Protocol Title

SickleInAfrica Protocol for Clinical and Implementation Research in Newborn Screening for Sickle Cell Disease Using Dried Blood Spots for Point of Care Tests

Short Protocol Title

Implementation Research: SickleInAfrica Protocol for Newborn Screening

Principal Investigator

Professor Obiageli Nnodu

Co-Principal Investigators

Dr Fred Sarfo, Dr Catherine Chunda-Liyoka, Dr Lulu Chirande, Prof Sarah Kiguli, Dr Brubacau Ali Toure, Dr Emmanuel Peprah

Version	Date	Authors	Details of changes	
1.0	4th March 2022	Obiageli Nnodu	first version	
1.1	23 March 2022	Obiageli	Sent for copy editing, but these copy edits could not be used	
1.2	25 March 2022	Obiageli Nnodu, Mario Jonas, Victoria Nembaware, Emmanuel Peprah, Nchangwi Munung, Valentina Ngo Bitoungui, Kevin Kum Esoh, Catherine Chunda-Liyoka, Jack Morrice, Upendo Masamu,	Google docs	
1.3	21 April 2022	7th SickleInAfrica attendees	Pdf version Used some of the edits from	

			copy editor to create this version	

Contents

Definitions/Glossary

Definitions are from The Sickle Cell Disease Ontology:
https://www.ebi.ac.uk/ols/ontologies/scdo

Newborn Screening (NBS) for Sickle Cell Disease (SCD): Testing of neonates to identify those with major sickling diseases. (SCDO:0000803)

Point-of-Care Test (POCT) for Sickle Cell Disease (SCD): A test for sickle cell disease that allows patient diagnoses in the physician's office, in other ambulatory settings or at bedside. (SCDO:1000904 in future SCDO release)

Dried Blood Spot (DBS): Capillary blood collected on blotting paper, typically from heel or finger stick. (NCIT:C113746 in future SCDO release)

Dried Blood Spot - Point-of Care Test (DBS-POCT) for Sickle Cell Disease (SCD):

Acronyms

SCD	Sickle Cell Disease
NBS	Newborn Screening
POCTs	Point-of-Care Tests
DBS	Dried Blood Spots
IEF	Isoelectric Focusing
HPLC	High-Performance Liquid Chromatography
CFIR	Consolidated Framework for Implementation Research
FGDs	Focus Group Discussions
PHCs	Primary Health Centres
EPI	Expanded Programme on Immunization
Hib	Haemophilus Influenzae Type B
VDRL	Venereal Disease Research Laboratory
CMV	Cytomegalovirus
TCD	Transcranial Doppler
ANCs	Antenatal Clinics
EID	Emerging Infectious Diseases
HIV	Human Immunodeficiency Virus

Abstract

Sickle cell disease (SCD) is a genetic blood disorder of high prevalence in sub-Saharan Africa where it is associated with high mortality of babies and children under the age of five years (1,2). Although newborn screening (NBS) for SCD and other evidence-based interventions have improved outcomes for individuals with SCD in developed countries, this has not been implemented beyond pilot projects in many African countries. This is due to the high cost of standard SCD screening equipment and reagents which require skilled personnel and a stable electricity supply (3,4). In recent years, highly sensitive low-cost point-of-care tests (POCTs) for SCD, which use monoclonal antibodies to identify different haemoglobin phenotypes HbA, S, and C in the presence of high foetal haemoglobin levels in newborns, have been developed to overcome these barriers of conventional screening (5,6).

It is therefore prudent to find innovative, low-cost, feasible, acceptable and sustainable strategies for newborn screening in low resource settings using these POCTs. Such strategies could help establish and integrate SCD NBS or Early Infant Diagnosis into existing public health programs in the consortium countries. In addition, such strategies could be followed up and provide evidence-based interventions for identified babies with SCD to reduce the morbidity and mortality due to SCD.

Based on our preliminary results (7–9) validation is needed of the diagnostic performance of a POCT using dried blood spots (DBS) (a cheap minimally invasive blood sampling technique used in standard NBS programs) against isoelectric focusing (IEF) and high-performance liquid chromatography (HPLC). Furthermore, there is a need to assess the adoption, implementation costs, appropriateness, and sustainability of the POCT technologies using frameworks such as the Consolidated Framework for Implementation Research (CFIR) (Ref. needed with a definition of CFIR version 2.0) within six African countries (i.e., Ghana, Mali, Nigeria, Tanzania, Uganda, Zimbabwe and Zambia) with SickleInAfrica sites.

Our objectives are as follows:

1. Assess the implementation outcomes using CFIR to:
    a. Evaluate the performance characteristics and cost of DBS POCT against IEF/HPLC.
    b. Determine the knowledge of the availability of POCTs and acceptability cost of the use of DBS POCT to health-care workers and patients versus standard POCT for screening in consortium countries with the use of a structured questionnaire and key informant interviews.
    c. Determine the cost of using DBS POCT for NBS and confirmatory testing using POCT versus conventional NBS and confirmatory testing with IEF/HPLC
    d. Apply DBS POCT in NBS versus Early Infant Diagnosis and compare the number of babies identified in each platform who enrol in comprehensive care.
2. Train SPARCO sites' health care workers on the use of DBS for POCT in newborn screening and follow up of babies identified in the programme using standardised guidelines.
3. Screen 500-2,500 babies in consortium countries using DBS POCT and enter the identified babies into REDCap using SPARCO CRF.

The SickleInAfrica consortium NBS research study will take place in the clinical networks of each consortium site (site, satellite sites, associated primary health care centres, and secondary health facilities). These sites must be carefully described to enable adequate follow up of SCD babies for health maintenance and comprehensive care.

This protocol outlines the entire process from validation, comparisons of test methods and screening platforms as well as follow up procedures of the babies identified in the programme. We anticipate that results from our study will pave the way for removing the remaining implementation barriers of inadequate infrastructure, for cost integration into existing public health programs and for the widespread implementation of NBS for SCD in high burden countries.

Personnel at the Clinical Sites have the SPARCO Standard of Care Guidelines for multidisciplinary management of SCD. The Consortium skills development program in year 2 will focus on skills development in health care using the SPARCO SoC Guideline and research especially implementation science research.

Introduction

Sickle cell disease (SCD) is the most prevalent genetic disorder in African. It is a major cause of morbidity and mortality in several SCD burdened countries. It is associated with high mortality of babies and children under the age of five years. Children surviving the first few years of life suffer recurrent painful crises, infections and anaemia, while adults with SCD have significant morbidity with shortened life expectancy (10,11). Since SCD is a genetic disease, early detection through screening of babies at birth or in early infancy followed by genetic counselling, education, infection prophylaxis, surveillance for risk of stroke and transfusion therapy have improved outcomes for individuals with SCD in high income countries (12–14).

Currently, most African countries (except Egypt) do not have a national newborn screening (NBS) program. Pilot screening programs have been carried out for several years in Ghana, Benin, Burkina Faso, Democratic Republic of Congo, Gabon, Mali, Nigeria Uganda, and Tanzania. There is a need for nationally scaled up NBS programs (3).

Applying frameworks, theories, methodological approaches, and outcome measures from Implementation science could facilitate faster translation of evidence-based interventions such as low-cost point- of- care testing into clinical practice and health policy.

Conventional NBS methods which include isoelectric focusing (IEF), high performance liquid chromatography (HPLC), (15) capillary electrophoresis and tandem mass spectrometry have been hampered by the high cost of equipment and/or reagents, lack of technical personnel, stable power source, as well as logistic support (supply chain management) in low and middle-income countries. In NBS IEF and HPLC yield test results as FS which though presumed to be HbSS may, in reality, be any of these- SCD-SS, SCD-Sβ^o, which are both clinically severe, S/HPFH, and SCD-S δβ (delta-beta)-zero which may be asymptomatic or mild, respectively.

Rationale

In recent years, highly sensitive low-cost point-of-care tests (POCTs), which use monoclonal antibodies to identify different haemoglobin phenotypes HbA, S, and C in the presence of high foetal haemoglobin levels in newborns, have been developed to overcome the barriers of conventional screening (6,7).

The effectiveness of a NBS programme depends on the smooth integration of sample collection, laboratory testing, diagnosis, follow-up, education and treatment in a public health system. Therefore, there is a gap to find innovative implementation strategies that are feasible, culturally acceptable, sustainable and transformational in deploying these POCTs. Such strategies could be to establish and integrate SCD NBS or Early Infant Diagnosis into existing public health programs in the SickleInAfrica consortium countries and to follow-up and provide evidence-based interventions for identified babies with SCD in order to reduce the morbidity and mortality due to SCD.

Literature Review

POCTs (6) have been recently developed to overcome barriers of conventional screening programmes (15,16). For example, we published the first real-world experience using POCT to screen 3,603 babies for SCD in Gwagwalada Area Council, Abuja (5). We demonstrated that screening with a POCT is feasible and acceptable to both healthcare providers and parents (5). However, we noted that in a busy immunization clinic, two or three personnel have to be involved in the process, making it more costly and thereby potentially reducing the effective use of normal POCT technique in mass screening.

On the other hand, dried blood spot (DBS) is a cheap minimally invasive blood sampling technique used in standard NBS programs (17). When blood is appropriately dried and stored, DBS remains stable at ambient temperature and thus valuable in resource-poor settings. We also explored the use of DBS with POCT to achieve throughput in another study and found 100% concordance between standard POCT with DBS POCT in the results of Hb AA, HbAS, Hb AC, HbSC. This makes the use of POCT even easier and cheaper to integrate SCD screening into both immunisation and HIV programs (WHO AFRO RC 70, 2020)(18).

Theoretical Framework

We will use the integrated Consolidated Framework for Implementation Research (CFIR)

Aims and Objectives

1. Assess the adoption of DBS for NBS using the three technologies POCT, IEF, HPLC among providers (i.e., midwives, physicians, nurses, councillors) in SickleInAfrica sites across six countries.

2. Evaluate the appropriateness of the 3 technologies implemented across implementing sites and assess the barriers and facilitators guided by CFIR, inner and outer settings.

3. Assess the technology and implementation costs and sustainability of the three technologies in the various healthcare centres among the six countries.

4. (Ancillary objective) perform a cost-effectiveness analysis of the three technologies. We will focus on the cost of the test and not manpower and systems at this stage.

Methods

Study Design

We will conduct an explanatory sequential mixed methods assessment of the use of the three technologies to facilitate (NBS) for SCD.

Preliminary Phase: The study will consist of a preliminary phase in which we evaluate the performance characteristics and cost of DBS POCT against IEF/HPLC

Phase 1 - Quantitative phase: We will employ a cross-sectional survey to collect data from providers (i.e., midwives, physicians, nurses, genetic counsellors). This practice capacity survey for SCD screening will be administered to implementing sites.

Phase 2: Qualitative phase: Qualitative data will be collected from focus group discussions (FGD), analysed and interpreted to further explain and give contextual meanings to the quantitative data. Components of the proposed package will be expected to help address the following barriers to screening: low level of awareness about SCD; poor access to screening centres; high out-of-pocket costs; shortage of healthcare workers; low awareness of diagnosis of SCD; low consideration of expert opinion in test methods chosen for screening; non-integration of NBS into existing public health programs; inadequate budgetary provision for NBS and the need for strong healthcare systems. Moreover, engagement with various stakeholders will inform the best strategy for the uptake and long-term scale-up of the best technologies for NBS.

Study Population

The study population will comprise key SCD stakeholders (policy makers, physicians, nurses, midwives, laboratory medicine experts, parents, SCD patients, patient leaders) from all SickleInAfrica Consortium sites in Ghana, Nigeria, Tanzania, Mali, Uganda, Zimbabwe, and Zambia.

Quantitative Data

Survey Data Collection

Survey data will be collected to address Aims 1, 2 and 3 (Site characteristics, number of health care workers trained in the 3 technologies, number of babies screened, etc.). Data will be de-

identified and recorded electronically into REDCap (Research Electronic Data Capture), which is a web-based application.

For Aim 1, adoption will be measured by the number of healthcare workers trained and competent in the 3 technologies, number of babies screened, and number of patients referred for further management. the data will be captured via clinical measures. Within the implementation science literature, Adoption/uptake is defined as “The intention, initial decision, or action to try or employ an innovation or evidence-based practice.” Within this protocol, we demonstrate Adoption/uptake by the outcome (i.e., Adoption also may be referred to as ‘‘uptake.’’ Adoption occurs in the early to mid-implementation stage and is assessed from the organizational or provider perspective.) thus, the outcome of babies screened or patients referred for further treatment after a positive test demonstrated the utilization of a POCT by a provider meets the definition of Adoption within the implementation science literature by demonstrating that the provider has; 1) followed an evidence-based protocol, 2) diagnosed a patient for SCD, and 3) referred the patient for further treatment once the patient is diagnosed with SCD.

For Aim 2, we will administer a practice capacity survey to understand the practice context of all implementation sites followed by a focus group discussion (FGD) described in the Qualitative Data section below.

For Aim 3, technology and implementation costs will be assessed according to the technology available in each country. Optimally this should be DBS POCT/IEF/HPLC. We will also measure sustainability of the three technologies using the Programme Sustainability Assessment Tool (19). The tool allows for assessment of a program’s current capacity for sustainability across a range of specific organisational and contextual factors. It captures sustainability strengths and challenges. The results can then be used to guide sustainability action planning for NBS. Each implementing site will complete the survey.

The surveys created on REDCap can also be administered offline, when internet connectivity is limited or unavailable. The data will be stored on the device (laptop or tablet) and will upload automatically into the cloud storage of REDCap once the device is connected to the internet. REDCap is secure and designed to support data capture for research studies. It provides a stream-lined process for rapidly building a database; an intuitive interface for collecting data, with data validation; automated export procedures for seamless data downloads to common statistical packages like SPSS, SAS, Stata, and R); advanced features such as branching logic, file uploading, and calculated fields and audit trails for tracking data manipulation and export procedures. When electronic collection of data is not feasible, paper form will be used, and later transferred into the electronic database. SickleInAfrica sites are already using REDCap for collecting data for the SickleInAfrica Registry.

Survey Data Analysis

Analysis of survey data will be conducted using the statistical software SPSS and R. Descriptive statistics including frequencies and means will be generated and reported in a tabular format for aggregate data. Any associations will be explored using the Chi-square or Fisher exact test (p-values will be considered significant if less than 0.05) where applicable. Adoption will be summarised across a composite of the adoption measures described above.

Qualitative Data

Focus Group Discussion Data Collection

We will conduct focus group discussions (FGDs) (N= 3-6/per site) with key stakeholders (policy makers, midwives, physicians, nurses, councillors, patients and parents of children with SCD) to explore preferences for NBS for SCD and the barriers and facilitators of the use of the three NBS technologies at the different SickleInAfrica sites. About 3-6 FGDs will be conducted per site. The final number of FGDs/sites will be guided by the principle of saturation. Each FGD will be made up of about 5-6 persons from the same/similar stakeholder group.

We will pilot the FGD guides developed based on CFIR and align data collection with recruitment strategies (see Appendix for FGDs). Piloting of the FGD guide will aim to improve clarity and reduce participant burden, will include sensitising concepts from CFIR domains, given their potential impact on implementation. Questions will be adapted for the target population of each FGD. The CFIR domains most relevant for clinical perspective are the individuals involved in implementation (knowledge and beliefs about the technology, self-efficacy to use the technology), inner and outer settings (implementation climate, structural characteristics, external policies, culture, networks, and communications).

FGD will occur in a private, quiet, safe and convenient room at a study facility or other community location. Where possible, we may consider having some of the FGD virtually via Zoom. Each FGD will have 5-6 persons) and will last approximately 40–60 min. All FGD will be audio recorded and transcribed verbatim. Repeat discussions will be considered if necessary and feasible. A trained moderator with expertise in qualitative research will lead the FGD. A trained note-taker will record content and non-verbal communication). Discussions will be in English/French/lingua franca (e.g Pidgin, Swahili), or one of the local languages as appropriate. Where needed an interpreter may be used to provide additional support.

Focus Group Discussion Data Analysis

Immediately following each FGD, the moderator and note taker will debrief and complete field notes that highlight the main emerging themes of the discussion and any pertinent information. All audio recordings will be transcribed and the transcripts and field notes will be imported into NVivo 12 for thematic analysis (20).

The thematic analysis will adopt a hybrid (inductive and deductive coding) approach (21). Two transcripts will be coded (deductively) using a pre-defined coding framework developed from existing literature and interview guide oriented by the CFIR (22–24)**.** We will also look out for themes emerging from the data (inductive) that are not

covered in the framework. This first round of coding will be done separately by two researchers. The transcript codings will be compared and discrepancies resolved with a third reviewer. Following this first round of coding, we will finalise the coding framework which would then be applied to the rest of the transcripts. Once coding is complete, we will use the framework method of Gale et al (25) to analyse data by different dimensions and commonalities of themes, patterns and linkages, and by participant characteristics, including comparing facilitators and barriers across the CFIR domains within and between stakeholder categories. Inductive codes will represent themes not expected by the researchers. A codebook will include detailed code description, code application criteria, and examples (26). Based on the facilitators and barriers indicated, a selection of implementation strategies will be identified from the literature (27). These strategies could then be tested in a subsequent trial. Qualitative analysis will occur independently and then will be integrated via joint analysis (28), mapped onto different themes or illustrative stakeholder quotes. Joint analysis will contextualise adaptations to the **NBS** technology use and adoption, providing a synergistically rich and broad understanding that would not have been possible with quantitative or qualitative designs alone (28).

Context

The SickleInAfrica NBS research study will take place in the clinical networks of each consortium site, (site, satellite sites, associated primary health care centres, and secondary health facilities). These sites have to be carefully described to enable adequate follow up of SCD babies for health maintenance and comprehensive care (29). In Nigeria, health care is provided by the local government authorities through primary care clinics/hospitals. The Primary Health Centres (PHCs) are run by the local government area councils, the district general hospitals, or secondary health care facilities are under the state governments, while the tertiary hospitals are under the federal government.

There is ordinarily little integration between these levels of health care. Under Five Care is also provided at PHC level. The PHCs are linked to the communities through ward development committees whose membership include representatives from major religious bodies, a teacher, women leaders, a representative of the PHC, and general hospital.

Facilities and Resources to Support Newborn Screening in Clinical Networks

1. Availability of prophylaxis for infection (oral penicillin and Expanded Programme on Immunization (EPI) administering pneumococcal, meningococcal and Haemophilus influenzae type B (Hib) vaccines and folic acid.
2. Materials and consumables: Filter paper cards, gloves, lancets, spirit swabs, dry gauze squares, Ziplock bags, racks for drying DBS etc.).

3. Laboratory Investigations: Isoelectric focusing (IEF) or High-performance liquid chromatography (HPLC) for confirmatory testing.
4. Full blood count, urea, creatinine electrolytes, liver function tests, urine analysis and microalbumin, blood grouping and cross match, antibody screening, pretransfusion venereal disease research laboratory test (VDRL) test, viral screening Hepatitis B and C, HIV, Cytomegalovirus (CMV).
5. Imaging: Chest X-Ray, transcranial doppler (TCD) ultrasound screening.
6. Education and Counselling Services: Education of healthcare workers, parents and caregivers on how to maintain good health and understand when to seek expert care if there is fever of 38^0C or more, dehydration, dactylitis, respiratory illness, enlarged spleen/liver with worsening pallor.

Target sites

The implementation science research on NBS will be carried out in SickleInAfrica sites in the following countries:

1. Ghana
2. Nigeria
3. Tanzania
4. Mali
5. Uganda
6. Zimbabwe/ Zambia

The minimum requirement for NBS is for sites to conduct at least one paediatric SCD clinic or paediatric haematology clinic per week that includes personnel dedicated to care of paediatric SCD patients. There are 25 sites in Nigeria and at least one site in each of the other countries. The following personnel should be available at each site: Personnel in charge of screening, follow-up and clinical care, nurses, laboratory scientists and technicians, onsite laboratory team, supervising haematologists (paediatric/adult) data entry clerk, managers personnel managing family education and counselling, study pharmacists, community health extension workers. Countries can adapt these requirements to their available resources and personnel

Participants

Babies attending immunisation clinics aged 0-3 months.

Implementation Strategy & Intervention

NBS for SCD is a public health programme and should be anchored on existing public health services such as the immunisation and early infant diagnosis of HIV services as done in Uganda. Therefore, the permission and collaboration of the government from local state and national levels should be sought. Investigators should engage the Health Department of the Area Councils to obtain information on existing services at the Primary Health Centres (PHCs)

including antenatal clinics (ANCs), deliveries and immunisation services and inform the PHCs about the NBS.

The following should be carried out as outlined in (5)

1. Seek the opinion of key personnel and other healthcare workers at the PHCs about integrating NBS with POCT into services at the PHCs. These are PHCs linked to the clinical sites
2. Map the PHCs in the Area Council.

Select the PHCs for the NBS which have at least 100 babies attending immunization clinics. Each country will decide what clinics to engage for screen and how many in order to reach required numbers within reasonable time

3.
4. For the selected PHCs, open-ended pretested questionnaires (**Appendix)** will be used to collect information from the Officers-in-Charge (hereafter In-Charges), other PHC healthcare workers in the facilities, parents/care givers and policy makers to assess existing resources, structures and services at the PHCs and to ascertain the feasibility of integrating NBS for SCD using DBS POCT.
5. Train supervising physicians and the In-Charges to give brief talk on SCD and NBS to mothers presented for immunizations at the PHCs throughout the study.
6. Screen babies of consenting mothers (see copy of consent form in **Appendix**).
7. Counsel mothers whose babies have not been screened and give them the opportunity to participate.
8. Obtain basic demographic information and contact details at enrolment.
9. Testing to be carried out on eluted DBS samples as per protocol for DBS POCT
10. Positive samples should be tested by IEF/HPLC in screening laboratories according to standard protocols. A clinical diagnosis of SCD will be given to all children by paediatrician (trained HCW)on the basis of screening and confirmatory results
11. The study nurse should inform the In-Charge at the health facility and deliver the results to the parents and perform the post-screening counselling. Parents whose children have the sickle cell trait will also be invited for counseling.
12. The study pharmacist/nurse should ensure that the baby is commenced on oral penicillin at an appropriate dose immediately.
13. The parents should be taught how to give the drugs to the baby by dissolving the penicillin V or folic acid tablets in a 10ml container before administration. For breastfed babies, breast milk could be used as a diluent.
14. Registration and first consultation fees to be paid for the babies to attend SCD clinic. The sum of $2-5 will be given for transportation if funds permit.
15. The research nurse to navigate the parents to the paediatric sickle cell programme for comprehensive care.
16. Educational materials that highlight health promotion habits and alert parents to danger signs such as fever, persistent headache, abdominal pain, vomiting and diarrhoea, the features of severe anaemia and chest pain with breathlessness to be provided for the parents
17. Dedicated pharmacists to maintain a register of screen-detected babies and supply folic acid and oral penicillin.
18. Parents/guardians to be informed of their babies' status and of the need to adhere to prescribed medication regimens in order to reduce complications that may arise from low immunity. This information to be reiterated on subsequent visits.

19. At each visit, parents/guardians will be encouraged to adhere to the medication regimen and not to share medications with other family members and friends.

Infection Prophylaxis

Expanded Programme on Immunisation

At Birth: BCG, OPV_0, Hep.B1
6 Weeks: $Penta_1$, HiB, OPV1
10 weeks: $Penta_2$, $HepB_2$, OPV_2
14 weeks: Penta3, OPV3
6 months: Penta4, OPV4
9 months: Measles, yellow fever
1 Year: Vitamin A

Antibiotics

Oral Penicillin V:
From two months to three years - 125 mg bd,
> three years - 250 mg bd.
This prophylaxis should be given in children up to 16 years.
In patients allergic to penicillin, erythromycin in the same dose will be given.

Malaria Prophylaxis

Health education, environmental control, indoor spraying of insecticides, distribution of insecticide treated bed nets, and chemoprophylaxis by daily proguanil

Chemoprophylaxis by proguanil if indicated in National Guideline
Daily from 6months of age for life
25 mg is given to patients of age 6 months to 1year
50 mg is given to patients of age 1-4years
75 mg is given to patients of age 5-8years

Nested Studies

Diagnostic Performance of POCT DBS

POCT will be performed from DBS according to manufacturer's instruction (Pages 36-37 of SOP). The d iagnostic performance of POCT with DBS against gold standard IEF/HPLC (HPLC (VARIANT IITM; Bio-Rad Laboratories, Marnes-la-Coquette, France) will be carried out according to standard methods (https://www.perkinelmer.com/product/migeletm-gel-

electrophoresis-unit-gener-2118-0020) (Diagnostic accuracy, turnaround time) in 100 samples obtained from newborns from each participating country. Given the prevalence rates of 1-2% in Sub Sahara Africa, this number will be able to identify babies with SCD as well as carriers.

Testing on Standard POCT will be on site and immediate. Testing with DBS POCT will be the same day but not immediate to allow for elution. IEF/HPLC tests are usually batched and will be done on a weekly basis.

The turnaround times for these tests of 10 mins HemoTypeSC standard, 30 mins and DBS 30 1-2 weeks IEF /HPL will be taken into consideration in planning.

Efficiency of Screening Platform

The percentage of mothers who complete screening and enrol their babies into care when screening is conducted at post-natal wards (NBS) versus early infant diagnosis through immunisation clinics/ emerging infectious diseases (EID) or human immunodeficiency virus (HIV) services. The registration and first consultation will be paid for the researchers and should be included in the budget ($2-5).

Evaluation of Methods

DBS samples will be collected from babies at post-natal wards, immunization clinics and transported in the standard way to a clinical laboratory for testing with DBS POCT protocol according to manufacturer's instructions. Positive samples will be confirmed by IEF/HPLC. Patient records, recruitment assessments, semi-structured key informant interviews, and focus-group discussions with participants. The following will also be collected:

1. Proportion of mothers who accepted/consented for screening at post-natal/maternity wards and immunisation clinics.
2. The percentage of mothers who complete screening and enrol their babies into care
3. Estimation of perceived social support, obstacles, barriers assessing the screening services and returning to bring their babies for regular follow up
4. The number of health care staff who are willing to perform the standard POCT compared to those willing to collect the DBS samples
5. To compare the time to results and cost of the three approaches (standard POCT, DBS POCT and IEF/HPLC)

All qualitative data will be analyzed using Nvivo-12 software and the Krueger's framework analysis approach which provides a clear series of steps for qualitative data analysis: familiarization, identifying a thematic framework, indexing and charting, mapping and interpretation.

Predefined Outcomes of the Implementation Strategy

a. The performance characteristics of the DBS POCT such as the sensitivity, specificity using IEF/HPLC as the gold standard will be calculated along with 95% confidence intervals.
b. The proportion of immunisation clinic staff willing to use DBS POCT in NBS will be determined
c. Adoption and implementation (Adoption rates, delivery fidelity and enactment fidelity in health care centres in using the new method for screening
d. Maintenance- institutionalization and sustainment

Discussion

Poor budgetary allocations, high cost of equipment, reagents and supplies, low availability of technical expertise, epileptic electricity supplies, long turnaround time, have hampered the implementation of NBS for SCD in high burden countries in Africa. The availability of easy-to-use low-cost point of care tests for SCD has removed most of these barriers making it possible to establish NBS in multiple health care settings without substantial investment in equipment or staff. Our study published in 2020 (5) demonstrated that point-of-care screening tests provide an affordable, reliable, and easy-to-use method to screen for SCD, ensuring the earliest diagnosis possible, the highest level of follow-up of participants, access to treatments locally (including penicillin prophylaxis, pneumococcal vaccinations, and hydroxycarbamide) and effective prevention procedures regionally (eg, transcranial doppler for risk of stroke). These outcomes are priorities to reduce the mortality and morbidity of sickle cell disease across sub-Saharan Africa and other countries of high prevalence. However standard POCT is limited by the number of staff who can conduct the test in a busy clinic hence the need to use DBS which is applicable in other well established public health programs which will make it possible to integrate NBS into other EID services thus removing the remaining barriers to establishing NBS programs in high SCD burden countries.

Summary of Expected Findings

In a pilot study the performance characteristics and costs of DBS has been obtained. In this protocol we want to compare three evidence-based technologies (DBS, IEF, and HPLC) within the context of the consortium to determine which technology is best positioned to be used as a POCT. For example, which technology is acceptable, feasible, and sustainable (using CFIR) for full scale implementation. This question has not been answered via a comparison of these 3 technologies.

Thus w e expect to validate the result of the performance characteristics and cost of DBS POCT against standard POCT and gold standard HPLC in other settings, acceptability of the use of DBS POCT in NBS and EID services, compare screening for SCD in newborns and early infant diagnosis in identifying babies and follow them up in comprehensive care.

Screening is a first line step which requires confirmation. Developing systems of low-cost POCT screening and confirmatory testing is a contribution which the SickleInAfrica can make in implementation research for NBS in low resource settings.

Expected Impact of Research

We anticipate that results from our study will pave the way for removing the remaining barriers (of inadequate infrastructure, cost integration into existing public health programs to the widespread implementation of NBS for SCD in high burden countries).

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