Implementation of the therapeutic use of hydroxyurea for sickle cell disease management in resource-constrained settings: a systematic review of adoption, cost and acceptability

Nessa Ryan, Lotanna Dike, Temitope Ojo, Dorice Vieira, Obiageli Nnodu, Joyce Gyamfi, Emmanuel Peprah

ABSTRACT

Objectives Mortality associated with sickle cell disease (SCD) is high in many low- and middle-income countries (LMICs). Hydroxyurea, a medicine to effectively manage SCD, is not widely available in resource-constrained settings. We identified and synthesised the reported implementation outcomes for the therapeutic use of hydroxyurea for SCD in these settings.

Design Systematic review.

Data sources PubMed, Embase, Cochrane, Web of Science Plus, Global Health, CMIAHL, and PsychINFO were searched February through May 2019 without any restrictions on publication date.

Eligibility criteria We included empirical studies of hydroxyurea for management of SCD that were carried out in LMICs and reported on implementation outcomes.

Data extraction and synthesis Two reviewers independently assessed studies for inclusion, carried out data extraction using Proctor et al.'s implementation and health service outcomes, and assessed the risk of bias using ROBINS-I (Risk Of Bias In Non-Randomised Studies - of Interventions).

Results Two cross-sectional surveys (n=2) and one cohort study (n=1) reported implementation of hydroxyurea for SCD management, namely regarding outcomes of adoption (n=3), cost (n=3) and acceptability (n=1). These studies were conducted exclusively among paediatric and adult populations in clinical settings in Nigeria (n=2) or Jamaica (n=1). Adoption is low, as observed through reported provider practices and patient adherence, in part shaped by misinformation and fear of side effects among patients, provider beliefs regarding affordability and organisational challenges with procuring the medicine. There was no difference in the cost of hydroxyurea therapy compared with blood transfusion in the paediatric population in urban Jamaica. Risk of bias was low or moderate across the included studies.

Conclusions This review rigorously and systematically assessed the evidence on implementation of hydroxyurea in resource-constrained settings such as LMICs. Findings suggest that knowledge regarding implementation is low. To address the know-do gap and guide clinical practice, implementation research is needed. Integrating effective interventions into existing health systems to improve hydroxyurea uptake is essential to reducing SCD-associated mortality.

Strengths and limitations of this study

► Rigorous, systematic search of peer-reviewed literature on hydroxyurea for SCD management and assessment of implementation and health services outcomes.
► Application of an implementation outcomes framework in the global context.
► Exclusion of articles with variable reporting quality and non-peer-reviewed literature (eg, grey literature).
► The small sample size did not allow for meta-analyses to be conducted.

BACKGROUND

Sickle cell disease (SCD), an inherited blood disorder, has significant financial, social and psychosocial impacts and drains individuals, families and health systems. The number of individuals born with SCD, particularly in sub-Saharan Africa (SSA), makes treating the disease of primary importance. Affected individuals may experience anaemia, severe pain and other vaso-occlusive complications, acute chest syndrome, disproportionate hospitalisation and early mortality. Within SSA, where ~75% of the global SCD burden remains, over 300,000 individuals are born with SCD each year. Although poor data collection practices and reporting make it difficult to determine the true rate of SCD-attributable death, estimates suggest that SCD under-5 mortality in SSA is about 50%–90%. In SSA’s most populous nation of Nigeria, for example, it is estimated that more than...
150,000 children with SCD are born annually with over 70% dying before reaching the age of five. The high prevalence of SCD in Nigeria and other malaria-endemic SSA nations is attributed to the protective effect of the sickle cell trait against mortality from malaria. Various multilevel factors contribute to SCD morbidity and mortality in these settings, including poorly developed neonatal SCD screening programmes, lack of awareness of effective management options, lack of access to medicines and clinical support services, and limited health infrastructure.

Despite the disproportionate burden of SCD in SSA, the use of hydroxyurea, an effective medicine for SCD management, is <1% among patients with SCD in the region. Hydroxyurea works by increasing fetal haemoglobin and reducing the level of adhesion molecules, which may result in reduced painful crises, decreased episodes of acute chest syndrome, reduced organ damage and decreased need for blood transfusions and hospital admissions for the aforementioned issues. Consequently, the alleviation or reduction of these SCD comorbidities increases the survival rates of patients with SCD.

Concerns of safety and feasibility due to malaria endemicity and malnutrition, which could complicate benefits and use, were addressed in various trials establishing clinical effectiveness of hydroxyurea to reduce SCD morbidity and mortality in SSA. In the review by Mulaku et al, the authors establish the efficacy, effectiveness and safety of hydroxyurea for children, including children in low- and middle-income countries (LMICs). Recently, the Novel Use Of Hydroxyurea in an African Region with Malaria (NO HARM) trial conducted in Uganda found that hydroxyurea does not increase malaria risk in children. The Realizing Effectiveness Across Continents with Hydroxyurea (REACH) trial conducted in four African countries provided further evidence demonstrating the efficacy, feasibility and safety of hydroxyurea for SCD management in African children. Although the NO HARM and REACH trials examined the effect within controlled clinical environments of a clinical trial, results from a prospective cohort study that examined the real-world experience of hydroxyurea utilisation in Malawian children with SCD further substantiates results from these trials.

The underutilisation of hydroxyurea is a multifaceted problem related to a lack of awareness of its benefits by patients and providers, which contributes to patient non-adherence to the medication when available. Moreover, the lack of awareness also manifests as negative perceptions of doctors towards prescribing hydroxyurea for patients with SCD and negative parental and community perceptions of hydroxyurea based on lack of knowledge about the drug, its mode of action and a misunderstanding of the benefits of its utilisation. Other factors including availability and costs can be significant barriers for consistent utilisation in LMICs.

In light of the challenges of implementing hydroxyurea for effective SCD management, we conducted a systematic review to seek evidence of hydroxyurea use and to understand the reporting of implementation outcomes, particularly Proctor et al’s implementation research outcomes from the published literature. These outcomes can be used to assess the success of implementation and are defined in Table 1. Specifically, the objective of the study was to assess how implementation outcomes for the therapeutic use of hydroxyurea for sickle cell disease.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acceptability</td>
<td>The perception among implementation stakeholders (beneficiaries and implementers) that the innovation is agreeable, palatable or satisfactory.</td>
</tr>
<tr>
<td>Adoption</td>
<td>The intention, initial decision or action to try or employ the innovation (ie, uptake).</td>
</tr>
<tr>
<td>Appropriateness</td>
<td>The perceived fit, relevance or compatibility of the innovation for a given practice setting, provider, or beneficiary; and/or perceived fit of the innovation to address a particular issue or problem (therapeutic use of hydroxyurea for sickle cell disease).</td>
</tr>
<tr>
<td>Cost</td>
<td>(Incremental or implementation cost) is defined as the cost impact of an implementation effort.</td>
</tr>
<tr>
<td>Feasibility</td>
<td>The extent to which the innovation can be successfully used or carried out within a given agency or setting.</td>
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<tr>
<td>Fidelity</td>
<td>Degree to which the innovation can be implemented as it was prescribed in the original protocol or as it was intended by the programme developer.</td>
</tr>
<tr>
<td>Penetration</td>
<td>The integration of a practice within a service setting and its subsystems.</td>
</tr>
<tr>
<td>Sustainability</td>
<td>The extent to which a newly implemented innovation is maintained or institutionalised within a service setting’s ongoing, stable operations.</td>
</tr>
</tbody>
</table>

Based on types of outcomes in implementation research reported within Proctor et al’s taxonomy for implementation outcomes (Proctor et al).
World Bank. A sample of the search strategy is provided in online supplemental file 1. A research librarian supported the selection of each search strategy to maximise results for the respective database. The search was conducted February through May 2019 and the resulting articles were imported into ProQuest, RefWorks and then into Covidence and deduplicated. In Covidence, we conducted screening via title and abstract and then via full-text articles. During each step of the review process, the articles were screened independently by two researchers (LD and NR). Discrepancies between the authors about the eligibility of retrieved studies were resolved by discussion. The study protocol was registered on PROSPERO CRD42020155953.

Inclusion and exclusion criteria
We followed the Population, Intervention, Control, Outcome (i.e., PICO) format to structure our search. The population of interest was adult and paediatric patients with SCD receiving treatment in resource-constrained settings (ie, LMICs), as well as their clinical providers. The intervention of interest was the therapeutic use of hydroxyurea for SCD. There was no control group specified. The outcomes of interest were implementation outcomes. We included any peer-reviewed studies published in English and based on our search strategy without restrictions on publication year. We excluded trial protocols (without results), review papers, conference presentations, and studies that did not discuss implementation outcomes.

Data extraction
Data extraction was carried out independently with a structured form. Pertinent information, including study design, sample, study size and implementation outcomes, was extracted from the eligible studies. We used the taxonomy developed by Proctor et al, which included implementation outcomes (table 1) and service outcomes (table 2) to guide the extraction of data reported in the articles. The planned and reportable primary outcomes included adoption, cost and acceptability. Implementation outcomes are defined as ‘the effects of deliberate and purposive actions to implement new treatments, practices and services’ and serve as indicators to measure the effectiveness and success of evidence-based interventions (EBIs). Adoption is defined as the uptake and utilisation of hydroxyurea for the management of SCD in LMICs. Cost is defined as the financial implications for patients with SCD and the cost-effectiveness of hydroxyurea therapy for systems, as well as opportunity costs for providers. Acceptability is defined as the user’s perception and satisfaction with hydroxyurea therapy for SCD management. The planned and reported secondary outcomes included service outcomes, such as efficiency, safety, effectiveness, equity, patient-centredness and timeliness.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficiency</td>
<td>The avoidance of waste, including waste of equipment, supplies, ideas and energy.</td>
</tr>
<tr>
<td>Safety</td>
<td>The avoidance of injuries to patients from the care that is intended to help them.</td>
</tr>
<tr>
<td>Effectiveness</td>
<td>Provision of services based on scientific knowledge to all who could benefit and refraining from providing services to those not likely to benefit (avoiding underuse and overuse, respectively).</td>
</tr>
<tr>
<td>Equity</td>
<td>Provision of care that does not vary in quality because of personal characteristics such as gender, ethnicity, geographical location and socioeconomic status.</td>
</tr>
<tr>
<td>Patient-centredness</td>
<td>Provision of care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions.</td>
</tr>
<tr>
<td>Timeliness</td>
<td>Reduction of waits and sometimes harmful delays for both those who receive and those who give care.</td>
</tr>
</tbody>
</table>

Table 2 Definitions of service outcomes

Based on types of outcomes in implementation research reported within Proctor et al’s taxonomy for implementation outcomes (Proctor et al) and informed by Institute of Medicine ‘Crossing the Quality Chasm: A New Health System for the 21st Century’ (IOM, 2001).

Quality assessment
We used the ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions) a tool for assessing risk of bias in non-randomised studies of interventions. The tool covers seven domains through which bias might be introduced in each study organised by preintervention (i.e., confounding, selection bias), at intervention (i.e., classification of interventions) or postintervention (i.e., deviations from intended interventions, missing data, outcome measurement, selection of the reported result). The judgements within each domain are interpreted and combined across domains to generate an overall risk of bias judgement for the outcome being assessed. Risk of bias can be categorised as low, moderate or serious. Further, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was completed for this study.

Patient and public involvement statement
It was not appropriate or possible to involve patients or the public in the design, conduct, reporting, or dissemination plans of our research.

RESULTS
An initial search of databases identified 1073 articles; 782 remained after duplicates were removed. Appraisal of titles and abstracts excluded 747 articles. Thirty-five full-text articles were assessed for eligibility; ultimately,
three were found to be relevant to the review topic. This process, as well as the reasons for exclusion at each stage, are presented in figure 1. Three articles were included from Nigeria (n=2) and Jamaica (n=1), both nations with large populations of individuals with SCD. Although our search did not have specific date ranges, all articles included in the final review and data extraction were recently published (ranging from 2014 to 2017) (tables 3 and 4). The studies were composed of adult and paediatric patients with SCD, as well as their clinical providers, and took place exclusively in clinical settings in resource-constrained settings. Only cross-sectional (n=2) and cohort (n=1) study designs were used. As across the ROBINS-I domains, the risk of bias was deemed low or moderate, each of the three studies represented a moderate risk of bias overall.

**Implementation outcomes**

Adoption (n=3) and cost (n=3) were the more frequently discussed implementation outcomes, compared with acceptability (n=1). These implementation outcomes were assessed either quantitatively (n=1) or qualitatively (n=2) (table 5). Outcomes were evaluated during implementation (n=2) or after implementation (n=1) of hydroxyurea therapy, but none evaluated implementation factors prior to rolling out the intervention. Implementation outcomes were assessed at the level of the patient (n=2), implementer (i.e., physician) (n=1) and health system (n=2).

Adoption of hydroxyurea therapy for SCD management was examined in all studies, primarily through self-reported provider practices. Within a hospital in Nigeria, 40% of surveyed adult patients with SCD had used hydroxyurea at least once. This cross-sectional survey reported that although 33% were currently using hydroxyurea for SCD management, only 7% of those adults completely adhered to the therapy.25 The mean starting dose and current dose for the study participant were 10.61 and 13.49 mg/kg daily, respectively, which the authors share is within guidelines of 10–20 mg/kg daily to initiate.25 This dose can be escalated at 2.5–5 mg/kg every 4 weeks to 6 months (average 8 weeks) until the maximum tolerable dose is achieved, while the patient is monitored for clinical and haematological responses.25 Within a cross-sectional survey of clinical providers serving both paediatric and adult patients with SCD throughout SCD clinics located in secondary and tertiary institutions across northern and southern Nigeria, the providers in almost half (44%) of clinics reported routinely prescribing hydroxyurea for SCD management.26 Although the authors surveyed only a small proportion of providers compared with the overall burden of disease, they noted the aforementioned is the typical representation of the services available in tertiary institutions in Nigeria.26 Whereas a cohort study from an urban hospital in Jamaica observed that 23% of the paediatric patient with SCD population received hydroxyurea therapy.27

Cost of hydroxyurea therapy was also discussed in all three studies. Cunningham-Myrie et al examined the cost-effectiveness of paediatric hydroxyurea therapy for the prevention of stroke recurrence in a hospital-based study in Jamaica.27 Findings from these studies show significantly shorter length of hospital stay and annual hospitalisation for the hydroxyurea group compared with the non-hydroxyurea group: 1.98 days and 11.14 (p<0.01), respectively.27 The authors concluded that there were no significant differences in the average daily and yearly cost of hydroxyurea therapy when compared with blood transfusion (p=0.5).27 The authors attributed the non-significant difference between both groups to the historically high patient monitoring cost associated with the early use of hydroxyurea.27 Further, the authors noted that these monitoring costs have since reduced because
of increased local and international hydroxyurea utilisation. Two studies from Nigeria noted that physicians only prescribed hydroxyurea therapy when they perceive the patient can afford the medicine, and patients reported they only use hydroxyurea therapy when they have funds to pay out-of-pocket. A proportion of adult patients (17%) who started hydroxyurea therapy, reported lack of funds as the reason for their non-compliance. The authors also discussed variability in the doctor’s prescription habits based on the patient’s ability to pay.

### Table 3  Characteristics of the studies and implementation outcomes (n=3)

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Country</th>
<th>Setting</th>
<th>Study design</th>
<th>Study duration (months)</th>
<th>Sample (N)</th>
<th>% female</th>
<th>Adoption</th>
<th>Cost</th>
<th>Acceptability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adewoyin (2017)</td>
<td>Nigeria</td>
<td>Hospital</td>
<td>Cross-sectional survey</td>
<td>3</td>
<td>Adult patients (60)</td>
<td>68</td>
<td>▶ 40% (24/60) of patients had ever used HU</td>
<td>▶ Reasons for poor adherence include lack of funds for the procurement of drugs</td>
<td>▶ 13% (3/24) patients with history of HU declined therapy due to fear of unknown adverse effects like cancer</td>
</tr>
<tr>
<td>Cunningham-Myrie (2015)</td>
<td>Jamaica</td>
<td>Hospital</td>
<td>Cohort (Comparing the cost of SCD management between patients on HU therapy vs patients not on HU therapy)</td>
<td>108</td>
<td>Paediatric patients (43)</td>
<td>55</td>
<td>▶ 23% received HU therapy</td>
<td>▶ No significant difference in the average daily and yearly cost of HU therapy for stroke recurrence compared with other SCD management options</td>
<td>▶ HU therapy was discontinued when patients reported fertility issues (3/24) and unbearable reactions (1/24)</td>
</tr>
<tr>
<td>Galadanci (2014)</td>
<td>Nigeria</td>
<td>18 clinics based in 11 Health centre and hospital (eight hospitals in the South and 3 in the North)</td>
<td>Cross-sectional survey</td>
<td>6</td>
<td>Providers in clinics serving both children and adults (18)</td>
<td>Not reported</td>
<td>▶ Only providers in 44% (8/18) clinics routinely prescribe HU as part of their SCD management practices</td>
<td>▶ Providers in 44% (8/18) clinics prescribe HU to patients who can afford it</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

SCD, sickle cell disease.
Acceptability was comparably less prioritised in the literature, as only one study reported on patient acceptability. Within a survey of adult patients with SCD at a hospital in Nigeria, the authors used patient refusal of hydroxyurea as a proxy indicator of low acceptability, as well as lack of perceived affordability for patients and organisational funds for procurement at facilities.

**Quality of evidence**

Indeed there is a lack of available peer-reviewed literature on this topic. Additionally, there is a lack of rigorous study design that moves beyond observational data collection to use of experimental design. As such, the risk of confounding, selection bias, bias in measurement classification of hydroxyurea, bias due to deviations from intended intervention, missing data, measurement of outcomes and reporting of the result was moderate to severe for all studies, except for the study by Cunningham-Myrie et al, wherein there was a low risk of bias for the domains of deviations from intended intervention, missing data and measurement of outcomes.

**DISCUSSION**

To the best of our knowledge, this is the first systematic review to evaluate the implementation outcomes of hydroxyurea therapy for sickle cell management in LMICs. The paucity of data on this topic is evident as only three articles could be included in the review. More research on the barriers of hydroxyurea utilisation focusing on the acceptability of patients and providers, accessibility, availability, cost and adoption should be conducted.

In LMICs such as Nigeria where the availability of other treatment options for SCD, such as blood transfusion and bone marrow transplant remain scarce, hydroxyurea could be a cost-effective treatment option for SCD management. The results from the articles included in this review were consistent with findings from the Pediatric Hydroxyurea Phase 3 Clinical Trial (BABY HUG) trial conducted by Wang et al in the USA; they examined the cost-effectiveness of hydroxyurea for SCD management in children in the placebo group versus hydroxyurea group. The findings suggest several benefits including respectively. Among a sample of paediatric patients with SCD in Jamaica hydroxyurea use was reported as a means to prevent stroke reoccurrence. In Nigeria, Adewoyin et al also assessed safety, as they discontinued hydroxyurea therapy for individuals who had unbearable reactions. Galadanci et al assessed equity, and they pointed out that doctors only prescribed hydroxyurea when patients could afford it.

**Facilitators and barriers to implementation**

Facilitators and barriers to implementation of hydroxyurea therapy in LMICs were included in all three studies (table 5). Facilitators include: reported patient awareness of hydroxyurea, previous use of hydroxyurea by patients with SCD and some routine prescription of hydroxyurea self-reported by providers, as well as cost-effectiveness for a paediatric population. Barriers include low adoption and patient adherence, perceived in part due to misinformation and fears of unknown side effects among patients (i.e., low patient acceptability), as well as lack of perceived affordability for patients and organisational funds for procurement at facilities.

**Service outcomes**

Effectiveness (n=2) was the more frequently discussed service outcome, compared with safety (n=1) and equity (n=1) (table 4). Effectiveness, reported as clinicohaematological benefits for a population of adult patients with SCD in Nigeria, was observed at a significant difference in the mean total leucocyte count (lower) and mean corpuscular volume (higher) ranges between regular and non-regular hydroxyurea users with p=0.024 and p=0.018, respectively.

**Table 4 Service outcomes of the studies included in the systematic review**

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Intervention components</th>
<th>Service outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adewoyin (2017)25</td>
<td>HU therapy for SCD adult patients in Nigeria.</td>
<td>Patterns of HU therapy (ie, adherence, non-compliance reason).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Mean starting dose=10. 61 mg/kg per day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Mean current dose=13.49 mg/kg per day.</td>
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<tr>
<td></td>
<td></td>
<td>– Median duration=12 months.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>► Lower MCV (p=0.02) and higher MCV (p=0.02) in the regular versus irregular HU groups. Safety</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– 1/24 (4.2%) participants reported skin rashes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– 1/24 (4.2%) skin hyperpigmentation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– 1/24 (4.2%) dizziness-lightheadedness, blurred vision.</td>
</tr>
<tr>
<td>Galadanci (2014)28</td>
<td>Current SCD management practices of providers serving dedicated SCD centres across Nigeria.</td>
<td>Equity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Doctors serving 8/18 surveyed clinics only prescribed HU to individuals who could afford it.</td>
</tr>
</tbody>
</table>

MCV, mean corpuscular volume; SCD, sickle cell disease ; TLC, total leucocyte count.
lower disability levels, lower disability-adjusted life years, greater productivity,\textsuperscript{26} and ultimately increased quality of life for the hydroxyurea group in comparison with the non-hydroxyurea group.

Like other health systems in LMICs, the Nigerian healthcare system is anchored on a three-tier system: primary, secondary and tertiary care.\textsuperscript{26, 29} Primary care is provided by the local government, secondary and tertiary care is delivered by the state and federal governments, respectively.\textsuperscript{26, 29} Medical services for patients with SCD are generally provided in secondary institutions, tertiary institutions and few clinics are dedicated solely to SCD management.\textsuperscript{26} These institutions are expected to provide the best possible care for patients with SCD. Both primary and secondary tiers should ideally feed to the tertiary tier but significant barriers exist; thus, improving outcomes for patients with SCD requires addressing the barriers that exist in the healthcare systems via system strengthening.

Another barrier to the implementation of hydroxyurea is the limited physician and patient education on hydroxyurea therapy; therefore, a potential implementation strategy should include training healthcare workers on the usefulness of the drug, guidelines for its use, standard hydroxyurea prescription practices, and patient counselling. Appropriate patient communication and education about the side effects of hydroxyurea could improve acceptability. Integrating the support of stakeholders, such as the government and other funders, could build advocacy to subsidise hydroxyurea therapy, which may address the cost burden on patients and improve patient adherence and subsequent health outcomes.

Adewoyin \textit{et al.} found that there was variability in the prescription habits among physicians in Nigeria because of the patient’s inability to pay and concerns about drug adverse effects.\textsuperscript{25} The physicians feared that hydroxyurea might contribute to the already fragile health state of patients with SCD.\textsuperscript{25} Luzzatto \textit{et al.} also reported fear of hydroxyurea therapy because of the lack of evidence of the safety profile of hydroxyurea in Africa.\textsuperscript{30} Proper definition and identification of these adverse symptoms can provide insightful information from which patients can make well-informed, evidence-based decisions about whether to use hydroxyurea and accept the therapy for the management of their condition, as long as they are able to afford the medication.

Poor affordability of hydroxyurea was one of the frequently cited reasons for lack of adherence in Nigeria. Similarly, in Tanzania, hydroxyurea therapy is cost prohibitive for some patients, as the price of the daily average hydroxyurea dose is US$1.20.\textsuperscript{30} In the Kenyan private sector, the Hydroxyurea 500 mg capsules of hydroxyurea is priced at US$0.47, which equates to US$14.00 for monthly hydroxyurea therapy.\textsuperscript{14} Aside from hydroxyurea costs, additional costs might be incurred from haematological lab tests and supplementary treatment for patient monitoring.\textsuperscript{14} Clearly, the development of novel methods for hydroxyurea cost reduction is imperative to address

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|}
\hline
\textbf{Studies} & \textbf{Adoption} & \textbf{Cost} & \textbf{Acceptability} \\
\hline
\textbf{Barriers} & \textbullet Only 4/24 (16.7\%) of adult patients completely adhered to HU therapy in a Nigerian hospital.* & \textbullet Lack of funds for utilisation of HU reported among adult patients in Nigerian hospital as reason for poor adherence * & \textbullet Three out of the 24 (12.5\%) patients who used HU at once opted out of HU because of the fear of unknown side effects.* \\
& \textbullet 23\% (10/43) paediatric patients received HU therapy in Jamaican hospital.† & & \\
& \textbullet 40\% (24/60) of adult patients utilised HU at least once in a Nigerian hospital.* & & \\
& \textbullet Only providers in (44\%) 8/18 of providers routinely prescribe HU as part of their SCD management practices in Nigerian clinic.‡ & & \\
\hline
\textbf{Facilitators} & \textbullet 57\% (34/60) of adult patients with SCD had heard of HU in a Nigerian hospital.* & \textbullet No significant difference in the average daily and yearly cost of HU therapy for stroke recurrence compared with other SCD management options.† & \textbullet Not reported \\
\hline
\end{tabular}
\caption{Facilitators and barriers to implementation of hydroxyurea (HU) for sickle cell therapy in low- and middle-income countries}
\end{table}


SCD, sickle cell disease.
the cost barrier associated with hydroxyurea utilisation. One recommendation would be for the local pharmacies to produce hydroxyurea or for qualified pharmacies to compound galenic hydroxyurea.30 Many researchers fail to acknowledge the presence of a highly effective locally manufactured brand of Hydroxyurea in Nigeria called Oxyurea by Bond Chemical Industries. The cost is N1313 for a 30 pack of 500mg, which, according to the national guideline, is less than US$4 per month for a child weighing up to 33kg.

Evidently, there is a paucity of peer-reviewed literature addressing EBIs for the effective implementation of hydroxyurea for SCD management in LMICs. Using the ROBINS-I tool for assessing risk of bias in non-randomised studies of interventions, we can see that most domains indicate moderate to serious risk of bias for the three included studies. There is a lack of rigorous study designs that move beyond observational data collection to the use of experimental design or even quasi-experimental design, as appropriate. This would allow for the testing of different intervention approaches and implementation strategies to be evaluated so that they can address the implementation context for a particular LMIC setting. Additionally, self-report of provider practices could be supplemented with the observation of patient–provider interaction to improve communication.

Study strengths and limitations
This study has several strengths including the use of rigorous, systematic search of peer-reviewed literature on hydroxyurea use for SCD management and assessment of implementation outcomes by multiple reviewers. While the studies provided useful information about the implementation outcomes, the following were some of the study specific limitations (1) Adewonyi et al did not explicitly state what constitutes the unbearable side effects listed as grounds for hydroxyurea therapy discontinuation (2) Galadanci et al set out to assess available SCD management practices by surveying doctors in SCD clinics to examine the number of SCD clinics that prescribe hydroxyurea for SCD management. Although the study’s aim was to describe the general services available, there was a missed opportunity to indicate how many providers actually prescribe hydroxyurea. This information, if provided, can help gauge doctors’ perception of hydroxyurea utilisation and help design interventions to rectify that. Finally, we did not include articles from the grey literature search as they have variable reporting quality, and the small number of included articles did not allow for meta-analyses to be conducted.

Considering the clinical effectiveness of hydroxyurea for SCD management, and documented low utilisation in LMICs, there is an urgent need and opportunity to reduce the burden of SCD as quickly as possible using EBIs. Evidence from existing systematic reviews suggests that effective implementation strategies are typically multilevel and tailored to the ecological context.31 However, communities and households in LMICs lack the resources and expertise needed to coordinate multilevel system changes without assistance. Effective collaboration with all three tiers of the healthcare system and experts in implementation science could prove useful in building the resources needed to implement effective EBIs to improve hydroxyurea uptake in Nigeria and other LMICs. The goal is to engage stakeholders who are versed in that context and can accurately inform the best strategy for the successful implementation of hydroxyurea in all settings for SCD management and potential barriers that may exist. These actions will foster health system strengthening and will ultimately facilitate effective SCD management strategies.31

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