Published in final edited form as:

J Pediatr. 2018 June ; 197: 177–185.e2. doi:10.1016/j.jpeds.2018.01.054.

HABIT, a Randomized Feasibility Trial to Increase Hydroxyurea Adherence, Suggests Improved Health Related Quality of Life in Youth with Sickle Cell Disease

Arlene Smaldone, PhD, CPNP^{1,2}, Sally Findley, PhD³, Deepa Manwani, MD⁴, Haomiao Jia, PhD^{1,3}, and Nancy S. Green, MD⁵

¹Columbia University School of Nursing, New York, NY

²College of Dental Medicine, Columbia University Medical Center, New York, NY

³Mailman School of Public Health, Columbia University, New York, NY

⁴Department of Pediatrics, Albert Einstein College of Medicine, New York, NY

⁵Department of Pediatrics, Columbia University Medical Center, New York, NY

Abstract

Objectives—To examine the effect of a community health worker (CHW) intervention, augmented by tailored text messages, on hydroxyurea adherence in youth with SCD. Here we report secondary outcomes: generic and disease-specific health related quality of life (HrQL) and youth-parent self-management responsibility concordance.

Study Design—We conducted a 2-site randomized controlled feasibility study (Hydroxyurea Adherence for Personal Best in Sickle Cell Treatment: HABIT) with 2:1 intervention allocation. Youth and parent participated as dyads. Intervention dyads received CHW visits and text message reminders. Data were analyzed using descriptive statistics, Wilcoxon sign rank tests and growth models adjusting for group assignment, time and multiple comparisons. Outcome change from 0 to 6 months was compared with its respective minimal clinically important difference.

Results—28 dyads (youth age 14.3±2.6 years, 50% Hispanic) participated (18 intervention, 10 control), with 10.7% attrition. Accounting for group assignment, time and multiple comparisons, intervention youth at 6 months reported improved generic HrQL total score (9.8 points, 95% CI 0.4, 19.2) and emotional subscale (15.0 points, 95% CI 1.6, 28.4); 3 disease-specific subscale scores: worry I (30.0 points, 95% CI 8.5–51.5), emotions (37.0 points, 95% CI 9.4, 64.5), communication I (17.8 points, 95% CI 0.5, 35.1); and 3 month dyad self-management

Corresponding Author: Arlene Smaldone, Professor of Nursing, Columbia University, Nursing, 630 W 168 St, NY, NY 10032, United States, +6317909290, FAX: 212 305 6937, ams130@columbia.edu.

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Portions of this study were presented at the Eastern Nursing Research Society 29th Annual Scientific Sessions, April 5–7, 2017, Philadelphia, Pennsylvania, the 45th National Convention on Sickle Cell Disease, October 25–28, 2017, Atlanta, Georgia, and the 59th American Society of Hematology Annual Meeting and Exposition, December 9–12, 2017, Atlanta, Georgia.

Trial Registration [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02029742) NCT02029742

responsibility concordance (3.5 points, 95% CI -0.2, 7.1). There were no differences in parent-proxy reported HrQL measures at 6 months.

Conclusions—These findings add to research examining effects of behavioral interventions on HrQL outcomes in youth with SCD.

Keywords

Sickle cell disease; medication adherence; hydroxyurea; community health worker; health related quality of life

Sickle cell disease (SCD) is an inherited disorder that affects approximately 100,000 Americans, especially those of African American and Latino race/ethnicity.^{1, 2} The disease is associated with chronic anemia, pain and organ dysfunction, leading to multiple acute and chronic complications, high healthcare utilization,^{3, 4} premature mortality⁵ and poor quality of life.^{6, 7} Hydroxyurea, the first FDA approved drug for SCD therapy, reduces hospitalization^{8, 9} and improves quality of life^{10, 11} in youth with SCD. Since 2014 national guidelines have recommended its use^{12, 13} for most children with the severe phenotypes of homozygous sickle cell disease (HbSS) and the compound heterozygous condition of HbS-beta⁰ thalassemia. Nonetheless, HU remains an underutilized therapeutic option.^{14–16}

The self-management roles of youth and parents change throughout childhood and adolescence with self-management responsibility transitioning from parent to youth. Adolescence is a critical time to optimize adherence to chronic drug therapy because treatment adherence often deteriorates during this time¹⁷ as youth assume greater responsibility for self-care. Similar to adolescents with other chronic conditions,¹⁸ adherence to a daily drug regimen is suboptimal for many youth prescribed HU.^{14, 19–21} Across age groups, older adolescents and young adults with SCD have the highest rate of hospitalization,²² highlighting the importance of interventions to improve health status in this age group.

Ideally, during adolescence the transfer of developmentally appropriate self-management responsibility occurs over time with parents remaining involved in a supportive role.²³ Often, however, this is not the case. Data synthesized from 28 studies that examined adherence barriers from the perspective of adolescents with chronic health conditions were reported in a recent systematic review.²⁴ Across studies, a salient theme for nonadherence was adolescent-parent conflict with conflict stemming from either parental difficulty with delegation of self-management responsibility or adolescent perception of lack of parental support. Maintaining communication between parents and youth about self-management is key. Use of community health workers has been successful in helping adults with chronic illness to improve self-management.^{25–27} To date, there have been few reports about CHW support of adolescents²⁸ or in those with SCD.²⁹

We hypothesized that a 6-month CHW intervention, augmented by text messages to help parent youth dyads formulate a HU daily habit (“Hydroxyurea Adherence for Personal Best in Sickle Cell Treatment: HABIT,”³⁰ [[ClinicalTrials.gov: NCT02029742](https://clinicaltrials.gov/ct2/show/study/NCT02029742)]) would be feasible, acceptable to youth-parent dyads, and provide data for estimating an effect size

towards improving HU adherence. This paper reports the effect of the HABIT intervention on secondary outcomes, specifically the change in youth HrQL from the perspectives of parents and youth, and dyad concordance about self-management responsibility. Although HrQL is higher among youth prescribed HU compared with those who are not,¹¹ little is known about how changes in HU adherence is related to self- and parent-proxy reported HrQL.

Methods

The HABIT study design has been described previously.^{30, 31} The study was a 2-site, 6-month randomized controlled trial to test the intervention's feasibility and acceptability and to estimate the effect of a CHW intervention for youth-parent dyads—augmented by tailored text messages—to improve HU adherence among youth with SCD. A computer-generated randomization scheme with a 2:1 allocation to the intervention group was employed. Dyads randomized to the intervention were contacted by the CHW to schedule visits either at home or another location based on dyad preference. Both groups received educational handouts about SCD and HU therapy and usual clinical care at monthly intervals. Institutional review board approval was obtained at each participating site prior to study initiation.

Study participants

Subjects were recruited during the period 9/4/2013 through 3/28/2015 from two pediatric SCD programs at academic medical centers in New York City. Both serve a diverse population. Potentially eligible youth with SCD were identified by review of history of HU therapy, including highest HbF value following HU induction (considered as the youth's "Personal Best HbF"²¹) compared with the average of three HbF levels obtained over the previous 12 months. Those with an average HbF value of 10% or less than "Personal Best" met criteria to be offered study participation if they also met all other study inclusion criteria as described elsewhere.³¹ Study procedures.

Following parental informed consent and youth assent, dyads completed baseline questionnaires, youth provided a blood sample for HbF assessment, and dyads were randomized to study group. Each intervention dyad member lacking a personal cell phone received a phone for use during the study. Dyads completed 7 monthly clinic visits (months 0–6) for survey completion and HbF assessment. Intervention dyads met with CHWs, on average, 4.9 ± 0.9 times during the first 3 study months. The majority of CHW visits were conducted at the subjects' home. Each visit had a specific focus, such as: an initial intake visit to identify pressing social issues, e.g. housing mental health (visit 1); a visit to identify and address barriers to HU use, e.g., incomplete understanding of benefits or adverse effects, forgetting daily dose (visit 2); a visit to discuss delegation of, and satisfaction with, level of responsibility for self-management tasks (visit 3); and, a visit to identify a habit upon which HU adherence could be built, e.g. tooth-brushing, eating dinner, bedtime (visit 4).

During the first two visits, CHWs reviewed educational handouts for sickle cell disease and HU with the parent and youth. Although each visit was structured, CHWs had the ability to be flexible to accommodate dyad needs. In collaboration with their CHWs, parent and youth each developed text message language to remind them to take daily HU, tailored by wording

of message, language (Spanish or English), and time of text message delivery (visit 5). At month 4, dyads transitioned from CHW visits to receipt of daily text messages for the duration of the study. CHWs met with study investigators biweekly to review visits, referrals made, and any concerns about dyad progress; in addition, ongoing fidelity to the protocol was assessed. If a “red flag” issue, e.g., suicidal ideation, was identified during a home visit, the CHW contacted the study PI for immediate guidance and/or confirmation of their plan. Two CHWs covered subjects at both sites.

Study outcomes and measures

The primary outcome—improved HU adherence—was measured by monthly progress of the biomarker HbF towards a participant’s Personal Best, proportion of days covered by HU using pharmacy prescription records³², and by the 4-item Morisky scale.³³ Each measure in the study protocol has been fully described³¹ and results of the primary outcomes recently reported.³⁴ Secondary outcomes of the study were generic- and disease-specific HrQL and dyad concordance regarding self-management responsibility. Youth and parents completed survey measures at months 0, 3 and 6 in either English or Spanish based on subject preference.

The PedsQL Generic Core Scale, a 23 item 5-point Likert scale measure, was used to measure generic HrQL. The instrument, available in both English and Spanish, has 4 subscales with high internal consistency for both the full instrument and its subscales.³⁵ It has been widely used in SCD disease.^{11, 36–38} In this study we used youth and parent proxy-report instruments for ages 8–12 years and 13–17 years. PedsQL total scores 60 and lower can be interpreted as impaired quality of life, whereas scores 80 and greater are consistent with a good quality of life³⁹ in youth with SCD.

The PedsQL Sickle Cell Disease (SCD) Module, a 43 item 5-point Likert scale measure, was used to measure disease specific HrQL. Internal consistency ranges from acceptable to high for the instrument and its 9 subscales.⁴⁰ Two subscales address worry (Worry I, concern about pain and hospitalization, and Worry II, concern about stroke and/or chest crisis) and two address communication (Communication I, communicating with health care team, and Communication II, difficulty communicating when others do not understand impact of living with SCD). Similar to the PedsQL generic core scale, youth and parent proxy-report were used for both age groups. Scores for the PedsQL and PedsQL SCD Module range from 0 to 100 with higher scores indicating perception of better quality of life. Both generic and disease specific HrQL measures are sensitive to change in clinical status over time in youth with SCD.^{41–43} Recently, longitudinal validity and estimations of change in PedsQL SCD module scores that can be interpreted as clinically meaningful were established using data from a sample of youth who participated in a multi-site clinical trial.⁴⁴

The Sickle Cell Family Responsibility (SCFR) Scale, adapted from the Diabetes Family Responsibility Questionnaire (DFRQ)⁴⁵, is a 10 item 3-point Likert scale questionnaire that examines the perception of both youth and parent regarding who takes responsibility for SCD self-management tasks. This scale was used to measure level of self-management responsibility and dyad concordance regarding self-management responsibility. The DFRQ has been widely adapted for use in other pediatric chronic diseases such as asthma,⁴⁶

inflammatory bowel disease⁴⁷ and HIV.⁴⁸ Scores for the SCFR range between 10 and 30, with higher scores indicating greater youth responsibility and lower scores indicating greater parent responsibility for self-management tasks. Dyad self-management concordance⁴⁹ was measured as the number of self-management tasks where both youth and parent agreed. Scores range between 0 and 10, with higher scores indicating greater dyad agreement.

When instruments were unavailable in Spanish, the English language version underwent a forward and backward translation process supervised by the Columbia University Medical Center's Spanish Translation Center. Following verification of the translated version, the instrument was piloted with Spanish speaking subjects. The PedsQL SCD module underwent an additional step in the linguistic validation process.⁵⁰ Ten Spanish-speaking youth-parent dyads completed the Spanish language youth or parent proxy version of the questionnaire for youth either 8–12 years (5 dyads) or 13–17 years (5 dyads). Following survey completion, each dyad member participated in a cognitive interview to determine whether questionnaire directions, question and response choices were clear, relevant to those with SCD, appropriate and easily understood.

Statistical analyses

An internal consistency reliability or Cronbach alpha coefficient was computed for each baseline measure and its subscales to determine scale reliability in the current sample. An alpha of 0.70 or higher was considered adequate reliability.⁵¹ Descriptive statistics were used to profile outcome measures at each data collection point for the intervention and control groups. Group differences at baseline were examined using the Wilcoxon sign rank test. We computed a minimal clinically important difference (MCID) of each total and subscale score, calculated as the standard error of measurement ($SEM = \delta \sqrt{1-\alpha}$),⁵² as a criterion to assess clinically meaningful improvement as a result of the intervention. An individual growth model,⁵³ a type of linear mixed model with random intercepts, was used to examine the difference in each outcome incorporating group assignment and study month. Using the estimated β of the interaction time*intervention and its corresponding standard error we compared the difference in score from baseline to 6 months to its respective MCID to assess if the change in score at 6 months represented a clinically meaningful change. To account for multiple tests, we conducted the Benjamini-Hochberg procedure⁵⁴ to adjust for false discovery. All subject data were used in analyses. Data were analyzed using SAS 9.4 (Cary, NC) statistical software.

Results

Demographic characteristics of the sample and effect of the intervention on primary outcomes have been previously reported.³⁴ In brief, 28 youth parent dyads (youth age 14.3 ± 2.6 years, 50% Hispanic) participated (18 intervention dyads, 10 control dyads) with 10.7% dyad attrition at month 6 (2 intervention dyads, 1 control dyad). Most (12 of 14) Hispanic parents and half (7 of 14) of Hispanic youth completed self-report measures in Spanish. Dyads were enrolled between October 2013 and March 2015. One in four intervention subjects (3 parents and 6 youth) required a mobile telephone for participation in the texting component of the intervention. The intervention was feasible and intervention

subjects enjoyed working with the CHWs. Incorporating group assignment and time, intervention subjects progressed to Personal best HbF by 2.3% per month during months 0 to 4 ($p=0.30$); four subjects (3 intervention, 1 control) exceeded their historical Personal best HbF by study completion. The Figure provides additional detail regarding dyad recruitment and enrollment, group allocation, subject attrition, and subjects included in the analysis.

Table I (available at www.jpeds.com) provides detail regarding the number of subjects eligible for survey completion at each time point. Table 2 compares HrQL, self-management responsibility and dyad concordance regarding responsibility of the intervention and control groups at study entry.

Internal consistency of each survey measure in this sample was acceptable for both youth and parent measures with Cronbach alphas ranging between 0.75 and 0.92 for total scores and 0.71 and 0.96 for subscale scores for all but the Worry II subscale ($\alpha=0.66$) of the PedsQL SCD module youth measure. At study entry, intervention youth-reported significantly lower scores for generic HrQL total score (71.8 ± 17.7 versus 85.8 ± 11.6 , $p=0.03$) and its emotional subscale (71.4 ± 22.5 versus 90.0 ± 9.4 , $p=0.02$) compared with control youth. There were no other differences in youth or parent-proxy reported scores. Overall, generic HrQL total scores were higher than disease-specific HrQL scores, with youth-reported scores higher than those reported by parent-proxy. Regarding generic HrQL subscale scores, the school subscale was rated lowest by both youth and parents (68.4 ± 22.8 and 57.8 ± 28.0). Of the disease-specific subscales youth and parents rated pain impact (57.6 ± 33.6 and 51.1 ± 27.3) and pain management (56.7 ± 33.6 and 58.9 ± 33.9) lowest. Regarding SCD self-management responsibility, youth reported having greater responsibility than that reported by their parents (20.1 ± 5.0 and 15.3 ± 3.6 respectively). On average, dyads were concordant regarding who takes responsibility for approximately half (4.4 ± 2.5) of the 10 self-management tasks with no differences between groups.

Table 2 also presents MCIDs for youth and parent-proxy reported total and subscale scores for each instrument. These values suggest that a change in score of 4.8 points in the youth-reported generic HrQL total score is a clinically meaningful difference. Similarly, based on this sample, a change in score of 5.5 points in the parent-proxy reported generic HrQL total score is a clinically meaningful difference. Overall, MCIDs ranged between 2.5 (self-management responsibility) to 14.6 (worry II disease specific HrQL subscale) for youth-reported measures and between 1.8 (self-management responsibility) and 11.4 (worry II subscale) for parent-proxy reported measures.

Table 3 (available at www.jpeds.com) reports HrQL and self-management responsibility scores for youth and parents at 0, 3 and 6 months. At 6 months, intervention youth reported improved total scores and 3 subscale scores (physical, school and emotional), whereas control youth scores either decreased (total score, school and emotional subscales) or remained stable (physical subscale).

For youth-reported disease specific HrQL, at 6 months intervention youth had improved in all scores whereas the majority of scores of control youth either remained stable (total score, pain impact, treatment, communication I and communication II subscales) or declined (pain

management and emotions subscales). For parent-proxy reported generic and disease-specific HrQL, at 6 months both intervention and control parents reported higher scores for all measures except one, the emotional subscale of generic HrQL, whereas, on average, control parent scores remained stable.

Table 4 (available at www.jpeds.com) presents findings of the individual growth model analyses for parent and youth reported outcomes. Incorporating group assignment and time and controlling for false discovery, intervention youth had a greater increase in the generic HrQL total score (9.8 points [95% CI 0.4, 19.2]) and its emotional (15.0 points [95% CI 1.6, 28.4]) and school subscales (14.1 points [95% CI -1.4, 29.6]) from month 0 to month 6 compared with the control group. Regarding disease specific HrQL, at 6 months intervention youth had a greater increase in three subscales compared with the control group: worry I (worried less about pain and need for hospitalization or emergency room visits) (30.0 points [95% CI 8.5–51.5]); emotions (less anger about having SCD) (37.0 points [95% CI 9.4, 64.5]); and communication I (easier to talk to others including health professionals about how they feel) (17.8 points [95% CI 0.5, 35.1]). Although there was a trend in improvement in dyad concordance regarding self-management responsibility at 3 months (3.5 points [95% CI -0.2, 7.1]), there were no differences at 6 months. There were no differences in parent-reported generic or disease specific quality of life measures.

Table 5 presents the HrQL score change and its respective 95% confidence interval from study entry to 6 months for each measure and its subscales adjusted for group assignment and time. For youth-reported measures, score changes exceeded MCID values for generic HrQL total score and its emotional subscale, and also for the disease-specific HrQL worry I, emotions and communication I subscales. For parent-reported measures no score change exceeded its respective MCID.

Discussion

In this feasibility study, youth parent dyads randomized to the HABIT intervention suggest an improvement of some, but not all, secondary outcomes. Sample HrQL scores at baseline were similar to other reports of youth prescribed HU,¹¹ with MCIDs for generic and disease-specific HrQL estimated from this sample similar to that of other samples of youth with SCD.⁴⁴ At 6 months there was a trend for improvement of youth-reported HrQL scores for the generic HrQL total score, emotional and school subscales, and three of nine subscales of the disease-specific HrQL measure: worry I, emotions and communication I and dyad concordance regarding self-management responsibility at 3 months. In most cases the score improvement exceeded that of its respective MCID. These findings suggest that the magnitude of improvement in these areas of HrQL was clinically meaningful to youth. Although not statistically significant when controlled for multiple comparisons, this feasibility study was not powered to detect changes at that level.

Although support for chronic disease self-management for adults with chronic disease is well established, it remains underutilized in pediatric care.⁵⁵ In this study, CHWs provided support to youth-parent dyads with the goal of improving HU adherence. Improvements in youth-reported HrQL centered on psychosocial domains: emotions, worry and

communication. It may not be surprising that these HrQL domains were affected in a positive way because the HABIT intervention specifically focused on HU adherence barriers and improving parent youth partnerships in self-management responsibility. Discussions with the CHW may have served as a catalyst for dyad conversations about their evolving roles and responsibilities in self-management, specifically HU adherence and barriers acknowledged and addressed. What remains uncertain is whether trends in improvement in youth-reported HrQL can be attributed to the process of improving HU adherence with support provided by CHWs, or improved dyad concordance regarding self-management responsibility. Of 17 studies included in a systematic review of randomized trials that examined use of lay health worker interventions for youth with chronic disease,²⁸ only one study⁵⁶ examined youth HrQL as an outcome. HrQL assessment in that study was measured solely by parent-proxy report and demonstrated no differences between groups at 12 months. Further research is needed regarding the impact of CHW interventions on HrQL of youth with SCD as well as youth with other chronic conditions.

Adolescents are expected to increasingly take on responsibility for self-management tasks. During this transfer, if youth and parent assume that the other is responsible for a self-care task, then it is possible that no one takes responsibility for the task and self-management is compromised. For example, parent-youth discordance has been associated with poor glycemic control in youth with type 1 diabetes^{45, 49} and poor medication adherence in youth with asthma.⁵⁷ For dyads randomized to the HABIT intervention, concordance between youth and parent about who was responsible for different aspects of SCD self-management showed a trend for improvement at 3 months. However, the trend was not sustained at 6 months when text message reminders were the primary means of HU adherence support. The CHW component of the intervention may have been too brief for dyads to develop sustained concordance. CHW interventions with parents and children to improve asthma medication adherence have tended to be fully supportive for 6 months prior to a reduced level of support.⁵⁸ Further research is warranted to examine dyad self-management responsibility concordance over time and whether it serves as a moderator of HU adherence in youth with SCD.

Evidence from multi-site randomized controlled trials examining the effect of interventions on HrQL outcomes in youth with SCD is accumulating.^{59–62} Although limited in number, the majority have examined effects of therapeutic interventions such as blood transfusion therapy,⁵⁹ interventions to alleviate pain crises,⁶⁰ and vitamin supplementation.⁶¹ Two of the studies^{60, 61} failed to detect a treatment effect on either the primary or HrQL outcomes. Only one study,⁵⁹ an intervention of chronic blood transfusions, found improvement in several physical health domains of the generic HrQL Child Health Questionnaire at 36 months. Similar to our findings, domain improvements in HrQL were consistent with the type of intervention tested.

A fourth study,⁶² a multi-site family-based behavioral intervention delivered at home, aimed to improve school functioning for youth age 6 to 12 years with SCD. There were no differences in HrQL or other study outcomes. In the HABIT study, although home visits often required scheduling after school hours or weekend days, dyad members engaged with the CHWs with high subject retention at 6 months.

Our findings must be considered in light of the study's limitations. The sample size was relatively small and so had limited statistical power. Despite randomization, there were group differences in some youth-reported generic HrQL scores at study entry. Further, although intervention youth-reported scores in some HrQL domains increased, those reported by the control group declined and may have influenced the interpretation of score change compared with MCIDs. Subjects and study investigators were not blinded to study group assignment, although allocation concealment was maintained. Study clinic visits were more frequent than usual for youth prescribed HU, currently every 2–3 months. The 6-month intervention may have been too brief to test its full impact on primary and secondary outcome measures. The Sickie Cell Family Responsibility measure was adapted from a frequently used diabetes measure and had not been formally tested with parents and youth with SCD prior to its use in this study. Despite these limitations, these findings add to a growing literature of HrQL outcomes for youth with SCD.

In summary, this trial demonstrated that the HABIT intervention was feasible and demonstrated promise to improve psychosocial domains of both generic and disease specific HrQL, as well as dyad concordance regarding self-management tasks. Testing intervention efficacy and outcome sustainability in a larger 4-site intervention trial is underway. Interventions to improve HU adherence have the potential to improve the health of youth with SCD. Structured support provided by CHWs may be a beneficial adjunct to clinic-based care to improve chronic disease self-management of youth with SCD.

Acknowledgments

Supported by the National Institutes of Health, National Institute of Nursing Research (R21 NR013745 to N.G. and A.S.) and a Clinical-Translational Science award from NCATS (UL1 TR000040 to Ginsberg)

Abbreviations

CHW	Community health worker
HABIT	Hydroxyurea Adherence for Personal Best in Sickie Cell Treatment
HbF	Hemoglobin F
HU	Hydroxyurea
MCID	Minimal clinically important difference
HrQL	Health related quality of life
SCD	Sickie cell disease

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Figure.
HABIT study flow diagram

Table 1

Subjects eligible for the PedsQL, PedsQL sickle cell disease module health related quality of life assessment, and sickle cell family responsibility measures at each study time point

	Baseline		3 months		6 months	
	Intervention	Control	Intervention	Control	Intervention	Control
Youth self-reported measures						
Total enrolled at study time point	18	10	16	9	16	9
Completed	18	10	16	9	16	9
Lost to follow up	0	0	2	1	2	1
Did not complete survey	0	0	0	0	0	0
Parent self-reported measures						
Total enrolled at study time point	18	10	16	9	16	9
Completed	18	9	16	9	16	9
Lost to follow up	0	0	2	1	2	1
Did not complete survey	0	1	0	0	0	0

Table 2

Comparison of Youth and Parents by Group at Baseline

	α	Total Sample N=28		Intervention group N=18			Control group N=10*			P value
		Mean $\pm$ SD	MCID SEM*	Mean $\pm$ SD	M	IQR	Mean $\pm$ SD	M	IQR	
Youth self-report										
PedsQL										
Total score	0.92	76.8 $\pm$ 17.0	4.8	71.8 $\pm$ 17.7	72.3	60.9, 87.0	85.8 $\pm$ 11.6	90.2	80.4, 92.4	0.03
Subscale scores										
Physical	0.87	77.0 $\pm$ 20.1	7.2	72.9 $\pm$ 20.1	70.3	65.6, 90.6	84.4 $\pm$ 18.9	87.5	81.3, 96.9	0.09
Social	0.84	83.8 $\pm$ 20.0	8.0	79.4 $\pm$ 22.7	82.5	65.0, 100	91.5 $\pm$ 11.3	97.5	85.0, 100	0.22
School	0.85	68.4 $\pm$ 22.8	8.8	63.1 $\pm$ 22.5	67.5	50.0, 80.0	78.0 $\pm$ 21.1	85.0	65.0, 95.0	0.09
Emotional	0.78	78.0 $\pm$ 20.7	9.7	71.4 $\pm$ 22.5	77.5	45.0, 90.0	90.0 $\pm$ 9.4	90.0	85.0, 100	0.02
PedsQL SCD										
Total score	0.95	68.7 $\pm$ 18.8	4.2	65.2 $\pm$ 18.8	64.2	55.8, 84.3	75.1 $\pm$ 18.2	79.7	62.8, 89.5	0.31
Subscale scores										
Pain Hurt	0.93	73.7 $\pm$ 24.4	6.5	71.8 $\pm$ 25.8	73.6	55.6, 94.4	77.2 $\pm$ 22.6	77.8	66.7, 100	0.55
Pain Impact	0.92	57.6 $\pm$ 33.6	9.5	54.6 $\pm$ 23.1	55.0	35.0, 62.5	63.0 $\pm$ 31.6	67.5	40.0, 90.0	0.55
Pain Mgmt.	0.92	56.7 $\pm$ 33.6	9.5	51.4 $\pm$ 34.8	50.0	25.0, 75.0	66.3 $\pm$ 30.6	75.0	50.0, 87.5	0.30
Worry I	0.80	67.1 $\pm$ 26.0	11.6	63.9 $\pm$ 26.5	60.0	45.0, 90.0	73.0 $\pm$ 25.4	80.0	50.0, 95.0	0.52
 Worry II	0.66	75.4 $\pm$ 25.1	14.6	77.1 $\pm$ 27.5	87.5	62.5, 100	72.5 $\pm$ 21.1	75.0	50.0, 87.5	0.33
Emotions	0.90	65.6 $\pm$ 36.3	11.5	54.9 $\pm$ 40.0	62.5	12.5, 100	85.0 $\pm$ 16.5	87.5	75.0, 100	0.06
Treatment	0.75	79.1 $\pm$ 17.4	8.7	75.0 $\pm$ 18.6	75.0	60.7, 92.9	86.4 $\pm$ 12.7	85.7	78.6, 100	0.12
Commun. I	0.77	77.1 $\pm$ 24.4	11.7	71.3 $\pm$ 26.5	70.8	50.0, 100	87.5 $\pm$ 16.3	91.7	75.0, 100	0.17
Commun. II	0.85	66.7 $\pm$ 33.7	13.1	62.0 $\pm$ 34.2	54.2	33.3, 100	75.0 $\pm$ 32.9	83.3	66.7, 100	0.43
Parent proxy-report										
Self-management Responsibility	0.75	20.1 $\pm$ 5.0	2.5	20.7 $\pm$ 5.3	22.5	18.0, 24.0	19.2 $\pm$ 4.7	20.0	18.0, 21.0	0.27
Dyad concordance	0.71	4.4 $\pm$ 2.5	1.4	4.2 $\pm$ 2.4	3.5	2.0, 5.0	4.7 $\pm$ 2.8	5.0	2.0, 6.0	0.58
PedsQL										

	α	Total Sample N=28			Intervention group N=18			Control group N=10*			P value
		Mean±SD	MCID	SEM*	Mean±SD	M	IQR	Mean±SD	M	IQR	
Total score	0.94	70.5±20.8	5.5		68.7±22.4	73.4	58.7, 83.7	73.9±17.7	66.3	64.1, 84.8	0.78
Subscale scores											
Physical	0.91	69.2±25.1	8.7		68.8±25.6	71.9	56.3, 84.4	70.1±25.6	78.1	50.0, 90.6	0.86
 Social	0.80	79.6±23.0	10.3		78.6±24.1	90.0	60.0, 100	81.7±21.7	90.0	65.0, 100	0.75
School	0.86	57.8±28.0	10.8		54.2±28.5	45.0	40.0, 75.0	65.0±27.3	50.0	45.0, 100	0.26
Emotional	0.83	75.9±22.7	9.1		73.3±25.7	80.0	60.0, 95.0	81.1±15.2	80.0	70.0, 90.0	0.62
PedsQL SCD											
Total score	0.97	62.1±20.4	3.5		60.2±22.6	60.5	44.7, 77.4	65.8±15.6	63.8	55.2, 79.7	0.66
Subscale scores											
 Pain Hurt	0.94	69.4±25.3	6.2		68.7±27.4	73.6	47.2, 94.4	70.9±21.9	75.0	47.7, 77.8	0.90
Pain Impact	0.96	51.1 ±27.3	5.5		47.2±27.4	45.4	25.4, 62.5	58.7±27.1	57.5	41.2, 77.5	0.44
Pain Mgmt.	0.95	58.9±33.9	7.6		57.7±36.0	62.5	25.0, 100	61.3±31.1	50.0	50.0, 87.5	0.88
Worry I	0.90	45.0±30.1	9.5		46.6±33.2	45.0	23.2, 60.8	41.8±24.4	41.6	25.0, 55.0	0.86
Worry II	0.91	58.9±37.9	11.4		60.1±40.2	75.0	14.5, 100	56.4±35.0	62.5	50.0, 75.0	0.69
Emotions	0.92	62.1±38.0	10.7		58.6±41.1	75.0	14.5, 100	67.1±32.7	75.0	50.0, 100	0.81
Treatment	0.82	71.8±22.5	9.5		69.4±26.2	72.0	51.7, 92.9	76.6±11.8	72.0	69.7, 86.3	0.61
Commun. I	0.86	81.5±28.4	10.6		79.5±31.8	100	66.7, 100	85.5±21.2	91.7	75.0, 100	0.93
Commun. II	0.89	66.8±31.0	10.3		62.0±32.9	58.3	41.7, 100	76.2±26.1	83.3	66.7, 100	0.28
Self-management Responsibility	0.75	15.3± 3.6	1.8		16.1± 3.9	15.5	13.0, 19.0	13.8± 2.3	14.0	12.0, 16.0	0.12

Note: α =Cronbach alpha; SD=standard deviation; M=median; MCID = Minimal Clinical Important Difference; SEM indicates standard error of measurement and was derived by multiplying the standard deviation by the square root of 1- α ; Commun. = communication;

* 10 control youth and 9 control parents completed surveys at baseline

Table 3

Youth and parent-proxy reported outcomes

	Baseline		3 months		6 months	
	Intervention N=18 Mean±SD	Control N=10* Mean±SD	Intervention N=16 Mean±SD	Control N=9 Mean±SD	Intervention N=16 Mean±SD	Control N=9 Mean±SD
Youth self-report						
PedsQL						
Total score	71.8±17.7	85.8±11.6	76.0±19.2	82.5±16.4	79.3±19.0	81.0±15.9
Subscale scores						
Physical	72.9±20.1	84.4±18.9	80.1±19.0	85.4±16.3	81.6±18.0	82.3±13.9
Social	79.4±22.7	91.5±11.3	80.6±24.4	87.8±15.4	80.9±25.8	86.7±18.9
School	63.1±22.5	78.0±21.1	67.8±23.0	71.1±23.7	74.1±22.3	72.8±26.7
Emotional	71.4±22.5	90.0± 9.4	73.1±25.2	83.9±21.3	79.4±25.0	81.7±13.5
PedsQL SCD						
Total score	65.2±18.8	75.1±18.2	74.5±16.5	76.8±18.3	77.7±18.5	74.6±21.2
Subscale scores						
Pain Hurt	71.8±25.8	77.2±22.6	79.5±16.2	84.3±22.3	78.1±19.7	81.5±23.9
Pain Impact	54.6±23.1	63.0±31.6	62.2±28.2	67.5±31.7	62.7±31.9	64.2±30.3
Pain Management	51.4±34.8	66.3±30.6	65.6±29.0	77.8±25.6	72.7±30.0	70.8±25.0
Worry I	63.9±26.5	73.0±25.4	73.4±26.2	66.1±20.0	81.3±22.6	56.7±36.5
Worry II	77.1±27.5	72.5±21.1	75.0±26.2	76.4±20.2	87.5±27.0	80.6±34.3
Emotions	54.9±40.0	85.0±16.5	73.4±24.9	72.2±24.8	82.5±23.0	73.6±32.7
Treatment	75.0±18.6	86.4±12.7	84.6±14.6	86.5±17.7	85.9± 14.1	86.5±17.4
Communication. I	71.3±26.5	87.5±16.3	84.4±20.2	81.5±23.9	91.7±14.3	88.0±21.7
Communication. II	62.0±34.2	75.0±32.9	75.5±26.6	78.7±22.1	82.8±25.0	75.9±30.5
Self-management responsibility	20.7± 5.3	19.2± 4.7	21.2± 5.6	21.0± 3.7	22.3± 3.6	19.6± 4.8
Parent-proxy report						
PedsQL						
Total score	68.7±22.4	73.9±17.7	80.3±18.6	82.0±13.0	81.9± 16.3	82.4±13.3
Subscale scores						

	Baseline				3 months				6 months			
	Intervention		Control		Intervention		Control		Intervention		Control	
	N=18	Mean±SD	N=10*	Mean±SD	N=16	Mean±SD	N=9	Mean±SD	N=16	Mean±SD	N=9	Mean±SD
Physical		68.8±25.6		70.1±25.6		83.2±19.0		81.3±20.6		78.1±19.8		80.6±19.9
Social		78.6±24.1		81.7±21.7		83.8±21.3		87.2±20.5		87.8±20.1		88.9±15/2
School		54.2±28.5		65.0±27.3		73.1±20.9		74.4±20.4		81.3±19.0		78.9±19.8
Emotional		73.3±25.7		81.1±15.2		79.4±20.9		85.6±15.3		82.5±21.5		82.2±17.3
PedsQL SCD												
Total score		60.2±22.6		65.8±15.6		76.3±20.0		75.5±18.4		81.9±18.5		83.9±15.3
Subscale scores												
Pain Hurt		68.7±27.4		70.9±21.9		82.0±18.5		87.3±18.1		85.9±14.7		86.1±23.3
Pain Impact		47.2±27.4		58.7±27.1		72.6±29.2		73.2±30.0		78.0±24.5		80.0±24.5
Pain Management		57.7±36.0		61.3±31.1		82.0±20.4		71.3±36.6		85.9±18.8		75.0±22.5
Worry I		46.6±33.2		41.8±24.4		59.5±36.3		47.6±29.6		75.4±30.1		67.0±36.0
Worry II		60.1±40.2		56.4±35.0		67.0±35.2		59.4±37.5		70.9±34.7		74.3±38.4
Emotions		58.6±41.1		67.1±32.7		74.6±33.8		69.2±43.8		82.3±27.7		97.2± 5.5
Treatment		69.4±26.2		76.6±11.8		82.2±20.6		84.0±24.7		84.4±16.4		92.5± 9.4
Communication. I		79.5±31.8		85.5±21.2		92.8±16.2		94.4± 8.3		88.8±24.5		98.1± 3.7
Communication. II		62.0±32.9		76.2±26.1		73.1±34.5		73.0±32.3		85.1±25.2		88.0±18.2
Self-management responsibility												
		16.1± 3.9		13.8± 2.3		17.0± 4.8		14.7± 3.7		17.8± 3.6		14.8± 2.8
Dyad concordance		4.2± 2.4		4.7± 2.8		5.8± 2.1		4.4± 3.2		5.3± 2.1		4.1± 2.1

* 10 control youth and 9 control parents completed surveys at baseline; SD=standard deviation; SCD=sickle cell disease

Table 4

Psychosocial outcomes as reported by youth and parents adjusting for group assignment, time and multiple comparisons

Measure	Youth reported outcome			Parent reported outcome		
	Estimate	SE	p value	Estimate	SE	p value
PedsQL						
Total score						
Intercept	85.6	5.50	<0.001	75.2	6.10	<0.001
Time	-0.61	0.64	0.34	1.40	0.97	0.15
Time × Intervention	1.64	0.80	0.04	0.36	1.21	0.77
Physical subscale						
Intercept	85.2	5.73	<0.001	72.1	7.26	<0.001
Time	-0.14	0.78	0.86	1.74	1.30	0.19
Time × Intervention	1.40	0.99	0.16	-0.53	1.61	0.74
Social subscale						
Intercept	91.2	6.88	<0.001	82.3	6.72	<0.001
Time	-0.68	0.79	0.39	1.20	1.32	0.36
Time × Intervention	0.65	0.98	0.51	0.12	1.63	0.94
School subscale						
Intercept	76.8	7.08	<0.001	65.8	7.40	<0.001
Time	-0.73	1.07	0.49	2.31	1.46	0.12
Time × Intervention	2.35	1.32	0.081	1.85	1.81	0.31
Emotional subscale						
Intercept	89.5	6.60	<0.001	82.4	7.06	<0.001
Time	-1.26	0.92	0.17	0.19	1.03	0.86
Time × Intervention	2.50	1.14	0.034	0.93	1.29	0.47
PedsQL Sickle cell disease module						
Total score						
Intercept	75.9	5.97	<0.001	66.0	6.36	<0.001
Time	0.18	0.95	0.85	3.02	1.10	0.008
Time × Intervention	1.51	1.18	0.21	0.16	1.37	0.91
Pain Hurt subscale						

Measure	Youth reported outcome				Parent reported outcome			
	Estimate	SE	p value	* p value	Estimate	SE	p value	* p value
Intercept	79.0	7.28	<0.001		73.9	6.90	<0.001	
Time	1.03	0.95	0.29	0.89	2.53	1.30	0.06	0.15
Time × Intervention	-0.76	1.19	0.53	0.61	-0.07	1.62	0.97	0.97
Pain Impact subscale								
Intercept	64.5	8.81	<0.001		60.0	8.72	<0.001	
Time	0.56	1.56	0.72	0.89	3.55	1.65	0.04	0.14
Time × Intervention	0.51	1.95	0.79	0.85	1.23	2.05	0.55	0.97
Pain Management subscale								
Intercept	69.2	8.90	<0.001		62.4	8.60	<0.001	
Time	0.94	2.06	0.65	0.89	2.28	2.12	0.29	0.36
Time × Intervention	2.46	2.57	0.34	0.46	2.42	2.63	0.36	0.97
Worry I subscale								
Intercept	73.6	7.98	<0.001		39.5	10.12	<0.001	
Time	-2.47	1.47	0.10	0.89	4.20	2.05	0.046	0.14
Time × Intervention	5.00	1.83	0.009	0.075	0.28	2.55	0.91	0.97
Worry II subscale								
Intercept	72.5	7.86	<0.001		54.5	11.86	<0.001	
Time	1.35	1.74	0.44	0.89	2.97	1.86	0.12	0.23
Time × Intervention	0.27	2.18	0.90	0.90	-1.65	2.32	0.48	0.97
Emotions subscale								
Intercept	82.9	8.71	<0.001		62.8	10.97	<0.001	
Time	-1.84	1.86	0.33	0.89	5.02	1.90	0.01	0.175
Time × Intervention	6.16	2.34	0.01	0.075	-1.81	2.37	0.45	0.97
Treatment subscale								
Intercept	86.5	4.84	<0.001		76.4	6.59	<0.001	
Time	0.13	0.92	0.89	0.89	2.65	1.18	0.029	0.14
Time × Intervention	1.61	1.14	0.17	0.32	-0.48	1.47	0.75	0.97
Communication I subscale								
Intercept	85.7	6.43	<0.001		86.4	7.00	<0.001	
Time	0.17	1.17	0.88	0.89	2.11	1.48	0.16	0.24

Measure	Youth reported outcome				Parent reported outcome			
	Estimate	SE	p value	* p value	Estimate	SE	p value	* p value
Time × Intervention	2.97	1.47	0.048	0.14	-0.70	1.84	0.70	0.97
Communication II subscale								
Intercept	76.2	9.04	<0.001		73.2	9.28	<0.001	
Time	0.43	1.50	0.78	0.89	1.96	1.91	0.31	0.36
Time × Intervention	2.45	1.88	0.20	0.32	1.63	2.37	0.50	0.97
Self-management responsibility								
Intercept	19.7	1.45	<0.001		13.9	1.13	<0.001	
Time	0.06	0.23	0.79	-	0.17	0.21	0.43	-
Time × Intervention	0.24	0.29	0.41	-	0.07	0.26	0.79	-
Dyad self-management responsibility concordance 3 months								
Intercept	4.7	0.79	<0.001					
Time	-0.08	0.22	0.75	0.75				
Time × Intervention	0.58	0.31	0.07	0.14				
Dyad self-management responsibility concordance 6 months								
Intercept	4.7	0.72	<0.001					
Time	-0.10	0.16	0.55	0.79				
Time × Intervention	0.27	0.20	0.18	0.27				

SE = standard error; Time was defined as a numeric variable: Time 0 = baseline; Time 1 = 3 months; Time 2 = 6 months;

* adjusted for multiple comparisons using Benjamini-Hochberg procedure

Table 5

Difference in score change in youth and parent proxy-reported health related quality of life and dyad concordance outcomes at 6 months

	Youth reported		Parent-proxy reported	
	$\beta \pm$ Standard error	Score change (95% CI)	$\beta \pm$ Standard error	Score change (95% CI)
PedsQL				
Total score	1.64 $\pm$ 0.8	9.8 (0.4, 19.2)	0.36 $\pm$ 1.21	2.2 (–12.1, 16.4)
Subscale scores				
Physical	1.40 $\pm$ 0.99	8.4 (–3.2, 20.0)	–0.53 $\pm$ 1.61	–3.2 (–22.1, 15.8)
Social	0.65 $\pm$ 0.98	3.9 (–7.6, 15.4)	0.12 $\pm$ 1.63	0.7 (–18.4, 19.9)
School	2.35 $\pm$ 1.32	14.1 (–1.4, 29.6)	1.85 $\pm$ 1.81	11.1 (–10.2, 32.4)
Emotional	2.50 $\pm$ 1.14	15.0 (1.6, 28.4)	0.93 $\pm$ 1.29	5.6 (–9.6, 20.8)
PedsQL SCD				
Total score	1.51 $\pm$ 1.18	9.1 (–4.8, 22.9)	0.16 $\pm$ 1.37	1.0 (–15.2, 17.1)
Subscale scores				
Pain Hurt	–0.76 $\pm$ 1.19	–4.6 (–18.6, 9.4)	–0.07 $\pm$ 1.62	–0.4 (–19.5, 18.6)
Pain Impact	0.51 $\pm$ 1.95	3.1 (–19.9, 26.0)	1.23 $\pm$ 2.05	7.4 (–16.7, 31.5)
Pain Mgmt.	2.46 $\pm$ 2.57	14.8 (–15.5, 45.0)	2.42 $\pm$ 2.63	14.5 (–16.4, 45.4)
Worry I	5.00 $\pm$ 1.83	30.0 (8.5, 51.5)	0.28 $\pm$ 2.55	1.7 (–28.3, 31.7)
Worry II	0.27 $\pm$ 2.18	1.6 (–24.0, 27.3)	–1.65 $\pm$ 2.32	–9.9 (–37.2, 17.4)
Emotions	6.16 $\pm$ 2.34	37.0 (9.4, 64.5)	–1.81 $\pm$ 2.37	–10.9 (–38.7, 17.0)
Treatment	1.61 $\pm$ 1.14	9.7 (–3.7, 23.1)	–0.48 $\pm$ 1.47	–2.9 (–20.2, 14.4)
Commun. I	2.97 $\pm$ 1.47	17.8 (0.5, 35.1)	–0.70 $\pm$ 1.84	–4.2 (–25.8, 17.4)
Commun. II	2.45 $\pm$ 1.88	14.7 (–7.4, 36.8)	1.63 $\pm$ 2.37	9.8 (–18.1, 37.7)
Self-management responsibility	0.24 $\pm$ 0.29	1.4 (–2.0, 4.9)	0.07 $\pm$ 0.26	0.40 (–2.6, 3.5)
Dyad concordance 3 months				
Dyad concordance 6 months	0.58 $\pm$ 0.31	3.5 (–0.2, 7.1)		
	0.27 $\pm$ 0.20	1.6 (–0.7, 4.0)		

Note: Commun. = Communication; Difference in score change = $(\beta \times 6) \pm (1.96 \times (\text{Standard error} \times 6))$; CI = Confidence interval; Score changes that exceed Minimal Clinically Important Differences are bolded