main analysis will be difference-in-difference (DID), comparison of changes in outcomes at 6 month from 0 month (improvement) and 12 month from 0 month (sustainability) between the intervention and the control group. We will use linear mixed model or generalized linear mixed model. Linear mixed models are used for most continuous outcomes (e.g. QOL score) and generalized linear mixed models are for categorical outcomes (e.g. whether or not a subject had an urgent outpatient visit with logit link function) or for outcomes with skewed distribution (e.g. length of stay with log link function). We will incorporate a site-specific random effect in the mixed models for controlling for clustering within each site. The mixed models are also used for outcomes that will be assessed every 2 months from 0 to 12 month visit to exam the difference in trend during the follow-up period. The mixed model is used to address the hierarchical data structure of multiple observations for each subject and multiple subjects in each family (i.e. youth-parent dyads) as well as for repeated measured data.

Missing data: Attrition or other missing data (survey or invalid HbF result due to recent transfusion) will be addressed by a plan to: (1) Apply a mixed model to include all subjects in the analysis; (2) Conduct a sensitivity analysis to estimate magnitude and direction of bias by imputing missing outcomes; and (3) Ask dyads who do not complete follow-up interviews about their reasons why and include such information in the model to correct the bias.

Aim 4: Qualitatively explore impact and sustainability of the intervention on developing a daily medication (HU) habit from the perspectives of the community health workers and youth-parent-dyads using focus group and individual interviews (*exploratory aim*).

Data analysis will be conducted by **Smaldone**[124-126] and **Findley**[37] both experienced in qualitative analysis. Each focus group and individual interview will be transcribed. The research team will ensure the credibility, confirmability, dependability and transferability of the qualitative data. To assure credibility we will conduct peer debriefing and triangulate findings across data sources (focus group, individual interview, survey data), use member checking, sharing of data interpretation with participants for accuracy. Triangulation of findings will enhance confirmability of findings. The research team will maintain an audit trail and maintain extensive field notes to facilitate transferability of findings. All transcripts and field notes will be analyzed using NVivo™ (QSR International, Victoria, Australia) software. Data will be sorted into categories by PRECEDE constructs: predisposing, enabling, and reinforcing to allow better understanding of the impact and sustainability potential of the HABIT intervention.

E. Scientific Rigor: Our interdisciplinary team has an outstanding track record of rigorous study design and implementation, including our prior feasibility trial. Several measures will be employed to generate valid and generalizable knowledge and to minimize bias. These include: 1) To avoid bias in study patient demographics, including sex, ethnicity and any additional medical conditions, offering study enrollment to sequential eligible patients at each site until the site sample is filled; 2) A 5-site study across differing study settings in three states assures greater diversity in subjects and circumstance and greater generalizability; 3) A careful central process for randomization of subjects within each site to help prevent bias in study arm assignment; 4) Use of objective data for assessing HU adherence, including determination of HbF when not affected by transfusion[33] and obtaining pre-study and 12 month study data on medication refills (**Aim 1**); 5) Self-reporting outcomes to augment staff report on acute hospital use, in case patients receive urgent care at other institutions during the 12-month study (**Aim 4)**.[76]

F. Study limitations and alternative strategies

Sufficient enrollment: Planned 20% over-enrollment and minimizing subject attrition will support full enrollment. In addition, three participating sites (Montefiore, CHOP and Cohen-Northwell) have excess capacity in case other sites cannot fully enroll.

Investigator and subject blinding: As CHWs have a major role in the intervention, blinding is not possible. Our procedure for allocation concealment minimizes potential bias regarding group assignment. Further, blinding will be maintained during the data analysis process.

Sample size insufficient to compare the effect of individual intervention components, CHWs and text messaging: Capture of dyad replies to text messages recorded by MIR3, as well as post-intervention focus groups, will provide qualitative information about any additive impact from text messaging.

Peer support for parents and youth: is not provided. Attending a peer support group would be difficult for this multi-ethnic sample, on top of busy families and working parents. Coaching youth and parent to develop identify individual support is intended to establish longer-term social support.

If intervention impact is not sustainable at 12 months: extended intensity of CHW support would require further testing. Post-intervention focus groups would identify subject recommendations for future trial design.

G. Study Timeline

Study Timeline*	**Y1** Q1	Q2	Q3	Q4	**Y2** Q1	Q2	Q3	Q4	**Y3** Q1	Q2	Q3	Q4	**Y4** Q1	Q2	Q3	Q4
IRB review and Approval	•	•														
Hiring and training Coordinators	•	•														
Hiring and training CHWs		•	•													
Subject Enrollment			•	•	•	•	•	•	•	•	•	•				
0-6 month Intervention				•	•	•	•	•	•	•	•	•				
7-12 month Sustainability						•	•	•	•	•	•	•	•	•		
Qualitative interviews						•	•	•	•	•	•	•	•	•		
Data Analysis															•	•
Dissemination															•	•

H. Dissemination Plan: will include multiple peer-reviewed publications and presentations at national meetings of experts represented by our multi-disciplinary team. We will continue to mutually co-inform the Sickle Cell Disease Association of America (SCDAA) regarding our respective multi-state CHW programs (LOS **Banks**) for program dissemination and shared efforts for enhancement and sustainability. Other partnerships will be developed to facilitate the adaptation of HABIT to other chronic pediatric conditions in underserved communities.

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