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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 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.
Trial registration: NCT02029742

1. 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].

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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.

2. Methods/design

2.1. 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.

2.2. 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 ([PB-recent]/PB*100). Poor HU adherence was defined as ≥15% deviation from PB at the baseline study visit.

2.3. 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). Fig. 1 illustrates the Self and Family Management Framework adapted for poorly adherent underserved youth with SCD.

2.4. 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].

2.5. 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