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# A randomised controlled provider-blinded trial of community health workers in sickle cell anaemia: effects on haematologic variables and hydroxyurea adherence

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## Summary

Hydroxyurea (hydroxycarbamide) (HU) for sickle cell anaemia (SCA) is underutilised. Case management is an evidence-based health management strategy and in this regard patient navigators (PNs) may provide case management for SCA. We hypothesised that HU-eligible patients exposed to PNs would have improved indicators of starting HU and HU adherence. We randomised 224 HU-eligible SCA adults into the Start Healing in Patients with Hydroxyurea (SHIP-HU) Trial. All patients received care from trained physicians using standardised HU prescribing protocols. Patients in the Experimental arm received case management and education from PNs through multiple contacts. All other patients were regarded as the Control arm and received specialty care alone. Study physicians were blinded to the study arms and did not interact with PNs. At baseline, 6 and 12 months we assessed and compared laboratory parameters and HU adherence indicators. Experimental patients had higher 6-month mean fetal haemoglobin (HbF) levels than controls. But at 12 months, mean HbF was similar, as were white blood cell count, absolute neutrophil count, total haemoglobin, platelet count and mean corpuscular volume. At 12 months there were fewer experimental patients missing HU doses than controls (mean 1·8 vs. 4·5, $P = 0·0098$), and more recent HU prescriptions filled than for controls (mean 53·8 vs. 92 days, median 27·5 vs. 62 days, $P = 0·0082$). Mean HU doses were largely similar. We detected behavioural improvements in HU adherence but no haematological improvements by adding PNs to specialty care.

**Keywords:** Hydroxyurea, sickle cell disease, adherence, case management.

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## Introduction

Improving the suboptimal quality, outcomes, cost and equity of Americans with chronic conditions and individuals in lower socioeconomic strata[1] requires improving communication and collaboration among patients, their families and care teams. Community health workers (CHWs)–lay members of a community who work in association with the local health care system–can improve such communication and collaboration.[2,3] They can improve self-care for diabetes, leading to better glycaemic control.[4] They can help reduce emergency department (ED) visits, length of stay, and the number of complications, and increase focus on family.[5] They can also be effective patient navigators (PNs), by helping clients obtain non-medical services, reduce barriers to care, such as transportation, build trust between providers and patients as well as increase providers' cultural sensitivity and the cost effectiveness of care.[6–8] Yet, despite strong evidence for its efficacy, care by CHWs is often not reimbursed, thereby excluding it from the mainstream of US health care delivery.[9]

Sickle cell disease (SCD) is a chronic genetic haemoglobinopathy affecting individuals, often in the lower socioeconomic strata, and in the US, mostly African-Americans.[10] SCD causes anaemia, fatigue, progressive organ failure and severe, ubiquitous pain. As a result of dramatic improvements in SCD care in the past 40 years,[11,12] however, the vast majority of SCD patients survive to adulthood rather than die in childhood.[13]

But quality of life and quality of care remain poor for adolescents and adults with SCD in the US.[14–21]

There is a paucity of adult SCD health care providers. Most experienced adult SCD providers are in large, regional referral centers,[22] while the majority of adults with SCD receive care from primary care and emergency providers. Furthermore, the quality of care and geographic access to specialists in SCD may be poor,[23] lagging behind that of patients with other special health care needs transitioning from paediatric to adult care.[17–19,24] Moreover, lack of a US public health care system leaves many adult SCD patients and their families without adequate care or insurance coverage. Thus, the National Academies of Science, Engineering and Medicine in 2020 declared SCD a disparities disease and a public health challenge, with mortality at stake.[25]

Hydroxyurea (hydroxycarbamide) (HU) is the first Food and Drug Administration-approved remittive drug for SCD.[26–28] In adults, HU reduces the incidence of pain, frequency of hospitalisations and need for blood transfusions by approximately 50%.[29] It reduces mortality[30] and increases long-term survival proportionally to the length of therapy[31] and it is cost-effective.[32,33] The National Heart, Lung and Blood Institute (NHLBI) issued consensus recommendations on HU in 2008. declaring it of public good.[34,35] NHLBI guidelines recommend that adult patients with genotypes HbSS and HbSbeta$^0$ thalassemia, together known as sickle cell anaemia (SCA), are eligible for HU.[36] Despite these recommendations and overwhelming efficacy data,[37] HU remains underutilised. Not only do providers under prescribe HU,[38] but also patients may not accept HU when it is offered.[39]

Although publications report that patients with SCD may benefit from the services of CHWs,[40] whether CHWs can independently increase new HU starts and/or improve SCA HU adherence has not been specifically studied. We, therefore, undertook a randomised controlled trial to rigorously test whether trained CHWs working as PNs would increase new HU starts and/or improve HU adherence, independent of other elements of SCA specialty care in patients with SCD.

## Methods

### *Design*

We conducted a specialty, provider-blinded, randomised controlled trial. Patients were electronically randomised. Randomisation was stratified by study site as well as blocked to assure treatment allocation balance over time. Block size was varied to help maintain blinding of allocation. Patients were strictly instructed not to reveal to physicians whether they were assigned a PN and not to unblind assessors or providers at clinical or study visits by mentioning their PN or activities related to their PN. Study physicians and PNs were both instructed not to collaborate with one another, in order to not unblind study physicians. If the blinding was broken during care or assessment, assessors or providers reported this to the site Principal Investigator, who made arrangements for an alternative assessor at subsequent contacts. The blinding was reported as broken a total of four times during the study.

### *Setting*

All patients were recruited while receiving care at one of six sickle cell clinical specialty sites. Study sites are each standalone regional SCD referral centres, but without geographically remote cooperating, referring (spoke) sites. Adult sites included those at Virginia Commonwealth University in Richmond and Eastern Virginia Medical School in Norfolk, Virginia, and East Carolina University in Greenville, North Carolina. Paediatric sites included those at the Children's Hospital of Richmond at VCU, Children's Hospital of the Kings Daughters in Norfolk, and Pediatric Specialists of Virginia in Falls Church, Virginia.

### *Patients*

We included adults with SCA either eligible for or previously prescribed HU, aged 15 or over. This included all patients with haemoglobin SS and SB0. Patients on chronic transfusions or transfused in the previous 3 months were excluded. Patients who were known to be pregnant or planned to



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become pregnant during the study period were also excluded. Six patients were enrolled and randomised who did not meet study inclusion criteria. Patients were compensated $50 at each study visit.

### *Interventions*

Subjects randomised to the Experimental arm received case management by PNs plus specialty care. Subjects randomised to the control Arm received specialty care alone.

PN case management in the Experimental arm was provided by specially trained CHWs. One PN was assigned to each Experimental arm patient. We developed a job description and job qualifications for the PNs (Appendix S1), a comprehensive, standard curriculum for PNs (Appendix S2) as well as behavioural standards for patient contact (Appendix S3) using consultants, our own research[41] and national standards.[42] PNs made patient contacts either in person or by phone after the baseline study visit, then at least weekly. They attempted monthly home visits for the initial 6 months after patient enrolment and a minimum of bi-weekly contacts for the second 6 months. PN caseloads were intended to be 1:10 for best outcomes and cases were reassigned to balance caseloads. The maximum caseload was 20 patients. Special progress notes were developed for PNs to document their activities. PNs were trained to assess individual barriers to HU uptake and adherence and techniques to address these barriers on an individual patient level at each visit.

All patients in both arms received specialty care that was designed to increase HU new starts and improve adherence. Physicians and advanced care providers at the specialty care sites provided all care. Not all sites used the same prescribing protocol. Prior to study enrolment, providers at four sites adopted a standardised HU prescribing protocol (Appendix S4), initially developed at the University of Florida, that was consistent with National Institutes of Health (NIH) guidelines subsequently published in 2014. The study protocol called for 3-month intervals for visits and escalation of HU dosing to the maximum tolerated dose. The remaining two sites joined after the guidelines were published and used their own prescribing guidelines.

### *Measurements*

All patients, regardless of arm, were assessed by trained research assistants blinded to patient assignment. Patients made in-person official study visits at 0 (baseline), 6, and 12 months, but often came to the sites or gave laboratory specimens more frequently. Patients were not assessed if they were in the ED or in hospital. During study visits, participants gave blood samples for full blood count (fBC) including white blood count (WBC), granulocyte or absolute neutrophil count (ANC), total haemoglobin (Hb), platelet count (Plt), mean corpuscular volume (MCV), percentage of fetal haemoglobin (HbF) via high performance liquid chromatography (HPLC) and electrophoresis, and pregnancy testing. The main outcome variable was HbF concentration measured by HPLC on an intent-to-treat (ITT) basis. All other haematological variables were secondary outcomes. Also, patients completed a written survey battery during visits at baseline, 6 and 12 months. HU dosing data were reported by providers and also independently by patient report. HU use and adherence data were also collected by patient report. Demographics recorded at baseline included age, race, gender, education, and self-reported household income. SCD genotype was determined locally at study entry, but specimens were sent to a central laboratory for HPLC haemoglobin determination and haemoglobin electrophoresis.

Potential moderators included general mental and physical health scales from the Patient-Reported Outcomes Measurement Information System (PROMIS),[43,44] sickle cell social support from the Transition Intervention Program Readiness for Transition (TIP-RFT) assessment,[45,46] self-efficacy,[47,48] coping,[49] site, baseline HU use (yes/no) and baseline HU adherence.

Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Virginia Commonwealth University.[50,51]

*Analysis. Modified intention-to-treat*—Analysis employed modified intention-to-treat (mITT) to comparison of study arms, which excluded the six inappropriately enrolled patients and which included any patient that had follow-up data (at 6 months, 12 months, or both). Any baseline laboratory data that were missing were imputed using a fully conditional specification regression method, with the final imputed baseline value being the mean of M = 10 replications. We imputed two values of MCV, three for HbF, WBC, Hb and Plt and 23 values for ANC and reticulocyte count. Baseline variables were compared between study arms to measure the adequacy of randomisation or assess for loss-to-follow-up bias.

Analysis of the main outcome used a mixed model approach with the HbF values at 6 and 12 months as outcome measures, random intercept to cope with multiple measurements over time, treatment arm as the main effect, a term for visit (6 or 12 months) and an interaction of visit with treatment arm. Covariates included the stratification variable of study site and the baseline value of HbF. When treatment differences varied by visit, results were presented separately by visit. Similar methods were used for the secondary outcome measures. A 95% confidence interval (CI) was presented for differences in mean between the experimental and control arms; a CI including 0 indicated the difference was not statistically significant.

For the main outcome HbF, we examined for potential effect modifiers. Analysis of covariance tested main effects of study site, baseline HbF, treatment arm and moderator, along with an interaction term between treatment arm and

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moderator. A significant interaction term indicated effect modification.

*Full intention-to-treat and per protocol*—We also performed identical comparative analyses for the full ITT sample of all randomised patients, all visits with laboratory data and a per-protocol analysis. For a visit to be part of the per-protocol analyses, laboratory values had to be from up to 45 days before or after the 6-month interval or 1-year interval from randomisation. Some mITT patients were completely excluded from the per-protocol analysis because they appeared to have been transfused within 3 months of the baseline visit (% HbA at baseline was >15).[8]

*Adherence*—Adherence for those taking HU was self-reported, measured by the number of days patients reported not taking HU as prescribed. The most recent HU date a prescription was filled was obtained either from the patient's prescription bottle, if brought to their appointment, and/or by a call to the patient's pharmacy. When sources disagreed about HU dose, we used the higher reported dose for analysis.

As missing more than 20% of days, or as a most recent HU prescription fill date greater than 90 days prior to assessment. We also compared the median number of days of missing doses and the time the prescription was filled. Analyses used the chi-square test and the non-parametric Wilson rank sum test.

Sample size—Sample size to achieve 80% power was estimated assuming an absolute difference of HbF level of 2·4% between arms, what we considered to be a conservative and small, but achievable change with behavioural intervention. With an HbF standard deviation (SD) of 5·5%, and the absolute values of HbF estimated from the literature and our own previous data, we needed 84 analysable patients per arm at a time point (168 total). Assuming a 20% dropout rate after enrolment, we needed to enrol 105 patients per arm (210 total). A later revision of sample size, using 25% dropout, increased the necessary enrolment to 112 patients per arm (224 total).

## Study results

### *Patient characteristics*

The CONSORT flow diagram in Fig 1 demonstrates that 912 patients were assessed for eligibility. Fully 688 patients were excluded yielding 224 randomised patients. Of the excluded patients, 345 had an excluded genotype, 19 were pregnant or planning to become pregnant, 45 were on chronic transfusions, 40 were excluded for miscellaneous reasons; 248 were not interested or were unresponsive to enrolment attempts, and two died before they could be randomised. The lost to follow-up rate or incomplete outcome evaluation rate at 6 or 12 months was approximately 20% in both arms, similar to recently published randomised controlled trials of new SCD

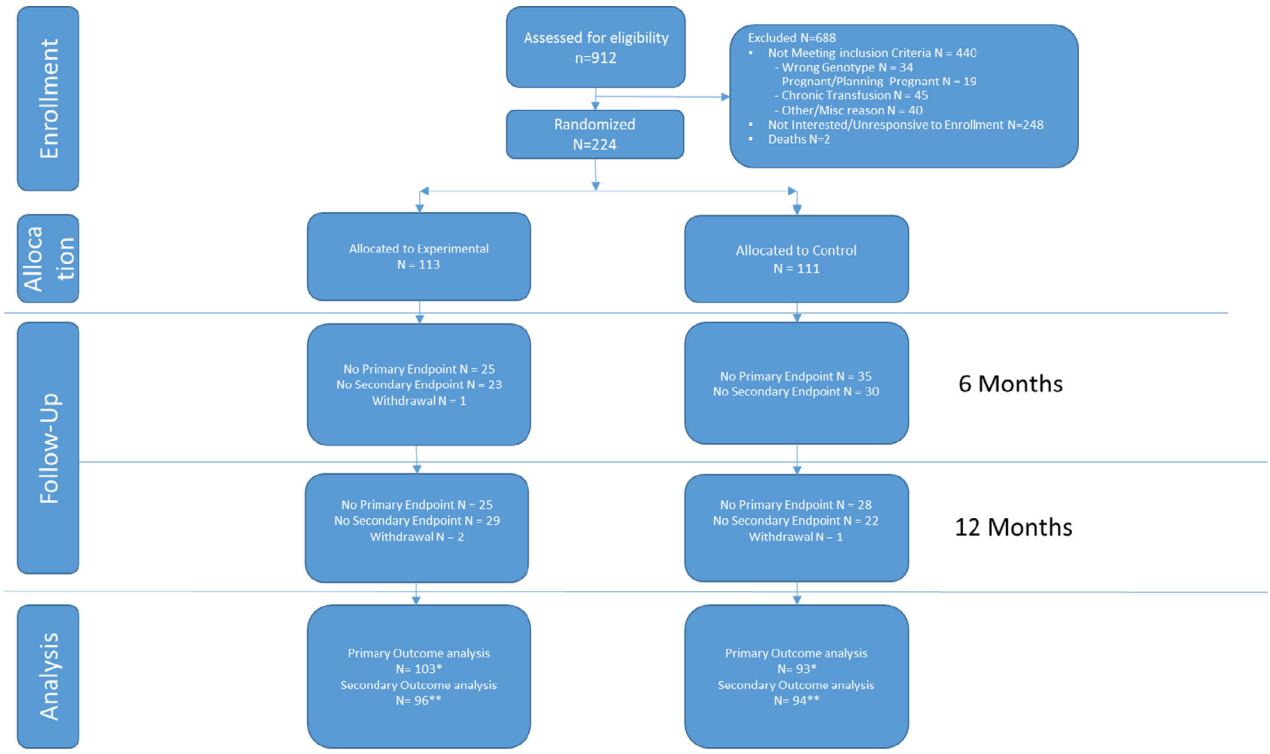


**Fig 1.** CONSORT diagram, Start Healing in Patients with Hydroxyurea randomized controlled trial. [Colour figure can be viewed at wileyonlinelibrary.com]



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**Table I.** Baseline characteristics of experimental and control patients, modified intention-to-treat sample.

| | Experimental $n$ = 99 Freq. (%) | Control $n$ = 101 Freq. (%) | $P$-value |
|---|---|---|---|
| Age, mean (± SD) years | 30·1(13·3) | 29·6 (12·0) | 0·7921 |
| Male | 47 (47·5) | 45 (44·5) | 0·6787 |
| Married | 25 (25·5) | 21 (20·8) | 0·4299 |
| HbSS | 85 (85·9) | 87 (86·1) | 0·9545 |
| On HU at baseline | 84 (84·8) | 79 (78·2) | 0·2273 |
| Education* | | | 0·1277 |
| <HS | 11 (11·5) | 13 (12·9) | |
| HS | 35 (36·5) | 44 (43·6) | |
| Some college | 39 (40·6) | 41 (40·6) | |
| College + | 11 (11·5) | 3 (3·0) | |
| Household income, US$* | | | 0·2223† |
| <10 000 | 38 (42·7) | 37(43·0) | |
| 10 000–19 999 | 18 (20·2) | 11 (12·8) | |
| 20 000–29 999 | 8 (9·0) | 19 (22·1) | |
| 30 000–39 999 | 5 (5·6) | 5 (5·8) | |
| 40 000–49 999 | 3 (3·4) | 4 (4·6) | |
| 50 000–59 999 | 6 (6·7) | 3 (3·5) | |
| > = 60 000 | 11 (12·4) | 7 (8·1) | |
| Sites | | | 0·9366 |
| A | 42 (42·4) | 46 (45·5) | |
| B | 9 (8·6) | 12 (11·9) | |
| C | 8 (8·1) | 6 (5·9) | |
| D | 8 (8·1) | 7 (6·9) | |
| E | 16 (16·2) | 13 (12·9) | |
| F | 16 (16·2) | 17 (16·8) | |

HS, high school; HU, hydroxyurea; SD, standard deviation.
Excludes six inappropriately enrolled and randomised patients. Includes patients with either 6-month or 12-month follow-up data or both.
*Missing responses: 25 for income and three for education.
†Fisher's exact test.

therapies.[52,53] Table I shows baseline characteristics for the mITT sample, consisting of the 200 of 224 randomised patients who had at least one HbF or FBC laboratory value at follow-up and were appropriately randomised. Patients' mean age was 30·1 years (range 15–70); 45·6% were male, 86% were genotype HbSS and 81·5% had been prescribed HU at baseline. There were more patients on HU at baseline in the experimental arm (84·8%) compared to the control arm (78·2%), although the difference did not reach statistical significance ($P$ = 0·2273).

Patients included in the mITT analysis were compared to those without any follow-up, on age, sex, marital status, HU status, education, household income, genotype, and clinical site to assess for potential bias. The only significant difference between the groups was that both the adult and paediatric sites at one geographic location was missing more follow-up than the others. Similar results were found when comparing those specifically with and without HbF at follow-up.

### *Fetal Haemoglobin levels*

Figure 2 is a waterfall plot of the change in HbF level by patient for both the experimental and control arms from baseline to 12 months. Changes in HbF varied from worsening to improvement in each arm, but there were extreme changes for only a few patients in each arm. Only nine patients (9·1%) in the experimental arm and 13 patients in the control arm (12·9%) improved their HbF by >5% ($P$ = 0·3929).

Table II compares haematological parameters between the experimental and control arms for the mITT sample. Supplemental Table SI shows exact sample sizes for Table II analyses. Table II presents crude baseline values as well as 6-month and 12-month visit values, adjusted for baseline and study site. The last column shows the differences between the experimental and control arms, and 95% CIs, controlling for baseline values and study site, as per the mixed-model analysis. Compared to the control arm, mean ± SD experimental arm HbF levels were statistically significantly higher at the 6-month visit (12·6 ± 0·6 vs. 10·8 ± 0·6, difference: 1·84, 95% CI: [0·32–3·37]). But they were slightly lower, though not statistically significantly lower, at the 12-month visit [11·4 ± 0·6 vs. 11·6 ± 0·6. difference: −0·25, 95% CI: (−1·76 to 1·26)].

Supplemental Table SII shows that results for HbF levels for the mITT sample were consistent across study sites ($P$ = 0·8043, 0·4987 at 6 and 12 months respectively). Supplemental Tables SIII and SIV show that results for the full ITT ($n$ = 224) and per protocol ($n$ = 154) analyses respectively, were analogous to the mITT result. These HbF level comparisons showed no significant difference between treatment arms at either the 6-month or 12-month visits.

Supplemental Table SV shows analysis of HbF results to determine whether effects were modified by baseline physical and mental health, self-efficacy, social support, or coping. Since in the mITT the treatment effect varied in opposite directions at 6 months *versus* 12 months, analyses were performed separately for the two follow-up time points. None of the potential modifiers was statistically significant at any time point. Also, neither baseline HU use (yes/no), any HU use during the trial (yes/no), baseline adherence among HU users, clinical site, nor baseline HbF group (≤5, 5–10, ≥10) was a modifier of the treatment effect at 6 or 12 months.

### *Other haematological parameters*

There were no significant differences between treatment arms at 6 or 12 months for any other laboratory variables, including Hb, WBC, Plt, MCV and ANC.

### *Adherence*

Table III shows that at 6 months, self-report adherence data from 119 patients showed no differences in the percentage of

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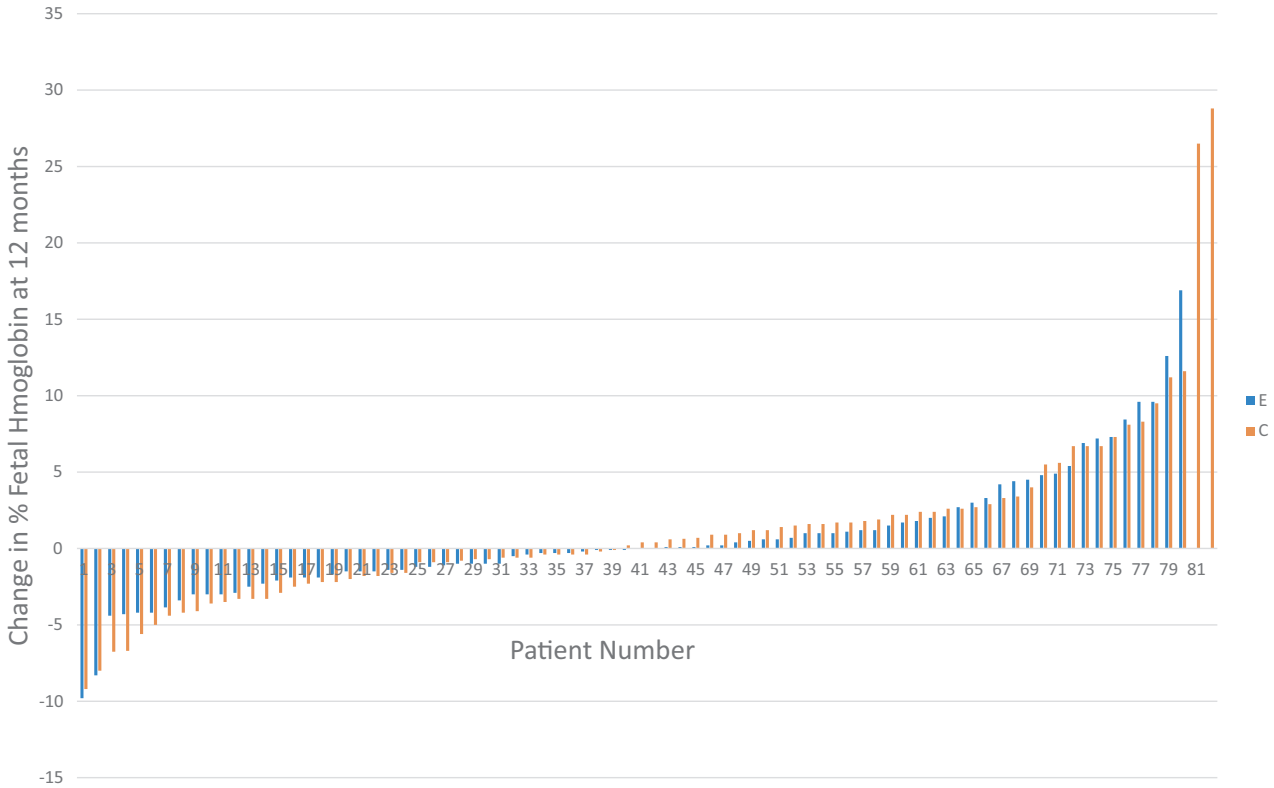


**Fig 2.** Waterfall plot of absolute change in % Fetal Hemoglobin, Experimental Arm (E, in blue) and Control Arm (C, in red). [Colour figure can be viewed at wileyonlinelibrary.com]

**Table II.** Modified ITT laboratory results, means ± standard error of the mean and experimental vs. control groups.

| | Baseline | | 6 months | | 12 months | | |
|---|---|---|---|---|---|---|---|
| | Experimental mean ± SEM ($n$ = 84–97‡) | Control mean ± SEM ($n$ = 89–94) | Experimental Adjusted mean ± SEM ($n$ = 68–83) | Control adjusted mean ± SEM ($n$ = 66–81) | Experimental adjusted mean ± SEM ($n$ = 65–80) | Control adjusted mean ± SEM ($n$ = 77–88) | Difference, Experimental – Control (95% CI)* |
| HbF† | 9·8 ± 0·7 | 11·9 ± 0·8 | 12·6 ± 0·6 | 10·8 ± 0·6 | 11·4 ± 0·6 | 11·6 ± 0·6 | 1·84 (0·32, 3·37)†<br>−0·25 (−1·76, 1·26) |
| MCV | 99·1 ± 1·5 | 98·3 ± 1·4 | 100·5 ± 1·1 | 101·3 ± 1·1 | 98·9 ± 1·2 | 100·2 ± 1·1 | −1·01 (−3·42, 1·40) |
| WBC | 9·2 ± 0·4 | 9·7 ± 0·4 | 9·2 ± 0·4 | 9·6 ± 0·4 | 9·2 ± 0·4 | 9·5 ± 0·4 | −0·27 (−1·07, 0·54) |
| ANC | 4·8 ± 0·3 | 5·2 ± 0·3 | 5·0 ± 0·4 | 5·4 ± 0·4 | 5·1 ± 0·4 | 5·2 ± 0·3 | −0·21 (−0·94,0·52) |
| Hb | 8·8 ± 0·2 | 8·6 ± 0·2 | 8·8 ± 0·1 | 8·7 ± 0·1 | 8·7 ± 0·1 | 8·9 ± 0·1 | −0·07 (−0·38,0·24) |
| Retic | 10·2 ± 0·6 | 10·4 ± 0·5 | 10·1 ± 0·6 | 9·7 ± 0·6 | 10·1 ± 0·6 | 10·1 ± 0·6 | 0·21 (−1·10,1·51) |
| Plt | 397·4 ± 19·9 | 368·7 ± 15·5 | 346·3 ± 16·6 | 361·8 ± 17·0 | 358·2 ± 17·2 | 371·8 ± 16·4 | −14·5 (−49·6,20·5) |

ANC, absolute neutrophil count; Hb, total hemoglobin; HbF, percentage of fetal haemoglobin; MCV, mean corpuscular volume; Plt, platelet count; Retic, reticulocyte count WBC, white blood cell count. Values at 6 and 12 months are adjusted for baseline and clinical site.

*If 95% confidence interval (CI) contains 0, then difference is not significant. If significant differences by visit, showing differences experimental-control and 95% CI separately for 6 months and 12 months.

†Significantly different.

‡Sample size for different laboratories vary, showing the range of values. Supplemental Table SI has exact values.

patients who reported that they missed any HU doses between treatment arms (experimental, 56·9%; control, 60·4%; $P$ = 0·7049) or in patients who missed more than 20% of their doses (experimental, 18·7% vs. control: 12·5%, $P$ = 0·3728). At 12 months, more patients in the control arm missed any dose of HU compared to the experimental arm (experimental, 43·3% vs. control, 63·3%, $P$ = 0·0281) and had >20% non-adherence (5·6% vs. 21·4%, $P$ = 0·0153).



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**Table III.** Hydroxyurea (HU) non-adherence, from self-report of missing at least one HU dose or taking HU differently in last 30 days, and time from last prescription fill to visit for experimental vs. control groups.

| | 6 months | | 12 months | | *P*-values | |
|---|---|---|---|---|---|---|
| | Experimental *n* (%) | Control *n* (%) | Experimental *n* (%) | Control *n* (%) | 6 months | 12 months |
| Any missed or different dose, last 30 days | 37/65 (56·9) | 32/53 (60·4) | 26/60 (43·3) | 38/60 (63·3) | 0·7049 | 0·0281 |
| >20% Missed or changed dose last 30 days | 12/64 (18·7) | 6/48 (12·5) | 3/54 (5·6) | 12/56 (21·4) | 0·3728 | 0·0153 |
| Prescription filled >90 days before visit | 13/57 (22·8) | 11/50 (22·0) | 7/50 (14·0) | 16/53 (30·2) | 0·9205 | 0·0486 |

**Table IV.** Hydroxyurea non-adherence, based on self-report of number of days missing at least one hydroxyurea dose or taking hydroxyurea differently from prescribed – last 30 days; and days from last prescription fill to visit.

| | 6 months | | 12 months | | *P*-values | |
|---|---|---|---|---|---|---|
| | Experimental | Control | Experimental | Control | 6 months | 12 months |
| Number of days missed or taken differently | 4·4 (7·4)<br>2 (4·5)<br>*n* = 64 | 4·2 (8·5)<br>2 (3)<br>*n* = 48 | 1·8 (4·7)<br>0 (2)<br>*n* = 54 | 4·5 (7·6)<br>2 (4·5)<br>*n* = 56 | 0·6194 | 0·0098 |
| Prescription fill time | 64·5 (79·0)<br>35 (71·0)<br>*n* = 57 | 65·2 (82·3)<br>31 (86)<br>*n* = 50 | 53·8 (79·8)<br>27·5 (44)<br>*n* = 50 | 92·0 (115·3)<br>61 (76)<br>*n* = 53 | 0·6642 | 0·0239 |

Mean (standard deviation) and median (interquartile range) and sample size presented.

**Table V.** Change in hydroxyurea utilisation at 6 months and 12 months, experimental vs. control groups.

| | 6 months | | 12 months | |
|---|---|---|---|---|
| | Experimental (*n* = 87) | Control (*n* = 80) | Experimental (*n* = 83) | Control (*n* = 75) |
| HU uptake | 3/14 (21·4) | 5/16 (31·2) | 2/14 (4·3) | 8/17 (47) |
| Loss of HU usage | 3/73 (2·9) | 0/64 (0) | 3/69 (4·3) | 0/58 (0) |

HU, hydroxyurea.

Table IV shows the median number of days of missing doses or taking HU not as prescribed was similar at 6 months but was significantly less for the experimental arm at 12 months (experimental vs. control: mean 1·8 vs. 4·5, median 0 vs. 2 respectively, $P = 0{\cdot}0098$). More than twice as many patients in the control arm as in the experimental arm had not filled their prescription for HU within 90 days of their 12-month study visit (experimental 14% vs. control 30·2%, $P = 0{\cdot}0486$). Patients in the experimental arm had filled their prescription prior to the 12-month study visit more recently (experimental vs. control, mean 53·8 vs. 92 days, median 27·5 vs. 62 days, $P = 0{\cdot}0082$).

Table V shows the change in HU utilisation status from baseline, by arm and at 6 and 12 months. Only patients in the experimental arm went from being on HU at baseline to not being on HU at 6 months or 12 months. Paradoxically, more control arm patients had initiated HU.

### *HU dosing*

The mean daily HU dose did not differ between the two arms at 6 months (experimental arm 1468 mg, control arm 1402 mg) or 12 months (experimental arm 1487 mg, control arm 1405 mg). The mean maximum HU dose achieved at 6 and 12 month visits (excluding doses reported at other clinical visits) also did not differ (experimental arm 1580 mg, control arm 1463 mg, $P = 0{\cdot}10$). However, the mean ± SD maximum HU dose achieved differed when all reported clinical visits were included (experimental arm 1656·8 ± 519·6 mg, control arm 1503·1 ± 443·3 mg, $P = 0{\cdot}0354$).

## Discussion

Although HU is an effective, well tolerated, disease modifying therapy for the treatment of SCD, patient adherence remains poor. This study sought to increase new HU initiation and improve HU adherence by employing the use of CHWs, a strategy that has been demonstrated to be effective in other chronic disease care. Established patients at sickle cell treatment centres were randomised to receive standard care, or standard care augmented by involvement of a CHW. They were followed over the course of 12 months to assess the impact of CHW involvement on new HU initiation and adherence, as reflected by change in laboratory variables. We found no difference in haematological variables used to monitor HU adherence and response among patients randomised to 1 year of exposure to PNs *versus* those randomised to usual care, with one exception. Although HbF was

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significantly higher at the 6-month visit for the experimental *versus* control arms, when controlled for baseline values, it was actually slightly lower (although not statistically) at 12 months. There were no significant differences between the study arms for any other haematological values studied, including WBC, ANC, Hb, Plt, and MCV. A waterfall plot showed quite a variable change in HbF, with worsening as well as improvement. Very few patients in either arm achieved an improvement of HbF of more than 5%. Early adult US efficacy trials of HU for SCA also produced quite variable changes in HbF across all patients, but a mean improvement of at least 5–7% in HbF was seen in the highest quartile of responders or the best adherers (>80%), and the best reported mean improvement was 11–12%.[54,55]

We found very similar results in a full ITT analysis, a per-protocol analysis and an analysis by site, all conducted to look for consistency of outcomes. Interestingly, we found no differences at 6 months in several self-reported HU behavioural adherence measures by study arm, but better adherence at 12 months for the experimental arm, even though there was no resultant difference in HbF or other haematological variables by arm.

Several factors may have impacted these outcomes. First, the actual baseline level HbF (10·5%) was higher than we anticipated (approximately 8·4). Likely to be underlying this was the high HU prescription rate of 81·5% of enrolled patients at baseline, which exceeded the rates we calculated based on the published literature at the time of study initiation.[56] Yet, neither baseline HbF group (≤5%, 5–10%, ≥10%) nor HU status was found to be an effect modifier of the treatment comparison at 6 or 12 months. Depending on whether mean prescribed daily HU dose or maximum prescribed dose was used, there was no difference in prescribed dose by study arm. An unanticipated finding was that the mean daily dose for each group was lower than anticipated. Clearly, fewer patients than we desired reached maximum tolerated dose (MTD) in either study arm. We tried to approximate the number of patients who achieved MTD during the study period by reporting maximum achieved HU dosing during the study period. It was far lower than HU MTDs reported previously [Ware[26]]. This likely contributed to the minimal change in HbF levels across all patients.

The restrictive study design may have inhibited the efficacy of the PN intervention. In an effort to determine the independent effect of PNs, we chose to blind physicians to whether their patients were receiving a PN intervention and forbade interactions among study physicians and PNs, essentially excluding PNs from the care team. We took great care to preserve blinding, including requiring study physicians to report when the blind was broken inadvertently by study patients. This effectively blocked potentially useful communication and collaboration between PNs and HU prescribers that may have otherwise enhanced HU use and adherence. Perhaps using implementation science methodology and outcomes in the study design would have improved our understanding of the impact of PNs.

Other possible explanations for our findings include the differential or poor efficacy of individual PNs. Though we were not powered to look at these individual PN differences, we do not believe they were important. An analysis of effect size by individual PN did not find numerical differences in change of HbF level from baseline until 12 months.

In addition, there could have been differential efficacy of the PN intervention for patients on HU at baseline *versus* not at baseline, or patients who were poorly adherent *versus* partially adherent or highly adherent to HU. Subanalyses of efficacy within the PN arm according to baseline HU use and according to HU adherence not show differential efficacy (analyses not shown).

We are aware that other measures of HU adherence may not correspond with the results we report here, and that using a non-standardised measure of adherence is a study limitation. We decided against using secondary adherence and persistence measures that have been used in other studies, including drug assays (HU concentration, pharmacokinetics) and direct observation. We also attempted to use pill counts/current adherence[57] as well as review of prescription records and claims,[58–64] but this was incomplete because much of the archival pharmacy data was missing. For practical reasons, we did not attempt electronic monitoring devices, which perhaps are the reference standard, but are expensive and not often used.[65] We note that for any drug, each adherence measure captures only a subset of behaviours or determinants, with limited predictive validity[66] or correlation among measure types.[67,68]

Our results support prior studies that have shown that, for any drug, no single intervention has proven effective in improving adherence across trials.[69,70] Almost all effective interventions are complex, including combinations of more convenient care, information, reminders, self-monitoring, reinforcement, counselling, family therapy, psychological therapy, crisis intervention, telephone follow-up and supportive care.[71]

We are also aware that physician reluctance to prescribe partly explains underuse of HU, as do access and financing barriers. However, our study physicians were all highly experienced sickle cell specialists working at centres giving care to large numbers of patients. They were asked to follow a prescribing protocol consistent with NIH guidelines to advocate HU use at every visit for both PN exposed and unexposed patients. Our study, therefore, may not generalised to clinics or to HU prescribers less experienced or as aggressive as those in our study.

Underuse of HU remains a public health challenge with mortality of patients at stake. Effective solutions to alleviate SCD patient fears and improve adherence with HU are still needed. All work to date emphasises that more patients must be reached and given ample opportunity to initiate HU, and better encouraged to adhere to HU. Future studies may confirm whether specially trained HU PNs encourage HU adherence and are more effective in environments where HU use



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and adherence is low. Future work must incorporate implementation-science strategies in order to improve understanding of how and why PNs may improve sickle cell care. Options for study design might include a randomised, but non-blinded, study where CHWs/PNs work in tandem with other members of a team of providers to intervene to improve HU adherence. Or, a non-randomised study in environments where PNs are already working within care teams designed to encourage HU uptake and adherence.

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## Conflict of interest

The authors declare conflicts of interest.

## Ethics approval statement

The study was approved by the Virginia Commonwealth University Institutional review board (approval letter available upon request), as well as the institutional review boards of Eastern Virginia Medical School, Children's Hospital of the King's Daughters, Pediatric Specialists of Virginia (ceded to INOVA in Fairfax, Virginia), and East Carolina University.

## Patient consent statement

Written informed consent was obtained for each enrolled patient (forms on file).

## Clinical Trial Registration

Registration: ClinicalTrials.gov Identifier: NCT02197845.

## Data availability statement

Data collected in this study are available from the authors, and because the study was funded by NHLBI, are public domain. They are not yet available in BioLinCC, NHLBI's biologic specimen and data repository information coordinating centre that is free to the public [https://biolincc.nhlbi.nih.gov/home/] but should be within the next 2–3 years.

## Supporting Information

Additional Supporting Information may be found online in the Supporting Information section at the end of the article.

**Table SI**. Sample sizes corresponding to Table 2 analyses

**Table SII**. Percent fetal haemoglobin by Site. Means ± standard error of mean, experimental vs. control groups. Values at 6 and 12 months are adjusted for baseline. Treatment comparisons consistent across site at 6 and 12 months (p value for interaction between site and arm 0.8043 at 6 months, 0.5484 at 12 months).

**Table SIII**. All randomised patients (Full ITT sample). Laboratory results, means ± standard error of the mean, experimental vs. control groups. *HbF= percent fetal haemoglobin. MCV=mean corpuscular volume. WBC=white blood cell count. ANC=absolute neutrophil count. Hb=total haemoglobin. Retic=reticulocyte count. Plt=platelet count. † If significant differences by visit, showing differences experimental-control, and 95% CI separately for 6 months and 12 months ; If 95% CI contains 0, then difference is not significant; *significant difference between experimental and control groups.

**Table SIV**. Per protocol analysis (mITT sample, excluding pts if %A>15 at baseline; excluding lab values if not in window), means ± standard error of mean; experimental vs. control groups. Values at 6 and 12 months are adjusted for baseline and clinical site; HbF= percent fetal haemoglobin. MCV=mean corpuscular volume. WBC=white blood cell count. ANC=absolute neutrophil count. Hb=total haemoglobin. Retic=reticulocyte count. Plt=platelet count. † If 95% CI contains 0, then difference is not significant. If significant differences by visit, showing differences experimental-control, and 95% CI separately for 6 months and 12 months; * significantly different; ††sample size for different labs vary the range of values.

**Table SV**. Significance (p) of interactions of potential modifiers with treatment arm, for percent fetal haemoglobin. None of the variables showed significant effect modification. FU=follow-up. HU=hydroxyurea. %HbF= percent fetal haemoglobin.

**Appendix S1**. Job Description and Job Qualifications for a Patient Navigator.

**Appendix S2**. Comprehensive, standard curriculum for Patient Navigators. Enhancing Use of Hydroxyurea in Sickle Cell Disease Using Patient Navigators.

**Appendix S3**. Patient Navigator(PN) Do's and Do Not's List.

**Appendix S4**. Hydroxyurea Demonstration Project Clinical Practice Protocol.

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