Pediatric Neurology 125 (2021) 9–15

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Research Paper

# Capacity Building for Primary Stroke Prevention Teams in Children Living With Sickle Cell Anemia in Africa

Djamila L. Ghafuri, MD, MPH [a, b, 1], Brittany Covert Greene, MPH [a, 1], Bilya Musa, BS [c], Awwal Gambo, MS [c], Abdulrasheed Sani, MIM [d], Shehu Abdullahi, MD [e], Binta J. Wudil, MBBS [c], Halima Bello-Manga, MBBS [f], Safiya Gambo, MBBS [c], Matin Ghafuri, PharmD [a], Holly Cassell, MPH [g], Kathleen Neville, MD [h], Fenella Kirkham, MD, FRCPCH, Research [i], Adetola A. Kassim, MD [j], Muktar H. Aliyu, MBBS, DrPH [k], Michael R. DeBaun, MD, MPH [a], Lori C. Jordan, MD, PhD [b, *]

[a] *Vanderbilt-Meharry Sickle Cell Center for Excellence, Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee*
[b] *Division of Pediatric Neurology, Department of Pediatrics, Vanderbilt University of Medicine, Nashville, Tennessee*
[c] *Department of Pediatrics, Murtala Mohammed Specialist Hospital, Kano, Nigeria*
[d] *Department of Pediatrics, Barau Dikko Teaching Hospital/Kaduna State University, Kaduna, Nigeria*
[e] *Department of Pediatrics, Bayero University/Aminu Kano Teaching Hospital, Kano, Nigeria*
[f] *Department of Hematology and Blood Transfusion, Barau Dikko Teaching Hospital/Kaduna State University, Kaduna, Nigeria*
[g] *Vanderbilt Institute for Global Health, Vanderbilt University Medical Center, Nashville, Tennessee*
[h] *Divisions of Pediatric Hematology-Oncology and Clinical Pharmacology and Toxicology, Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, Arkansas*
[i] *Department of Pediatrics, University of Arkansas for Medical Sciences/Arkansas Children's Hospital, Little Rock, Arkansas*
[j] *Division of Hematology and Oncology, Department of Medicine, Vanderbilt University Medical Center, Vanderbilt-Ingram Cancer Center, Nashville, Tennessee*
[k] *Health Policy, Vanderbilt Institute for Global Health, Vanderbilt University Medical Center, Nashville, Tennessee*

ARTICLE INFO

*Article history:*
Received 14 June 2021
Accepted 28 August 2021
Available online 4 September 2021

*Keywords:*
Stroke prevention
Low-resource setting
Clinical research
Sickle cell anemia
Global health

ABSTRACT

*Background:* Nigeria has the highest proportion of children with sickle cell anemia (SCA) globally; an estimated 150,000 infants with SCA are born annually. Primary stroke prevention in children with SCA must include Nigeria. We describe capacity-building strategies in conjunction with two National Institutes of Health–funded primary stroke prevention trials (a feasibility trial and phase III randomized controlled trial) with initial hydroxyurea treatment for children with SCA and abnormal transcranial Doppler (TCD) velocities in Nigeria. We anticipated challenges to conducting clinical trials in a low-resource setting with a local team that had not previously been involved in clinical research and sought a sustainable strategy for primary stroke prevention.

*Methods:* This is a descriptive, prospective study of challenges, solutions, and research teams in two trials that enrolled a total of 679 children with SCA.

*Results:* As part of the capacity-building component of the trials, over eight years, 23 research personnel (physicians, nurses, research coordinators, a statistician, and a pharmacist) completed a one-month

Funding: Research reported in this publication was supported by the National Institute of Neurological Disorders, United States and Stroke of the National Institutes of Health, United States Grants R21NS080639, R01NS094041, K24-HL147017, Vanderbilt Endowed Chair Funds, and philanthropic awards from the Phillips Family and Afolabi Family. The findings and conclusions in this report are those of the authors and do not necessarily represent the National Institutes of Health's official position.

Author's Contributions: M.R.D, D.L.G., and L.C.J., had full access to all the data in the study and take responsibility for the integrity of the data and the data analyses' accuracy. The trials were designed by M.R.D, B.C.G., S.A., and L.C.J. The transcranial Doppler training was completed by H.B.-M., A.S., B.J.W., S.G., H.B.-M., S.A., A.S., and K.N.; L.C.J. and F.J.K. verified the strokes with video of neurological examinations; B.C.G. and D.L.G. collected and audited data integrity; M.G. and M.R.D. developed and initiated the e-prescription system at all sites; H.C., B.C.G., H.B.M., A.G., and M.R.D. were responsible for all VIRDE activities; A.A.K., A.G., and S.G. monitored the safety of the participants; B.C.G. and B.J.W. performed the analyses; M.R.D., B.C.G., S.A., L.C.J., and M.H.A. interpreted the results; and D.L.G., B.C.G., A.A.K., L.C.J., and M.R.D. wrote the manuscript. Prior to submission, all authors reviewed the manuscript.

Consent for Publication: The authors agree to sign a statement attesting authorship, disclosing all potential conflicts of interest, and releasing copyright.

Competing Interests: The authors declare no competing financial interests.

* Communications should be addressed to: Jordan; Division of Pediatric Neurology; Department of Pediatrics; 2200 Children's Way 11212; Nashville, TN 37232.

*E-mail address:* lori.jordan@vumc.org (L.C. Jordan).

[1] Co-first authors: DLG and BCG were equally responsible for the work described in this article.

https://doi.org/10.1016/j.pediatrneurol.2021.08.010

research governance and ethics training program at Vanderbilt University Medical Center, USA. A lead research coordinator for each site completed the Society of Clinical Research Professionals certification. TCD machines were donated; radiologists and nonradiologists were trained and certified to perform TCD. A scalable E-prescription was implemented to track hydroxyurea treatment. We worked with regional government officials to support ongoing TCD-based screening and funding for hydroxyurea for children with SCA at a high risk of stroke.

*Conclusions:* Our trials and capacity building demonstrate a sustainable strategy to initiate and maintain pediatric SCA primary stroke prevention programs in Africa.



## Introduction

Nigeria has the highest number of newborns with sickle cell anemia (SCA); more than 150,000 live births are affected with SCA annually, which is approximately 50% of newborns with SCA in the world.[1] Assuming no deaths, an estimated 16,500 children from each birth cohort born per year will have a clinically evident stroke by adolescence.[2] In high-income settings, transcranial Doppler (TCD) screening coupled with regular blood transfusion therapy for individuals with SCA and abnormal TCD velocities is associated with a reduction in the incidence rate of stroke from 11% to less than 1%.[3] However, limited strategies exist for primary stroke prevention in Africa, specifically in Nigeria, where most children with SCA are born. Significant barriers to preventing strokes in low-resource settings include inadequate safe blood supply and parent apprehension regarding the costs, safety, and feasibility of monthly blood transfusions.[4]

As part of the National Institutes of Health (NIH)–funded feasibility trial (**S**troke **P**revention **i**n **N**igeria **[**SPIN] trial, NCT01801423) and a subsequent R01-funded randomized controlled trial (Primary Prevention of Stroke in Children with Sickle Cell Disease in Nigeria, **S**troke **Pr**evention **i**n Ni**g**eria [SPRING] trial, NCT02560935), we engaged in research capacity building, quality improvement efforts, and partnerships with state Nigerian governments to build a sustainable strategy for primary stroke prevention in children with SCA living in a low-resource setting. The purpose of this report is to describe the opportunities and challenges in setting up and conducting a clinical trial in a low-resource setting. We focused on a sustainable approach for primary stroke prevention that would be viable after the trial was over to implement trial findings into clinical care for children with SCA living in a region of Africa where no prior pediatric SCA stroke prevention programs existed.

## Materials and Methods

Both the SPIN and SPRING trials were focused on primary stroke prevention with hydroxyurea in children with SCA in northern Nigeria. SPIN was a pilot, single-arm feasibility trial conducted at one site, Aminu Kano Teaching Hospital, Kano, Nigeria.[5] SPIN tested the hypothesis that moderate fixed-dose hydroxyurea (20 mg/kg/day) for primary stroke prevention was acceptable, feasible, and safe in a low-income setting (Kano, Nigeria). Twenty-nine children with abnormal TCD measurements in the middle cerebral artery (≥200 cm/second) were identified and treated with moderate fixed-dose hydroxyurea for primary stroke prevention, and 206 children were included in the comparison group without abnormal TCD measurements.

The SPRING trial was a three-site, double-blind, randomized controlled trial that assigned 220 children with SCA and abnormal TCD velocity (≥200 cm/second) to receive either low-dose (10 mg/kg/day) or moderate-dose (20 mg/kg/day) hydroxyurea and included a comparison group of 220 children with normal TCD velocity (≤170 cm/sec).[4] The catchment area for the SPRING trial in northern Nigeria included at least 40,000 children with SCA.

Study ethical approval was obtained from the institutional review boards of Aminu Kano Teaching Hospital, Kano, Nigeria; Murtala Mohammed Specialist Hospital, Kano, Nigeria; Barau Dikko Teaching Hospital, Kaduna, Nigeria; and Vanderbilt University Medical Center, Nashville, Tennessee, United States. The National Agency for Food and Drug Administration and Control in Nigeria approved the trial. A Data and Safety Monitoring Board appointed by the National Institute of Neurological Disorders and Stroke reviewed serious adverse events and study progress.

Participant inclusion criteria were children with confirmed hemoglobin SS or hemoglobin Sβ0 thalassemia, five to 12 years of age. Exclusion criteria were prior overt stroke (a focal neurological deficit of acute onset) based on history, focal neurological deficit on standardized neurological examination or concern for moderate or severe neurological deficit based on a positive "10 questions" screening,[6] hemoglobin less than 6 g/dL, and prior hydroxyurea prescription. All participants' guardians provided written informed consent prior to screening and enrollment, and children age 7 and above provided their assent. The clinical features of the population screened for eligibility are described elsewhere.[4,7]

This descriptive study focused on specific study challenges encountered in a low-resource setting and how these challenges were addressed with a goal of building capacity for research and clinical care with ongoing quality assurance and improvement processes.

## Results

### *Capacity building strategies*

#### *Selection of study sites for capacity building with no previous NIH-funded activity*

Before initiating the SPIN and SPRING trials,[8,9] the collaborating institutions had limited research activity and lacked existing infrastructure that met US government research governance requirements. Participant recruitment in the SPIN trial occurred at Aminu Kano Teaching Hospital in Kano, Nigeria. Participant recruitment in the SPRING trial included Aminu Kano Teaching Hospital in Kano, Nigeria; Murtala Muhammed Specialist Hospital in Kano, Nigeria; and the Barau Dikko Teaching Hospital in Kaduna, Nigeria (Table 1).

#### *Research governance training to improve the knowledge base of study personnel*

Given the inexperience in conducting any research for the three different research teams at each clinical trial site, we identified training capacity goals prior to and during the trials (Fig 1).

A formal portion of our strategy required vital members of each team to attend the Vanderbilt Institute for Research Development

and Ethics (VIRDE) program. The one-month course curriculum includes intensive training in research development and productivity tailored explicitly for research teams from low-resource settings. The structured course focuses on developing skills pertinent to the conduct of human subjects' research and grant writing techniques for individuals preparing a grant proposal for submission. After the training, a mock study section is held to enable review of the grant proposal and feedback by experts that are not involved in the proposed trial.

Additionally, all VIRDE scholars complete nine contact hours of tailored coursework in research ethics and governance. A review of the VIRDE's training milestones is displayed in Fig 1. A total of 23 individuals, including 15 physicians, 1 statistician, 2 nurses, 1 pharmacist, and 4 research coordinators, from the study sites completed the VIRDE training at Vanderbilt University Medical Center. For capacity building, the training was extended at the Nigerian study sites with peer-to-peer training for a team of more than 39 individuals (19 physicians, 3 nurses, 9 study coordinators/managers, 4 pharmacists, and 4 laboratory attendants). All study personnel were required to have completed human subjects research and Good Clinical Practices training before initiating the trials.

To maintain access to clinical research educational resources beyond the duration of the trials, research personnel became members of the Society of Clinical Research Professionals (SOCRA), a nonprofit, educational organization committed to providing education, certification, and networking opportunities to all persons involved in clinical research activities.[10] The SOCRA has more than 50 chapters worldwide. The Nigeria research team and graduates of the VIRDE program established the first Nigerian SOCRA chapter in 2019. Six research staff members working with the SPIN and SPRING trials passed the SOCRA international credentialing examination. Formal credentialling of research staff and the establishment of a SOCRA chapter in Nigeria demonstrate the feasibility of building research capacity and strengthening networking opportunities through collaborative efforts between an established international professional organization and local partners.

### *Communication plan to access completion of study milestones and accountability of study personnel*

For the duration of SPIN and SPRING trials, two one-hour meetings every week were held between the local site investigators and the members of the data coordinating centers to discuss operational metrics, study recruitment, data entry, solutions to new study site challenges, and other logistics pertinent to the conduct of the trials (Supplement Table 1).

A standing agenda was developed for all meetings and made available via email before the scheduled meeting. After each session, action items were circulated to investigators, study personnel, and collaborators, with responsible persons and deadlines. If a meeting was not held owing to scheduling conflicts, the study team submitted their respective weekly report via REDCap. All serious adverse events or study endpoints required immediate reporting to the principal investigator by the study site investigator, study personnel, or both. These events were discussed at the weekly meetings with an assessment of the appropriate research governance paperwork required for submission. A minimum of 6 hours per week was devoted to preparing, conducting, and following up postmeeting action items.

### *Unique challenges for clinical research in low-resource settings: low literacy rates, local industrial action, and the COVID-19 pandemic*

Low literacy or illiteracy is an obstacle to informed consent for clinical trials. Approximately 25% of the guardians of participants in the SPRING trial were unable to sign their names as part of informed consent. The team identified several strategies to address limited literacy in the guardians, including providing the informed consent and the intervention drug hydroxyurea handbook in Hausa (the participants' local language) that was subsequently taken to their home for others to review. A research coordinator also read and explained the informed consent in Hausa to the guardians. For those guardians that could not write their name, we used a thumbprint to acknowledge their consent with a witness.

Based on prior experience, the leadership team was aware of the risk of health care provider strikes during the trials. Thus, before starting both trials, study personnel at each respective study site developed proactive strategies to overcome the barriers anticipated by health care worker strikes. During the two trials (2012-2020), at least ten health care worker strikes occurred, for a minimum and maximum duration of 2 to 8 weeks, respectively.

In response to the COVID-19 pandemic, trial leadership promptly implemented strategies to protect participants, parents, caregivers, and study personnel by suspending all face-to-face contact, including monthly follow-up visits to complete physical examinations and laboratory assessments. Limited patient contact was allowed for participants who developed symptomatic medical concerns or experienced sudden onset neurological deficits. The overall objective continues to be the safety of patients, caregivers, and the clinical research community.

### *Ongoing formal training of Nigeria physician-scientists*

A significant impact of the capacity building during the conduct of these two trials was physician professional development. One of

**TABLE 1.**
Patient Population and Participant Recruitment at the Sites in the SPIN and the SPRING Trials in Kano and Kaduna, Nigeria

| Study | SPIN | SPRING | | |
|---|---|---|---|---|
| Study site | AKTH | | MMSH | BDTH |
| Location | Kano, Nigeria | | | Kaduna, Nigeria |
| Number of children with SCA seen in the last two years | +1700 | | +16,000 | +2100 |
| Number of children with SCA seen annually | 2010 | | 17,810 | 2100 |
| Number of children with SCA seen daily in clinic | 80 | | 72 | 10 |
| Number of active study personnel | 9 | 13 | 13 | 8 |
| Number screened for stroke prevention trials | 330 | 960 | | |
| Number of participants followed up in both study arms | 239 | 440 | | |

Abbreviations:
AKTH = Aminu Kano Teaching Hospital
BDTH = Barau Dikko Teaching Hospital
MMSH = Murtala Muhammad Specialist Hospital
SCA = sickle cell anemia
SPIN = Stroke Prevention Trial In Nigeria
SPRING = Primary Prevention of Stroke in Children with Sickle Cell Disease In Nigeria Trial

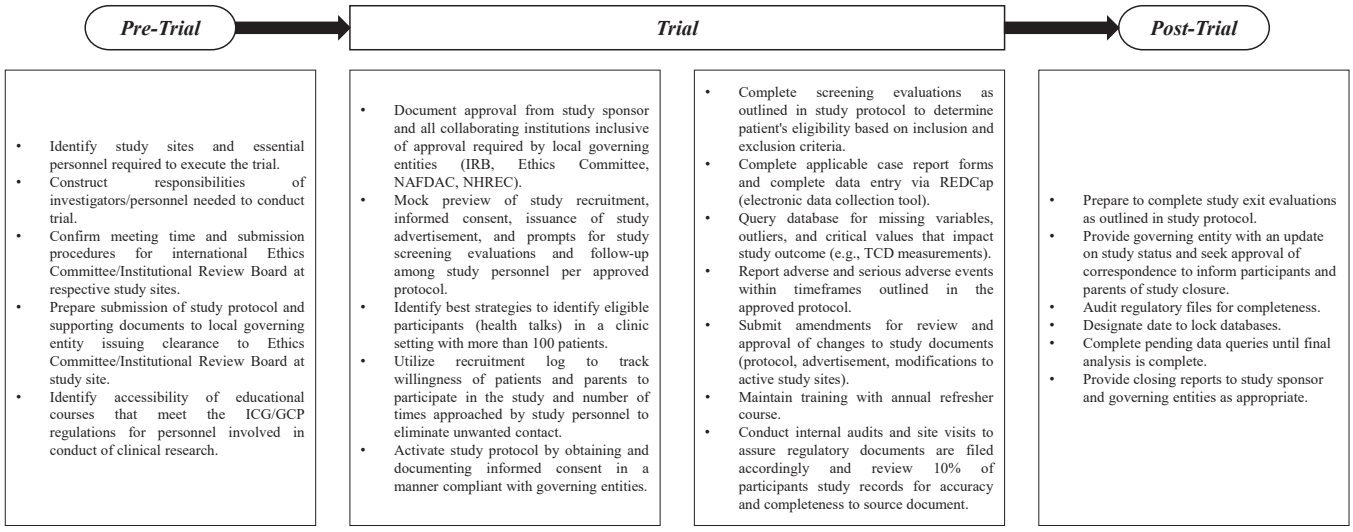


**FIGURE 1.** Pretrial and post-trial activity for stroke prevention trials in a low-resource setting. ICG, IRB, institutional review board; GCP, Good Clinical Practices; NAFDAC, National Agency for Food and Drug Administration and Control; NHREC, National Health Research Ethics Council; TCD, transcranial Doppler.

the multiple principal investigators for the SPRING trial is currently enrolled in a Ph.D. program in Epidemiology at the University of Alabama at Birmingham. Three physician-investigators received a one-year NIH-sponsored Fogarty training program award. Two physician-investigators received the American Society of Hematology Clinical Research Training Institute Award, a one-year education and mentoring program for hematology fellows and junior faculty at academic medical centers. One physician received the Fogarty International Center K43 Emerging Global Leader Award, a five-year NIH mentored research training grant. After eight years of conducting the two trials, the Nigerian research teams were able to complete all aspects of the trial without support from the data-coordinating center in the United States. Their responsibilities included screening children with SCA for abnormal TCD velocities, verifying abnormal velocities, starting hydroxyurea therapy for primary stroke prevention, and identifying children with stroke.

*Implementation of TCD ultrasound screening*

There were not enough TCD machines or qualified operators to conduct the trials or for use in clinical practice. With a large charitable donation, we were able to purchase ten TCD machines. We then focused on training health care personnel to perform TCD. Two Nigerian radiologists were trained in TCD by an experienced ultrasonographer from the United Kingdom, and their measured velocities were showed to have a low coefficient of variation and to be reproducible when compared with TCD velocities measured by their trainer.[5] Using a similar methodology, one of the two trial radiologists then trained and certified three nonradiology Nigerian physicians (medical officers) to determine TCD measurements and subsequently this radiologist trained additional Nigerian physicians to perform TCD. We realized that a sustainable post-trial solution for all children with SCA to receive TCD as part of clinical care required training of nonphysician health care workers to perform TCD. Radiology technicians were not readily available. However, pediatric nurses in the SCA clinic were able to be trained to perform TCDs.

*Implementation of the Pediatric NIH Stroke Scale as a basic screening neurological examination*

Three Nigerian research physicians were initially trained and certified to perform a modified version of the Pediatric NIH Stroke Scale[11] by two pediatric neurologists (L.C.J. and F.J.K.). Modifications included pictures for naming objects that are appropriate for a Nigerian child's experience (a soccer ball rather than a skate board, for example). Subsequently, online training and power point lectures were utilized for additional training. Neurological examinations were videotaped and verified by study neurologists. Each trained study physician was provided with printed laminated cards that were sized to fit in a lab coat pocket and contained instructions for completing the Pediatric NIH Stroke Scale (Supplemental materials).The Pediatric NIH Stroke Scale was utilized along with the "10 questions" screening[6] and parental history to screen for acute stroke or history of stroke.

*Implementation of an inexpensive and scalable electronic prescription system (eFree Hydroxyurea e-Prescription) for stroke prevention program in an environment with no prior infrastructure for paperless prescriptions*

Electronic prescription systems are scant in low-resource settings, denying physicians and pharmacists a systematic platform for communication and maintenance of patients' active treatment plans and recommended safety measures. SPIN and SPRING trials' coordination highlighted the urgent need for an electronic prescription system to distribute hydroxyurea or any prescribed medication for SCD clinics in Kano and Kaduna states. A standard electronic prescription system includes an information exchange between the prescriber, pharmacy, and health insurer or pharmacy benefit manager of the payer.[12] SPIN and SPRING sites are geographically located in northern Nigeria, where the vast majority of families pay out of pocket for all medications and hospitalizations owing to the lack of state or federal health insurance, except when parents are employed by the state.

The electronic prescription system requires each clinical site designee to assess the patient and document why hydroxyurea therapy is indicated, dose based on real-time weight, and pre-calculated hydroxyurea dose. Assessment of the clinical facilities revealed 1) clear evidence of inefficiencies and inaccuracies of handwritten prescriptions, including the lack of prescription pads; 2) the lack of electronic health records resulting in a massive paper trail of patient information in folders and boxes improperly stored throughout the facilities; 3) inadequate inventory management systems to track hydroxyurea, and 4) the lack of clinical integration

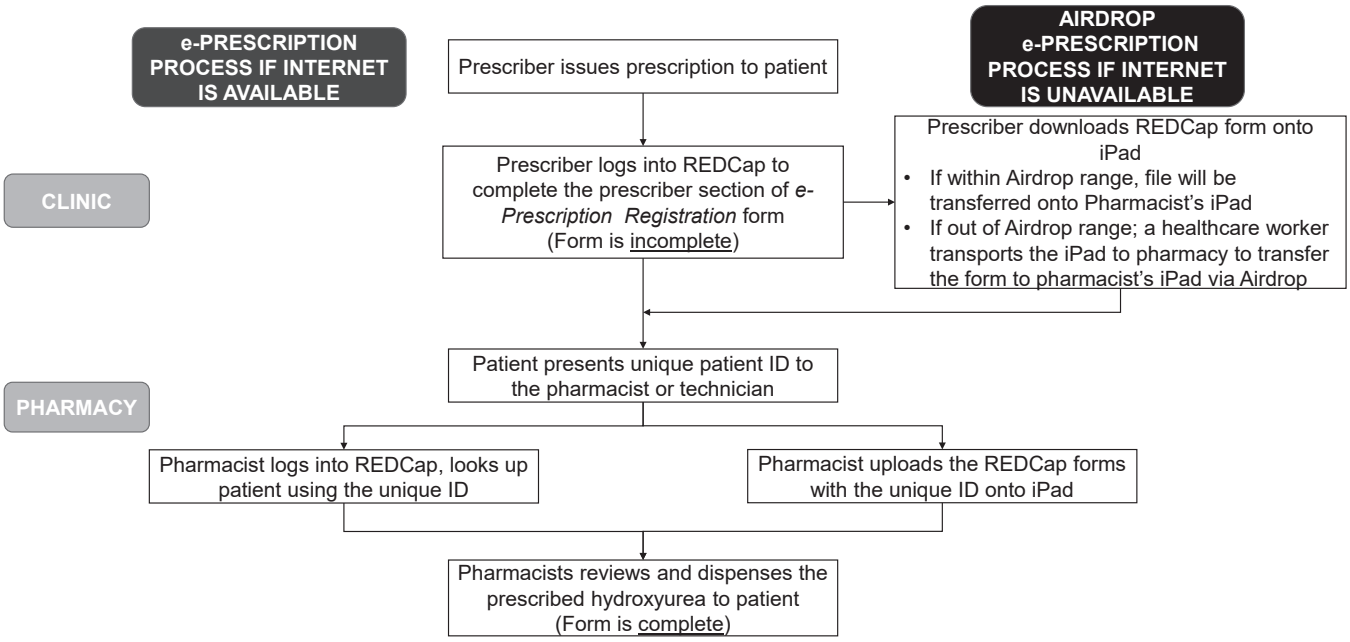


**FIGURE 2.** eFree Hydroxyurea prescription flow diagram: the system was implemented at five sites in northern Nigeria, including SPIN and SPRING trial study sites. SPIN, Stroke Prevention In Nigeria; SPRING, Primary Prevention of Stroke in Children with Sickle Cell Disease In Nigeria.

between the prescribers and pharmacists. Dialogue among the health care team verified our assessments.

We faced two initial challenges to execute our vision of an electronic prescription process at all three sites: the lack of high-speed internet and the absence of electronic health records. The three health facilities utilize a direct GSM network data plan (for devices supporting sim cards), staff mobile devices as personal hotspots, or a wireless router that acts as a mobile Wi-Fi hotspot devices for internet access, which are slow compared with those used in more developed areas. As a secondary measure, if the internet was unavailable or too slow, we applied Apple's Airdrop technology using iPads to facilitate communication between the health care providers and pharmacists. With AirDrop, an internet connection is not required. Instead, Bluetooth is used to create a peer-to-peer Wi-Fi network between the devices. Each device creates a firewall around the link, and sent files are encrypted.

We utilized REDCap case report forms in place of paper for electronic patient profiles, prescriptions, medical history, and medication inventory management. REDCap is a secure web application for building and managing online surveys and databases. REDCap can be used to collect virtually any type of data, is Health Insurance Portability and Accountability Act (HIPAA)-compliant, and is specifically geared to support online or offline data capture for research studies and operations.[13] To ensure safety and integrity, the prescriber and pharmacist must review and mark all fields before submitting the forms for completion (access to the REDCap e-Prescription system is available from a coauthor [M.R.D.] on request).

With a secure connection in place, the pharmacist receives the prescription in real time on an iPad with REDCap access to cross-check all critical variables. Following each accurate patient assessment, the patient is given instructions and a three-month supply of hydroxyurea by the pharmacist (Fig 2).

**TABLE 2.**
ePrescription for Hydroxyurea

| Sites | Total Number Enrolled | Total Number of Prescriptions | Total Hydroxyurea Dispensed (# of Tablets) | Hydroxyurea Indication | | | |
|---|---|---|---|---|---|---|---|
| | | | | Secondary Stroke Prevention | Primary Stroke Prevention (Abnormal TCD) | Priapism Prevention | Others |
| AKTH | 192 | 660 | 6892 | 86 | 104 | 2 | 0 |
| MMSH | 320 | 777 | 3914 | 118 | 192 | 5 | 4 |
| HBPH | 120 | 346 | 2179 | 83 | 19 | 5 | 13 |
| BDTH | 55 | 263 | 1499 | 8 | 47 | 0 | 0 |
| AWSH | 3 | 5 | 77 | 3 | 2 | 0 | 0 |

Abbreviations:
AKTH = Aminu Kano Teaching Hospital
AWSH = Abdullahi Wase Specialist Hospital
BDTH = Barau Dikko Teaching Hospital
HBPH = Hasiya Bayero Pediatric Hospital
MMSH = Murtala Muhammed Specialist Hospital
SPIN = Stroke Prevention Trial In Nigeria
SPRING = Primary Prevention of Stroke in Children with Sickle Cell Disease In Nigeria
TCD = transcranial Doppler.
As part of standard (not part of the clinical trial), the total number of prescriptions and hydroxyurea dispensed, from October 2019 to April of 2021, our electronic prescription system (*eFree Hydroxyurea e-Prescription) was activated at five sites in northern Nigeria, including SPIN and SPRING trial study sites.*

**TABLE 3.**
Challenges to Feasibility and Sustainability of Research and Clinical Care for Stroke Prevention in Children With Sickle Cell Anemia

| Perceived Challenge | How Challenge Was Addressed | Outcome |
|---|---|---|
| Lack of research experience in a low-resource setting | Formal research training program and ongoing education for coordinator | Local investigators have initiated and lead additional research studies |
| One pediatric neurologist in the region | Training of nonpediatric neurologist physicians to recognize the signs and symptoms of stroke and complete the Pediatric NIH Stroke Scale. Neuro examinations recorded via iPad for review by study neurologists to confirm examinations during the trials. | Increased expertise in stroke detection by non-neurologist physicians |
| No electronic medical records | Set up e-prescription system using web-based REDCap to track hydroxyurea use | Continues to be used at all sites |
| Lack of TCD machines and trained operators | Generous donor provided funds for multiple TCD machines for these 4 hospitals. TCD training provided to Nigerian radiologists who then trained other health care providers. | Sustainable long term as radiologists have trained other physicians and nurses to perform TCD. |
| Hydroxyurea not affordable for many families outside of the trial | As no public health insurance system is available, trial leadership worked with regional government officials regarding the importance of access to hydroxyurea. | State leadership committed to providing free hydroxyurea for primary stroke prevention for children identified as having abnormal TCD measurements |

Abbreviations:
NIH = National Institutes of Health
TCD = transcranial Doppler

From October of 2019 to April of 2021, our electronic prescription system was activated at five sites in northern Nigeria, including SPIN and SPRING trial study sites (Table 2). We have registered 690 children into our ePrescription system. Furthermore, the eFree Hydroxyurea ePrescription system has provided a connectivity platform to streamline collaboration and patient care between the pharmacists and prescribers at the local facility and all five facilities as a central database.

## Discussion

We describe a sustainable approach for primary stroke prevention in children with SCA living in a low-resource setting built on a team of clinical personnel that had not previously conducted clinical trials or systematic stroke prevention clinical care. Table 3 summarizes major challenges to the feasibility of both stroke prevention clinical trials and providing long-term stroke prevention care and how these challenges were addressed. The SPIN and SPRING trials teams' efforts resulted in robust and sustainable processes for regulatory oversight in compliance with local, national, and international research governance entities for primary and secondary stroke prevention (Table 4). Weekly, the Nigeria research staff conducted two one-hour meetings with the Data Coordinating Center in Nashville and a one-hour meeting for all research coordinators in Nigeria without data-coordinating center personnel. In addition, the Nigeria team completed a one-month clinical research training program in the US and passed the SOCRA certification examination focused on good clinical research practice. These efforts have continued after completion of the two trials.

Before starting the trials, SPIN and SPRING principal investigators and the entire research team committed to a sustainable approach to preventing strokes after trial completion. This effort required multiple face-to-face meetings with Nigerian state government health officials to inform them that hydroxyurea was a low-cost intervention to prevent strokes in children with SCA and

**TABLE 4.**
Priorities and Processes for Capacity Building and Conduct of Stroke Prevention Randomized Controlled Trials and Clinical Research in Low-Resource Settings

Priorities for capacity building to conduct stroke prevention randomized controlled trials in low-resource settings:
1. Identify study personnel needed to complete all study evaluations and serve as a point of contact with participants/legal guardians for study duration and closeout.
2. Identify and communicate with local institutions and government leadership.
3. Test all technology components and resolve any technology concerns.
4. Provide a stepwise approach for all study procedures and evaluations.
5. Identify educational resources pertinent to the disease condition and clinical research resources accessible to international study sites/collaborators.
6. Develop and implement a communication plan for internal and external collaborators.
7. Conduct regular periodic data queries for data completeness and quality.
8. Provide pretrial and ongoing peer-to-peer training for sustainability.
9. Utilize digital technologies for internal communication.
10. Initiate and continuously implement cross-functional communication plans and plan for resolution of new challenges.

Processes for conduct of clinical research in low-resource settings:
1. Active communication plan: Individual meetings for 1) study leadership (operations meetings), 2) study personnel and coordinating center (data meetings), and 3) internal meetings at the study site. Each meeting to last at least 1 hour.
2. Regulatory governance and education: Initial approval from all study collaborating institutions, study sponsor, domestic and international governance entities (IRB, ethics committee, NAFDAC, NHREC). Complete educational courses pertinent to human subject research and Good Clinical Practices.
3. Study-specific participant evaluations: Contact participants during study phases: recruitment, screening, follow-up, study exit, and routine care. Train designated personnel on completion of transcranial Doppler assessments, stroke evaluation, and standard care practices (complete blood count).
4. Data collection and entry: Weekly reporting of study activity for the past seven days, including screening and enrollment activity, withdrawals, hospitalizations, study milestone evaluations, and serious adverse events.

Abbreviations:
IRB = institutional review board
NAFDAC = National Agency for Food and Drug Administration and Control (Nigeria)
NHREC = National Health Research Ethics Council

the requirement for the partnership to ensure a sustainable effort. The importance of a state solution to preventing strokes, regardless of the randomized controlled trials' outcome, was emphasized to state officials. Despite changes in local government leaders during the SPIN and SPRING trials, the state public health officials committed to three rate-limiting steps: 1) Permitting task-shifting for TCD screening. Previously, nurses were not allowed to perform TCD measurements. Subsequently, not only can trained nurses perform TCD measurements but also they are now part of the permanently employed staff on the TCD screening teams; 2) Offering free hydroxyurea for primary stroke prevention for children identified as having abnormal TCD measurements; 3) Documentation of ongoing commitment to sustaining this effort via an active memorandum of understanding to provide hydroxyurea for children with SCA and increased risk of stroke at no cost beyond the study duration.

Paramount to our partnership with the Kano and Kaduna state health leadership was developing an easy and accessible automated system to address the impact of hydroxyurea therapy for stroke prevention in their state. We created an easily automated approach to track the hydroxyurea purchased from Bond Chemical (Awe, Oyo State of Nigeria) at a subsidized price of $0.15 per 500 mg capsule. The tracking included the number of children receiving standard-care hydroxyurea therapy for primary and secondary stroke prevention, the dose of hydroxyurea, and date of onset of treatment with hydroxyurea. The ability to have each hospital's pharmacy provide institution-specific details allowed for comparison between institutions.

In summary, we outline a reproducible strategy for establishing a research infrastructure for future patient-oriented research and clinical care in a low-income setting focused on SCD. The capacity building strategies described are multifactorial, with leadership and stakeholders at multiple levels, including institutional, local government, and health care officials. After completion of the two NIH-funded trials, the Nigerian physicians and research staff members are poised to undertake future clinical trials to advance the care of children and adults with SCD.

## Acknowledgments

We are grateful to the SPIN and SPRING research teams who tirelessly coordinated and facilitated administrative and operational tasks required for the successful conduct of the trials. We thank the members of the DeBaun laboratory at the Vanderbilt-Meharry Center of Excellence in Sickle Cell Disease for their support of this work and the Afolabi Family and the Phillips Family for their donations of TCD machines and other financial support for capacity building in Nigeria.

## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pediatrneurol.2021.08.010.

## References

1. World Health Assembly. Sickle-cell anaemia: report by the secretariat. Geneva SWHOwwiihAN. Geneva, Switzerland: World Health Organization; 2006. Available at: Www.Who.Int/iris/handle/10665/20890. Accessed June 5, 2021.
2. Ohene-Frempong K, Weiner SJ, Sleeper LA, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood. 1998;91:288–294.
3. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med. 1998;339:5–11.
4. Abdullahi SU, Wudil BJ, Bello-Manga H, et al. Primary prevention of stroke in children with sickle cell anemia in Sub-Saharan Africa: rationale and design of phase III randomized clinical trial. Pediatr Hematol Oncol. 2021;38:49–64.
5. Galadanci NA, Umar Abdullahi S, Vance LD, et al. Feasibility trial for primary stroke prevention in children with sickle cell anemia in Nigeria (spin trial). Am J Hematol. 2017;92:780–788.
6. Mung'ala-Odera V, Meehan R, Njuguna P, et al. Validity and reliability of the 'ten questions' questionnaire for detecting moderate to severe neurological impairment in children aged 6-9 years in rural Kenya. Neuroepidemiology. 2004;23:67–72.
7. Bello-Manga H, Galadanci AA, Abdullahi S, et al. Low educational level of head of household, as a proxy for poverty, is associated with severe anaemia among children with sickle cell disease living in a low-resource setting: evidence from the spring trial. Br J Haematol. 2020;190:939–944.
8. Galadanci NA, Abdullahi SU, Ali Abubakar S, et al. Moderate fixed-dose hydroxyurea for primary prevention of strokes in nigerian children with sickle cell disease: final results of the spin trial. Am J Hematol. 2020;95:E247–E250.
9. Galadanci NA, Abdullahi SU, Abubakar S, et al. Primary prevention of strokes in nigerian children with sickle cell disease (spin trial): final results. Blood. 2019;134(Suppl 1):521.
10. The society of clinical research associates (SOCRA). Available at: https://www.Socra.Org/certification/certification-program/introduction/. Accessed May 6, 2021.
11. Ichord RN, Bastian R, Abraham L, et al. Interrater reliability of the pediatric national institutes of health stroke scale (PEDNIHSS) in a multicenter study. Stroke. 2011;42:613–617.
12. Grossman JM, Cross DA, Boukus ER, Cohen GR. Transmitting and processing electronic prescriptions: experiences of physician practices and pharmacies. J Am Med Inform Assoc. 2012;19:353–359.
13. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (redcap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42:377–381.