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Study protocol for a randomized controlled trial to assess the feasibility of an open label intervention to improve hydroxyurea adherence in youth with sickle cell disease

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Abstract

Background—Community health workers (CHW) are increasingly recognized as a strategy to improve health outcomes for the underserved with chronic diseases but has not been formally explored in adolescents with sickle cell disease (SCD). SCD primarily affects African American, Hispanic and other traditionally underserved populations. Hydroxyurea (HU), an oral, once-daily medication, is the only approved therapeutic drug for sickle cell disease and markedly reduces symptoms, morbidity and mortality and improves quality of life largely by increasing hemoglobin F blood levels. This paper presents the rationale, study design and protocol for an open label randomized controlled trial to improve parent-youth partnerships in self-management and medication adherence to HU in adolescents with SCD.

Methods/Design—A CHW intervention augmented by text messaging was designed for adolescents with SCD ages 10–18 years and their parents to improve daily HU adherence. Thirty adolescent parent dyads will be randomized with 2:1 intervention group allocation. Intervention

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Authors' contributions

AS, NSG, HJ, SB, SF, AM, SR and DM were involved in the conception and in the design of the study.

AS, NSG, AM, SM and SF were involved in designing the training and supervision of the community health workers.

AS and NSG drafted the manuscript with all authors contributing to the manuscript.

All authors approved the final manuscript.

dyads will establish a relationship with a culturally aligned CHW to identify barriers to HU use, identify cues to build a habit, and develop a dyad partnership to improve daily HU adherence and achieve their individualized “personal best” hemoglobin F target. Intervention feasibility, acceptability and efficacy will be assessed via a 2-site trial. Outcomes of interest are HU adherence, dyad self-management communication, quality of life, and resource use.

Discussion—Despite known benefits, poor HU adherence is common. If feasible and acceptable, the proposed intervention may improve health of underserved adolescents with SCD by enhancing long-term HU adherence.

Keywords

sickle cell anemia; hydroxyurea; youth; randomized trial; community health worker; protocol

Background

Sickle cell disease (SCD), an inherited blood disorder, affects 80–90,000 African American, Hispanic and other traditionally under-served populations in the United States [1, 2]. The disease is characterized by chronic anemia, painful crises, organ damage, reduced quality of life (QOL) and high health care utilization [3–5]. Hydroxyurea (HU), an oral, once-daily medication, is the sole approved drug for SCD disease. Recommendation for HU use has become standard practice for most youth with SCD [6, 7] as it markedly reduces symptoms, morbidity, mortality [3, 8–12] and health care use [12, 13] and improves quality of life [14].

Fetal hemoglobin (HbF) helps to ameliorate disease by inhibiting polymerization of sickle hemoglobin [13, 15]. Daily HU use induces a stable, dose-dependent increase in HbF in children and adolescents [13, 15–19]. HbF, a standard laboratory assay, is an excellent biomarker to monitor adherence and correlates strongly with other HU-sensitive hematologic measurements [12, 16–18]. Unlike the biomarker hemoglobin A1c used to monitor glycemic control for individuals with diabetes, no uniform HbF target exists. Instead, HU-induced HbF levels should reach a stable HbF “personal best” [12, 16–20].

Medication nonadherence is common across chronic pediatric conditions [21–28], especially in populations with social, economic, linguistic and cultural barriers [18, 29–34]. The consequence of uneven HU use is that patients fail to maintain personal best HbF over time [9, 20, 21, 28, 35]. Poor adherence to HU may occur frequently in this age group, especially outside of clinical trials [9, 20, 28]. Older adolescents and young adults with SCD utilize health care at the highest levels of all age groups [36–38], and may be protected from cumulative disease burden by stable HU use starting in childhood [8], underscoring the imperative of establishing self-management of HU prior to adulthood.

Barriers to medication adherence in underserved populations include cultural misalignment with medical staff [22–25], incomplete knowledge of drug benefit and logistic impediments such as prescription refill [26, 27, 39]. Medication adherence is a challenge especially during adolescence, presaging the transition to young adult self-management [21, 40–42]. Challenges to daily HU include limited awareness of its benefits and concerns about its safety, in addition to barriers to regular use of other medications commonly used by children

with SCD [33]. Interventions to improve HU adherence by addressing multi-faceted barriers must be tailored culturally, socially and developmentally. Youth also require a developmentally appropriate gradual transition of self-management responsibility to be established with parents over time [29, 43–45]. Many youth do not fully benefit from HU due to inadequate integration of HU into a daily habit [21, 46].

Chronic disease management often deteriorates during adolescence [40, 43, 44] as youth assume greater self-management responsibility [43, 47–50]. Shared responsibility [48, 51] in youth-parent partnerships for self-management [29, 45, 52] supports adolescents by a gradual self-management transition [52], with the goal of achieving competence at the time of transition from pediatric to adult care [53, 54].

The intervention described in this protocol aims to improve HU adherence in youth, decrease avoidable healthcare utilization, and improve psychosocial outcomes by supporting parent-adolescent dyads with community health workers (CHW) and tailored text messaging. CHW integration with the health team was successfully integrated into asthma care for young underserved children and decreased hospital admissions and other morbidities by 42–63% [55, 56]. Subjects for the asthma intervention, primarily young children and their parents, were identified at the time of an emergency room visit for asthma exacerbation. The intervention consisted of a CHW home visit to identify potentially modifiable environmental factors as well as education regarding the daily use of control medication. Since CHWs are not commonly used with youth with chronic disease, the success of the asthma program sparked our interest in developing an intervention for youth with SCD. In this study, we extend the model of CHW use to underserved adolescents with SCD and augment CHW support through the use of tailored text messaging reminders.

Methods/design

Aims and hypotheses

This 6 month multi-site two-arm randomized controlled trial (RCT), Hydroxyurea Adherence for Personal Best in Sickle Cell Disease “HABIT”, is designed to test the feasibility and acceptability, compared to standard treatment, of a CHW intervention augmented by tailored text messaging to improve HU adherence of youth with SCD. The trial’s primary outcome is to assess the efficacy of the intervention on HU adherence, as measured by progress to Personal Best HbF (PB HbF) from baseline, prescription refill adherence and self-reported adherence. We hypothesize that, compared to the control group receiving standard care, dyads randomized to the intervention will demonstrate improved adherence at 6 months. Secondary outcomes are to assess dyad concordance about self-management responsibility, quality of life (QOL) and resource use. We hypothesize that dyads randomized to the intervention will demonstrate improved communication about developmentally appropriate youth-parent self-management responsibility and quality of life and will demonstrate decreased resource use (urgent outpatient appointments, emergency room visits, hospitalizations, missed days from school) at 6 months compared to the control group, and that parent-youth dyads randomized to the intervention and the CHWs who deliver the intervention will deem the intervention acceptable.

Definitions

For the purpose of the HABIT trial, the following definitions are used: Personal Best (PB) HbF was defined as a child's highest historical HbF value at maximum stable dose following initiation of HU therapy. PB HbF is concept that is used due to the lack of standard for HU-induced HbF level to assess adherence [12, 13, 21, 30, 34]. In this study, PB HbF is used as a personalized minimum target goal and motivational aid to improve HU adherence. Deviation from PB was defined as the proportional difference between the HbF value at study entry (baseline) and that at PB ($(\text{PB-recent})/\text{PB} \times 100$). Poor HU adherence was defined as 15% deviation from PB at the baseline study visit.

Theoretical Model

The Self and Family Management Framework [57] guides study design and informs variable and study instrument selection by addressing key risk and protective factors for youth and family management of chronic illness, including aspects related to health status, individual, family, psychosocial, environment and developmental aspects. Youth ages 10–18 years with SCD are targeted because transition of responsibility for self-management occurs throughout this time [42, 43, 58]. In this study we test the feasibility and acceptability of a community intervention employing CHWs (protective factor) on HU adherence (primary outcomes) and individual and family outcomes (secondary outcomes). Figure 1 illustrates the Self and Family Management Framework adapted for poorly adherent underserved youth with SCD.

Study sample and setting

The study sample will consist of 30 dyads of youth age 10–18 years of age with SCD and a parent (or guardian). Subjects will be recruited from two independent pediatric sickle cell clinics located in northern Manhattan and the Bronx. Columbia Pediatric SCD clinic provides care to approximately 200 youth, with approximately one third of youth age 10–17 years currently on HU therapy. Approximately half of youth at the Columbia site are Hispanic, primarily from the Dominican Republic [59]. Some parents speak Spanish as a primary language. The second study site at Montefiore Medical Center is located 7 miles from the Columbia site. Its Pediatric SCD clinic serves approximately 600 children, the majority of African descent, with a similar proportion of youth on HU therapy. Barriers to HU use are similar across sites and include uncertainty about the risks and benefits of treatment, concern about future fertility, and risk of potential carcinogenic effects [27].

Recruitment and training of community health workers

Realizing the requirement for the cadre of CHWs to have a core of knowledge for working in a variety of settings, researchers at Columbia had previously developed, tested and utilized a set of comprehensive skills and competencies needed for a CHW to be effective in an 8 day core competency program [60, 61]. This training program is now widely implemented in New York City. CHWs for the HABIT study will be recruited from among the graduates of this CHW training program. In addition to the established CHW training program, 2 additional project specific training modules were developed to provide CHWs with entry level competency about (1) SCD and role of HU therapy and (2) developmentally appropriate disease self-management with gradual transition of responsibility from parent to

youth, including facilitating communication and problem-solving for youth-parent dyads. CHW training will focus on identifying and addressing adherence barriers at multiple cultural, logistic and developmental levels, maintaining youth and parent confidentiality where appropriate, working with dyads in management of conflict, and identifying social, psychological or behavioral “red flags” requiring prompt intervention (e.g. truancy, depressive symptoms, possible interest in self harm, domestic violence). For this feasibility study, given the geographic proximity between the 2 study sites, the project CHWs and our community based organization partner will serve intervention subjects at both sites.

Recruitment of youth/parent dyads

Eligible dyads will be screened from the clinic rosters at both study sites and offered enrollment at their routine clinical appointment with the goal of equal enrollment (15 youth/parent dyads) at each site. Reasons for and rate of refusal to participate will be tracked. Parent consent and youth assent will be obtained for: study enrollment; pharmacy release of HU refill data for the period 1 year prior to study participation through study completion and communication of HbF results and urgent clinical events to the CHW by study staff (intervention arm only). All study materials will be available in English and Spanish. Parents and/or youth lacking a cell phone will receive a cell phone with a text message plan to allow participation for the 6 month study.

Parents and youth participate as a dyad and both must meet all inclusion and exclusion criteria. Dyads are eligible for participation in the HABIT study if the youth is (1) between the ages of 10 and 18 years and (2) diagnosed with Sickle type HbSS or HbS-B⁰ thalassemia, (3) has been prescribed HU for a minimum of 18 months, (4) has had a minimum of 3 HbF assessments of the past year with HbF at least 15% below the calculated “personal best” value, (5) is able to use a cell phone with text message capability, (6) can speak and read either English or Spanish, and (7) is willing to participate in clinic and community health worker study visits. Parents are eligible for the study if their youth meets all inclusion criteria and if the parent (8) speaks English or Spanish, (9) is willing to participate in clinic and community health worker study visits, and (10) the family expects to reside in their present community for the next two years.

Dyads are excluded from study participation if the youth’s (1) sickle cell type is a variant other than HbSS or HbS-B⁰ thalassemia, (2) age is <10 years or >18 years, (3) not prescribed HU for their SCD, (4) has had less than 3 assessments of HbF level over the past year, (5) if the youth does not currently reside with the parent or legal guardian, (6) is a sibling of a youth enrolled in the study, or (7) has cognitive impairment of greater than one grade level. Female youth are also excluded if they are (8) sexually active and not using a form of contraception due to HU’s teratogenic risk to the fetus or are (9) pregnant. Parents are excluded from study participation if he/she is not the primary caregiver or if the youth is in foster care. Lack of a cell phone is not a reason for study exclusion. Subjects lacking a sufficient cell phone plan will be compensated to purchase or upgrade plans to accommodate texts for the duration of the study. Those lacking a cell phone will receive a loaner phone to be returned upon study completion.

Randomization process

A randomization plan across sites for 2:1 assignment to the intervention group will be generated via a computerized random number generator function prior to study initiation. Assignments will be placed in sequentially numbered sealed envelopes; following completion of baseline measures the next sequential ID envelope will be opened by study staff and assigned to the dyad. Dyads will be randomized following informed consent and completion of baseline measures. Dyads will be informed of their randomization group via telephone.

Study protocol

Study participation will include 6 monthly clinic visits for both the intervention and control groups. At each visit a blood sample for assessment of HbF will be obtained from the youth. Because monthly assessment of HbF is not standard practice for youth prescribed HU, laboratory costs were budgeted for months 1, 3 and 5 and considered clinical care for months 0, 2, 4 and 6. While not specifically measured as part of this study protocol, other hematologic parameters such as mean corpuscular volume (MCV) that are affected by HU use will be tracked when measured as part of clinical care.

At each study visit the parent and youth will complete study questionnaires with monthly self-report of adherence and resource use and more comprehensive assessments at months 0, 3 and 6 months. Surveys will be self-administered. A bilingual research assistant will be available to ensure that submitted forms are complete and to answer dyad questions if needed. For dyads who find monthly clinic visits overly burdensome, arrangements will be made for home visits by the research assistant and a certified phlebotomist on the alternate month. For dyads choosing this option, the home visit will include survey completion and blood sample for HbF.

Table 1 provides detail regarding the study timeline and study procedures at each timepoint. Primary and secondary outcomes are described in the Primary and Secondary Outcomes sections. Procedures to minimize attrition will include convenient scheduling of study visits generally to coincide with clinic appointments, and subject incentives for extra clinic time spent on questionnaires, weighted to completion. While parent and youth receive the same monetary incentive, the amount of incentive for months 0, 3 (\$20/visit for each dyad member) and 6 (\$30 for each dyad member) is greater than those received at months 1, 2, 4 and 5 (\$10/visit for each dyad member) because of greater time for completion of questionnaires. Educational materials appropriate for language, culture and literacy will be provided to dyads regarding SCD and HU at reading levels appropriate for low literacy communities. Social services, such as access to applications for city housing and employment training programs, will be provided by Community League of the Heights (CLOTH), our community-based partner which employs the project CHWs. Use of such services will be tracked and included in analysis. Prior to study initiation all surveys and educational materials were designed for low literacy populations in collaboration with the health literacy service of Columbia's Irving Institute for Clinical and Translational Science, translated to Spanish in collaboration with the Columbia University Medical Center Spanish Translation Center, and pretested with parents and youth with SCD.

In addition to monthly clinic visits, those assigned to the intervention group will meet with their CHW as described below. Dyads randomized to the control group will continue usual clinic-based care, including monitoring and review of HbF levels, and similar frequency of clinic visits and access to sickle cell team staff.

Intervention group

Following randomization, CHWs will contact the family to schedule visits with the dyad. Meetings with subjects will occur at home, by telephone or at the office of our community partner, CLOTH, based on the preference of the dyad. Dyads whose schedule make CHW visits difficult to complete, even with an option for weekend home visits, will be met at clinic following a regular appointment in a separate area or room to ensure privacy. While the intervention is structured across subjects, it is tailored to meet the needs of youth across the age range of 10 through 18 years and flexible in terms of development of the habit and location of the visit.

Table 2 outlines the structure and tailoring of the CHW intervention by month. During the first month, the focus of CHW visits will initiate a relationship with the youth and parent, both individually and as a dyad, to assess social, educational and self-management needs and barriers to HU adherence. CHWs will help dyads prioritize adherence barriers, address knowledge gaps about HU benefits/risks, and formulate HU adherence goals. During the second month the CHW will attend a clinic appointment with the dyad to strengthen linkage with the SCD medical service, and aid the dyad in reviewing plans to reduce adherence barriers. The CHW will assist the dyad to develop mutually agreed upon developmentally appropriate goals for youth self-management responsibility.

During months 3 and 4 CHWs will support dyads on their roles and steps toward self-management and will facilitate problem-solving as needed. Interim goals and progress toward goal achievement will be reviewed at each visit. Self-management issues will be addressed based on the youth's age and developmental stage. In month 3 the CHW will begin to prepare each dyad member for receiving text message reminders about taking HU. First, the CHW will help each dyad member to identify an established habit which will become the cue for HU use; following habit identification, each dyad member will formulate a text reminder including time of day for text delivery to promote HU adherence.

In month 4, youth parent dyads will receive daily tailored text message reminders with the goal of augmenting habit-forming behavior and extending on-going CHW support. The text message will be delivered daily during month 4 with the option of either continuing daily or decreasing text message frequency to every other day during months 5 and 6. The "MIR3 Notification Solution", a secure, web-based, texting service (www.mir3.com) will be used to automatically deliver and collect data on text messages. This commercial texting system has been successfully used by Columbia colleagues for community-based research subjects [62–65].

During months 5 and 6, the CHWs will continue to focus on self-management, adherence and personal best HbF. CHW contact will primarily occur by telephone, unless barriers to adherence or self-management persist or a face-to-face visit is requested by the dyad. To

avoid habituation, during month 5 the frequency of text messages will be negotiated based on preference by each dyad member. At study completion, youth, parents and the CHWs will be surveyed for acceptability of the intervention, including their qualitative feedback on the CHW and text message components.

Control group

Dyads randomized to the control group will continue usual clinic-based care, including monitoring and review of HbF levels, and similar frequency of clinic visits and access to sickle cell team staff. They will receive the same education materials and information about CLOTH services as do those assigned to the intervention group. A bilingual research assistant will be available to ensure that submitted forms are complete and to answer dyad questions.

Baseline demographic data and supplemental data collection

At the baseline (month 0) visit, in addition to the laboratory and survey measures described below, data collection will include demographic characteristics of the parent and youth including how long the family has lived in the United States, parent employment, whether other people in the family have SCD, the youth's hospitalization and emergency room use over the past year, and whether the parent and youth own a cell phone with text messaging capability sufficient for study participation. A validated Medication Barriers scale [66] will be administered at months 0, 3 and 6. Nine items were added to address barriers specific to HU [27].

Primary study outcomes

The primary study outcome is HU adherence achieved through an intervention deemed feasible and acceptable by study participants. Data on intervention feasibility will be collected from parents and youth randomized to the intervention arm of the study via a monthly investigator developed comment form and evaluation survey from all enrolled subjects at the final study visit at 6 months, the final study visit. The comment form is designed to obtain "real time" information about response to the community health worker as well as parent and youth perceptions regarding their progress toward parent/youth self-management teamwork. The 6 month intervention evaluation is more comprehensive in scope and asks about usefulness of the educational materials, access to services provided by CLOTH, our community partner in this project, perceptions about working with the CHW and utility of the text messages. Evaluation survey questions for the control group are restricted to the educational materials and access to CLOTH services.

For this study, the goal is to determine if the intervention is feasible and, if so, if the intervention would be efficacious. Because Personal Best HbF is a novel method of assessing HU adherence, data related to HU adherence will be obtained by 3 measures: monthly laboratory assessment of HbF, self-report survey, and prescription refill adherence. Deviation from PB will be calculated using monthly HbF values. Parents and youth will complete the 8 item Morisky Medication Adherence Scale (MMAS-8) [67], a validated measure that has been used in prior SCD research [29]. Scores of 0, 1–2, and 3 are categorized as high, medium and low adherence respectively. At the baseline study visit,

parental consent to obtain pharmacy refill information covering the period of one year prior to study enrollment to the time of study completion will be obtained. Prescription refill adherence will be defined as the proportion of days covered (PDC) [68]. The PDC calculation is based on prescription fill dates and days supplied for each prescription refill. The denominator for the PDC is the number of days between the first and last fill dates of the medication during the measurement period.

Secondary study outcomes

Secondary study outcomes are communication about developmentally appropriate youth-parent self-management responsibility, quality of life and decreased resource use (urgent outpatient appointments, emergency room visits, hospitalizations, missed days from school, parent work and non-work related productivity). The Sickle Cell Family Responsibility Scale measures communication about self-management responsibility and dyadic agreement [69] regarding the division of self-management tasks. This 10 item scale was adapted from the Diabetes Family Responsibility Questionnaire [48] and has been previously adapted for use in other pediatric chronic illnesses such as asthma [40], inflammatory bowel disease [70] and HIV [43] to measure youth-parent perceptions of division of responsibility [45, 71]. In this study we focus on improved dyadic agreement regarding self-management responsibility.

Quality of life will be measured using the PedsQL Generic Core Scale and the PedsQL Sickle Cell Disease Module. The PedsQL 4.0 is a 23 item 5 point Likert scale survey with 2 versions for youth (ages 8–12; 13–18 years) and parallel parent proxy version. The instrument has high internal consistency for total score ($\alpha=0.91$) and its subscales ($\alpha=0.81$ – 0.89) [72] and has been validated in youth with SCD [14, 73–75]. The PedsQL 4.0 has been validated in Spanish. The PedsQL Sickle Cell Disease Module is a 43 item survey similar in format to the PedsQL 4.0 developed to measure disease specific quality of life in youth with SCD [76]. The instrument has excellent reliability ($\alpha=0.95$) [76].

Resource use will be measured each month using the Resource Use Questionnaire (RUQ), an 11 item instrument adapted for SCD from the Resource Utilization Questionnaire for Type 1 diabetes (RUQ-T1DM) [77]. The instrument has established content and criterion validity using a societal perspective. Items include hospitalization, emergency room and acute outpatient visits as well as time lost from school due to not feeling well or healthcare related appointments. Caregiver productivity items from the Work Productivity and Activity Impairment: General Health questionnaire [78, 79] were incorporated into the RUQ to allow for measurement of lost productivity due to the parent caregiving role.

Data analysis plan

Qualitative responses of parents, youth and CHW regarding intervention acceptability will be analyzed using content analysis. To meet the primary and secondary aims, 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. Psychosocial and self-management assessments will be made at the 0, 3 and 6 month visits, with more limited assessment at

months 1,2,4,5. A growth model [80] will be applied to examine the difference in trend of outcomes and to compare outcomes between intervention and control groups at 6 months. A growth model is a type of linear mixed model with random intercepts and slopes for continuous outcomes (e.g. QOL score) or generalized linear mixed model for categorical outcomes (e.g. whether or not a subject had an urgent outpatient visit during the past month) for repeated measured data. Its main advantage is in the use of all subjects, including those who were lost to follow-up, for the estimation at 6 months. The growth model also can address the hierarchical data structure of multiple observations for each subject and multiple subjects in each family (i.e. youth-parent dyads). Attrition or other missing data will be addressed by a plan to: (1) Apply a growth 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.

Data Management

Subjects will be assigned a unique identification code for data entry to a Research Electronic Data Capture (REDCap) database (<http://project-redcap.org/>) and stored on a Columbia University Medical Center IRB approved server. REDCap is a web-based research application that is supported at Columbia. Study data will be converted to a SAS data file for analysis and stored on a password-protected computer. Data analyses will be performed using SAS version 9.3 (SAS Institute, Cary, NC).

Study Fidelity

The HABIT operations manual will contain 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, patient education materials about SCD and HU, and exemplars of “red flag” situations such as unresolved conflict regarding self-management or other serious issues such as drug use, truancy or depression that warrant prompt communication with the study principal investigators and referral. As in Columbia’s asthma treatment study [55, 56, 81], CHWs will be supervised jointly by CLOTH personnel (administrative/employment) and by the study PIs (program). PIs will meet with CHWs bi-weekly, and ad hoc as needed, to review: forms, cases, automated text messaging reports, information on SCD, and tailoring of the intervention based on dyad needs and age/developmental stage of the youth. As appropriate, the CHW will independently recommend or make referrals through CLOTH or the SCD clinic for professional counseling or other services. Clinical events requiring emergency care or hospitalization will result in intensified, weekly CHW visits through home, clinic and/or hospital visits.

Study Acceptability and Feasibility

Dyads will provide monthly qualitative feedback about their experience via a Comment form. At study completion, youth, parents and CHWs assigned to the HABIT intervention will provide qualitative feedback about acceptability of the intervention, including interactions with CHWs and the text messaging. Study feasibility [82] will be assessed by

review of CHW visits and at the team and project meetings. Lessons learned will inform refinement of the intervention for a future efficacy trial.

Ethical considerations

The institutional review boards of Columbia University Medical Center and Albert Einstein-Montefiore Medical Center have approved the study, and it poses no obvious risks to subjects. Eligible parent/youth dyads willing to participate will sign a written consent (and assent for youth). They will be informed that their participation is voluntary, that they may withdraw at any time, and that their survey responses cannot be linked to or influence their usual medical care. Completed questionnaires and study data will be kept in a locked area and accessible only to authorized study personnel. All subject study documents are available in English or Spanish.

Discussion

Evidence from clinical trials supporting HU treatment benefits [16, 83, 84] and long-term safety [8, 85] in youth with SCD is translating to clinical practice. In 2014, the National Heart, Lung, and Blood Institute released an expert panel report for evidence based management of SCD specifically addressed use of HU in children with SCD and strongly recommended its use to reduce long term complications of SCD [7]. However to attain full treatment benefit, adherence to HU is critical. Recently published data from a cohort of 273 New York State Medicaid insured children born during 2006–2009 demonstrated that by 2014 approximately half were prescribed HU. While this is good news, HU treatment adherence of these youth is more sobering, as approximately two thirds of those treated met criteria for suboptimal adherence based on their pharmacy refill records [86]. Clearly interventions to improve HU adherence for youth with SCD are needed.

There is a growing body of evidence regarding the effectiveness of community health workers in helping those with chronic disease improve their self-management [87]. While promising, their use in SCD has been limited. A recent white paper [88] highlights the various roles that CHWs could play in SCD and encourages greater use of CHWs in SCD care. A 2013 systematic review of 17 CHW interventions in pediatric chronic disease [89] failed to identify studies targeted to youth with SCD. To the best of our knowledge, the RCT described in this protocol is the first to employ a CHW intervention for youth with SCD to improve medication adherence. The intervention employs the novel approach of youth parent dyads, culturally aligned CHWs and tailored text messaging.

Use of two study sites will enhance available patient pool for study recruitment, enlarge the representation of the variety of clinic-family interactions and broaden generalizability of study findings. Study limitations include the 6 month period for developing relationships with parents and youth and the inability to assess the impact of the intervention on HU adherence following study completion. Our sample size is insufficient to compare the intervention components and their individual effects on adherence. Findings from this feasibility study will inform planning for a larger multi-site study with sufficient power to examine these issues. Peer support for parents and youth is not provided. Sample size, language differences and study duration preclude organized peer support, but could be

included in a subsequent larger study. This project has the potential to improve the health of underserved children with SCD by enhancing long-term self-managed HU adherence, as measured by a powerful biomarker and adherence measures.

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List of abbreviations

CHW	Community health worker
CLOTH	Community League of the Heights
HABIT	Hydroxyurea Adherence for Personal Best in Sickle Cell Disease
HbF	hemoglobin F
MCV	Mean corpuscular volume
MMAS-8	Morisky Medication Adherence Scale
PB	Personal Best
PDC	Proportion of days covered
QOL	Quality of life
SCD	Sickle cell disease

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Adapted from Grey et al, 2006

Figure 1.
Self and Family Management Framework

Table 1**HABIT study timeline**

Month	Study Procedures	Survey completion	
		Parent	Youth
0	Prior to randomization:		
	Parent consent/youth assent	•	•
	Parent release for pharmacy refill data	•	
	Education materials and information about CLOTH	•	•
	HbF (other hematologic parameters if collected as part of clinical care)		•
	Survey completion:		
	Demographic	•	
	Medication barriers	•	•
	SCD Family responsibility	•	•
	Morisky scale	•	•
	PedsQL generic core scale	•	•
	PedsQL sickle cell disease module	•	
	Resource use questionnaire	•	
	Randomization to group assignment		
	Obtain pharmacy refill data for year preceding study entry		
	CHW contacts dyad; schedules and initiates visit ^a		
1	HbF (other hematologic parameters if collected as part of clinical care)		•
	Survey completion:		
	Morisky scale	•	•
	Resource use questionnaire	•	
	Comment form ^a	•	•
2	CHW visit(s) ^a		
	HbF (other hematologic parameters if collected as part of clinical care)		•
	Survey completion as in month 1	•	•
3	CHW visit(s) ^a		
	HbF (other hematologic parameters if collected as part of clinical care)		•
	Survey completion:		
	Medication barriers	•	•
	SCD Family responsibility	•	•
	Morisky scale	•	•
	PedsQL generic core scale	•	•
	PedsQL sickle cell disease module	•	•
	Resource use questionnaire	•	
	Comment form	•	•
4	CHW visit(s) ^a		
	HbF (other hematologic parameters if collected as part of clinical care)		•
	Survey completion as in month 1	•	•

Month	Study Procedures	Survey completion	
		Parent	Youth
5	Tailored text message reminders begin; less frequent CHW contact ^a		
	HbF (other hematologic parameters if collected as part of clinical care)		•
	Survey completion as in month 1	•	•
6	Tailored text message reminders ^a		
	HbF (other hematologic parameters if collected as part of clinical care)		•
	Survey completion as in month 3 plus Project evaluation survey	•	•
	Obtain pharmacy refill data for study months 0–6		

Note: Other hematologic parameters = hemoglobin, mean corpuscular volume, actual number of reticulocytes/ml, white blood cell count, absolute neutrophil count;

^aIntervention group only

Table 2

Intervention structure and tailoring

Month	Focus	Structure	Tailoring
1	<ul style="list-style-type: none"> Relationship Social issues Assessment 	<ul style="list-style-type: none"> Face-to-face visits (every 1–2 weeks) 	<ul style="list-style-type: none"> Visit location Barrier identification Service referrals Goal-setting
2	<ul style="list-style-type: none"> Continued assessment Linkage with SCD clinic Improved adherence 	<ul style="list-style-type: none"> Face-to-face (biweekly) Clinic visit (one) Deliver SCD and HU education 	<ul style="list-style-type: none"> Address adherence barriers Developmentally based self-management dyad goal setting Adherence and personal best goal set
3	<ul style="list-style-type: none"> Cue identification Personal best as motivator Habit formation 	<ul style="list-style-type: none"> Face-to-face (biweekly) Cue for habit identified Monthly HbF feedback 	<ul style="list-style-type: none"> Age appropriate self-management responsibility goals Cue identified Text messaging content developed with dyad Relationship between HbF and individual personal best
4	<ul style="list-style-type: none"> Habit formation Initiate text messaging 	<ul style="list-style-type: none"> Phone contact (weekly) Implement daily text messages 	<ul style="list-style-type: none"> Reinforcement of individual goals Referral follow up Progress to personal best
5–6	<ul style="list-style-type: none"> Habit maintenance Continued text messaging 	<ul style="list-style-type: none"> Phone contact (weekly), or more if needed 	<ul style="list-style-type: none"> Dyad can request home visit Frequency of text messages determined by dyad Reinforcement of individual goals Progress to personal best

Note: SCD= sickle cell disease; HU=hydroxyurea; HbF=hemoglobin F