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blood advances

The Consortium on Newborn Screening in Africa for sickle cell disease: study rationale and methodology

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Key Points

- American Society of Hematology–led 7-country sub-Saharan consortium (CONSA) for implementation research on newborn SCD screening and early clinical intervention.
- The primary objectives are to determine SCD birth incidence and effectiveness of early standardized care for preventing U5M.

Sickle cell disease (SCD) is a common condition within sub-Saharan Africa and associated with high under-5 mortality (U5M). The American Society of Hematology instituted the Consortium on Newborn Screening in Africa (CONSA) for SCD, a 7-country network of sites to implement standardized newborn hemoglobinopathy screening and early intervention for children with SCD in sub-Saharan Africa. CONSA's overall hypothesis is that early infant SCD screening and entry into standardized, continuous care will reduce U5M compared with historical estimates in the region. Primary trial objectives are to determine the population-based birth incidence of SCD and effectiveness of early standardized care for preventing early mortality consortium-wide at each country's site(s). Secondary objectives are to establish universal screening and early interventions for SCD within clinical networks of CONSA partners and assess trial implementation. Outcomes will be evaluated from data collected using a shared patient registry. Standardized trial procedures will be implemented among designated birth populations in 7 African countries whose programs met eligibility criteria. Treatment protocol includes administering antibacterial and antimalarial prophylaxis and standard childhood vaccinations against infections commonly affecting children with SCD. Infants with a positive screen and confirmation of SCD within the catchment areas defined by each consortium partner will be enrolled in the clinical intervention protocol and followed regularly until age of 5 years. Effectiveness of these early interventions, along with culturally appropriate family education and counseling, will be evaluated by comparing U5M in the enrolled cohort to estimated preprogram data. Here, we describe the methodology planned for this trial.

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Data are available on request from corresponding author, Nancy S. Green (nsg11@cumc.columbia.edu).

The full-text version of this article contains a data supplement.

Introduction

Sickle cell disease (SCD) is a serious inherited red blood cell disorder with stark regional differences in childhood survival, partly depending on the level of health resources.[1-5] For the 300 000 to 400 000 babies born with SCD annually in sub-Saharan Africa, under-5 mortality (U5M) has been estimated as ≥50%.[6-8] This was confirmed in recent assessments and is several-fold higher than U5M in children without SCD.[8-11] Deaths before SCD diagnosis lead to underestimates of disease-associated mortality and underscore the importance of early population-based screening.[4,9]

Major causes of U5M in sub-Saharan African children with SCD include malaria and other infections, severe anemia, respiratory and diarrheal illnesses, malnutrition, and stroke.[12,13] These etiologies overlap with regional health threats to children without SCD. Barriers to survival include the paucity of large, population-based early infant screening programs for early accurate diagnosis of SCD and prompt entry into standardized continuous comprehensive care programs. Implementation of such programs in many middle- and high-resource countries has led to substantial improvement in the survival of children affected by SCD.[14,15] Similar programs have been introduced in some sub-Saharan African countries with high SCD burden.[16-24] However, many of these were pilot programs with limited scale and/or sustainability and did not demonstrate the impact of the program on U5M.

Multinational population-based research on the impact of early screening linked to the delivery of standardized care on U5M is crucial for demonstrating the potential of low-income countries with high SCD burdens to improve outcomes.[25-28] Here, we describe an implementation research trial to assess the hypothesis that a multinational sub-Saharan African standardized newborn screening, with early intervention and continued follow-up, can be implemented, and that the overall intervention will improve U5M outcomes of affected children compared with historical data. Assessment of local collaboration, program support and uptake, protocol fidelity and multiyear sustainability will be additional key objectives in demonstrating program implementation.[29,30]

Methods

Consortium hypothesis, goals, and objectives

To address the challenges facing patients with SCD in sub-Saharan Africa, the American Society of Hematology (ASH) launched the Consortium on Newborn Screening in Africa (CONSA) for SCD. CONSA's hypothesis is that early infant SCD screening and entry into standardized continuous care will reduce U5M compared with historical estimates. The primary objectives of this implementation trial are to determine (1) the population-based birth incidence of SCD and (2) the effectiveness of early standardized care in preventing early mortality in children with SCD consortium-wide at each country's site(s). The secondary objectives are to (1) measure the overall 5-year survival rate of affected children enrolled in the newborn screening cohorts; (2) assess the program uptake, reach, fidelity; (3) evaluate sustainability; and (4) assess the costs of newborn screening and early interventions for each site. To facilitate this initiative, ASH is supporting the 5-year CONSA trial with the overarching goal of establishing a coordinated network of programs throughout sub-Saharan Africa, which institute sustainable national, population-based newborn SCD screening and early standardized intervention procedures to reduce disease-associated pediatric mortality. The ASH Research Collaborative will be the coordinating entity for data collection and analysis.[31]

CONSA is a registry trial based on standard screening and diagnostic procedures and early intervention therapies, specifically penicillin prophylaxis and childhood immunizations (supplemental Appendix 1).[16] Clinical SCD standards for the consortium were established by the National Heart, Lung, and Blood Institute 2014 report and adapted for low-resource settings by public health care networks and pediatric guidelines (eg, the World Health Organization's Expanded Programme on Immunization), consortium's members, and other global SCD experts drawing on SCD care guidelines and the region's newborn screening experience.[16,20,32,33]

The consortium's implementation trial components are to (1) register patient data and medical history of babies diagnosed with SCD within the first 3 months of life in a shared database, (2) initiate antibacterial and antimalarial prophylaxis within the first 3 months of life, (3) ensure immunization of each baby against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib), (4) monitor each patient at required intervals and update the patient's record in the registry after each visit, and (5) estimate the incidence of specific SCD genotypes and identify other hemoglobin variants among populations in CONSA countries.

CONSA organizational structure

CONSA leadership is provided by a steering committee (supplemental Appendix 2) with expertise in SCD in low-resource settings and global health. Any substantive changes to CONSA policies, treatment protocols, requirements of members, and any other proposed alterations must be approved by the full steering committee. Subcommittees have been established and approved (Table 1) to provide guidance and oversight in specific areas.

ASH's contributions to the consortium

The ASH Executive Committee committed $3.15 million to support CONSA over a 5-year period. Funding has been earmarked for each partner country to purchase reagents and consumables for newborn hemoglobinopathy screening; stipends for nursing staff, laboratory staff, data managers, and other project costs; convene stakeholders twice annually; and quality management initiatives. ASH has committed 2 full-time staff dedicated to implementing CONSA through coordination and logistical support for national coordinators. In-kind contributions include coverage of costs for laboratory staff training, registration for the ASH annual meeting, and community educational events for World Sickle Cell Day. ASH negotiated discounts and in-kind donations from industry partners for key consumables and equipment. Furthermore, ASH has facilitated discussions with key US agencies (eg, Department of Health and Human Services) and international bodies (eg, World Health Organization) to support sustainability.

Minimum requirements for country participation in CONSA

Through the ASH leadership, experts from a number of countries were invited to submit applications for membership in CONSA for

Table 1. Summary of CONSA subcommittees and key responsibilities

Subcommittee	Responsibilities
Treatment	Draft, review, and approve any proposed changes to the clinical protocol.
	Support for questions regarding clinical care by CONSA members.
Laboratory diagnostics	Draft the CONSA policy on laboratory and testing standards and coordinate quality assurance (QA) and quality improvement (QI) processes (eg, periodic review of the technical accuracy of screening results).
	Review of training materials from laboratory systems.
	Provide capacity-building training to laboratory staff, as needed.
Data management	Ensure clinical research forms (CRFs) are standardized and follow approved clinical protocols.
	Review data regularly to ensure compliance with data policy.
	Support training activities on data collection and management.
Family education and counseling	Develop and review educational materials, as needed, to be used by clinical sites in family education, counseling, outreach, and training.
Publications	Propose and develop publications for journal articles authored by CONSA members and report on the consortium activities and progress.

Supplemental Appendix 2 lists the CONSA subcommittee members.

Table 2. Requirements for CONSA partner sites

Role	Essential elements
Site leadership	One qualified National Coordinator must be identified to represent all CONSA participants within a single country. This individual must reside in the member country and must demonstrate leadership characteristics necessary to advance the mission of the consortium.
Bloodspot sampling, handling, and testing	The ability to perform population-based newborn sample collection, timely transport to, and testing by 1 or more in-country central laboratory(ies) for hemoglobinopathy testing by isoelectric focusing (IEF).
Clinical services	Access to an established clinical care center for babies identified with SCD to receive standardized care, including availability of folic acid, antimicrobial prophylaxis with penicillin, and antimalarial chemoprophylaxis (or insecticide-treated bed nets [ITNs]).
Immunization services	Access to an established public health immunization program, including standard early childhood vaccines and vaccines against *Pneumococcus* and Haemophilus influenzae type B (Hib).
Family support	Ability to provide adequate family education and counseling services for babies screened and enrolled in the consortium protocol.
Institutional review board–approved program implementation	Local and/or national support for program implementation in 1 or more defined catchment areas, including institutional review board approval before implementation for conduct of human participant research.
Database	Data management capacity and agreement to use the CONSA database.
QA and QI	Willingness to participate in program quality control and interventions, as needed.

review and approval by the steering committee. Membership criteria included capabilities to constitute a program for newborn screening and standardized early childhood SCD care (Table 2), substantial public support from the regional and/or national political leadership, and agreement to follow CONSA requirements, for example, use of the ASH Data Hub for data collection and reporting and participation in program QA and QI measures.

CONSA bylaws require that before enrolling patients in the protocol and capturing data in the shared registry, participating countries demonstrate that the proposed networks (referral hospital/clinics) have the requisite infrastructure and access to clinical services, and are able to provide the required drugs and immunizations. Although the ultimate goal of the consortium is to extend newborn screening and early intervention to the whole country, this was not a prerequisite for participation.

CONSA partner countries

Seven countries joined the consortium: Ghana, Kenya, Liberia, Nigeria, Tanzania, Uganda, and Zambia (Figure 1; Table 3; supplemental Appendix 3). All sites except Kenya had previously performed infant SCD screening. Several other countries were invited to apply, but ultimately chose not to owing to local and/or national barriers to meeting requisite standards.

The CONSA program of each partner country was publicly launched between 2020 and 2021. Each program has garnered support from the regional and/or national political leadership, including leadership from the respective Ministries of Health. CONSA sites also work with local advocacy organizations to raise awareness and educate populations on SCD, diagnosis, and care.

Ethics approvals

For each partner country, ethics approval from the participating institutions and/or designated national bodies for review of human research was required for trial initiation. Each national coordinator was responsible for obtaining initial approvals, and any in-country requirements for approved protocol amendments, data sharing, and renewals. Participating institutions agreed to acquire verbal consent for blood sample collection and written parental consent for clinical follow-up care data collection in accordance with local regulations. CONSA stipulates that all clinical treatment responsibilities for individual patients or research participants shall remain under the sole control and be the sole responsibility of local treating physicians and researchers as per informed consent.

Study population

All newborns within the catchment areas defined by each CONSA participant (referral hospital and local clinics) constitute the study population. Newborns with a positive screen for SCD will undergo confirmatory testing. If positive, the baby will be enrolled in the early intervention protocol (pending parental consent and institutional/regulatory approval) and followed until 5 years of age. The "newborn cohort" will consist of all babies enrolled in the protocol before reaching 3 months of age. Children enrolled at an older age will be treated according to protocol, but their data will be analyzed as a separate "referral cohort." Our hypothesis is that earlier enrollment will lead to the greatest benefit from intervention, but that the referral cohort will benefit from trial interventions to some

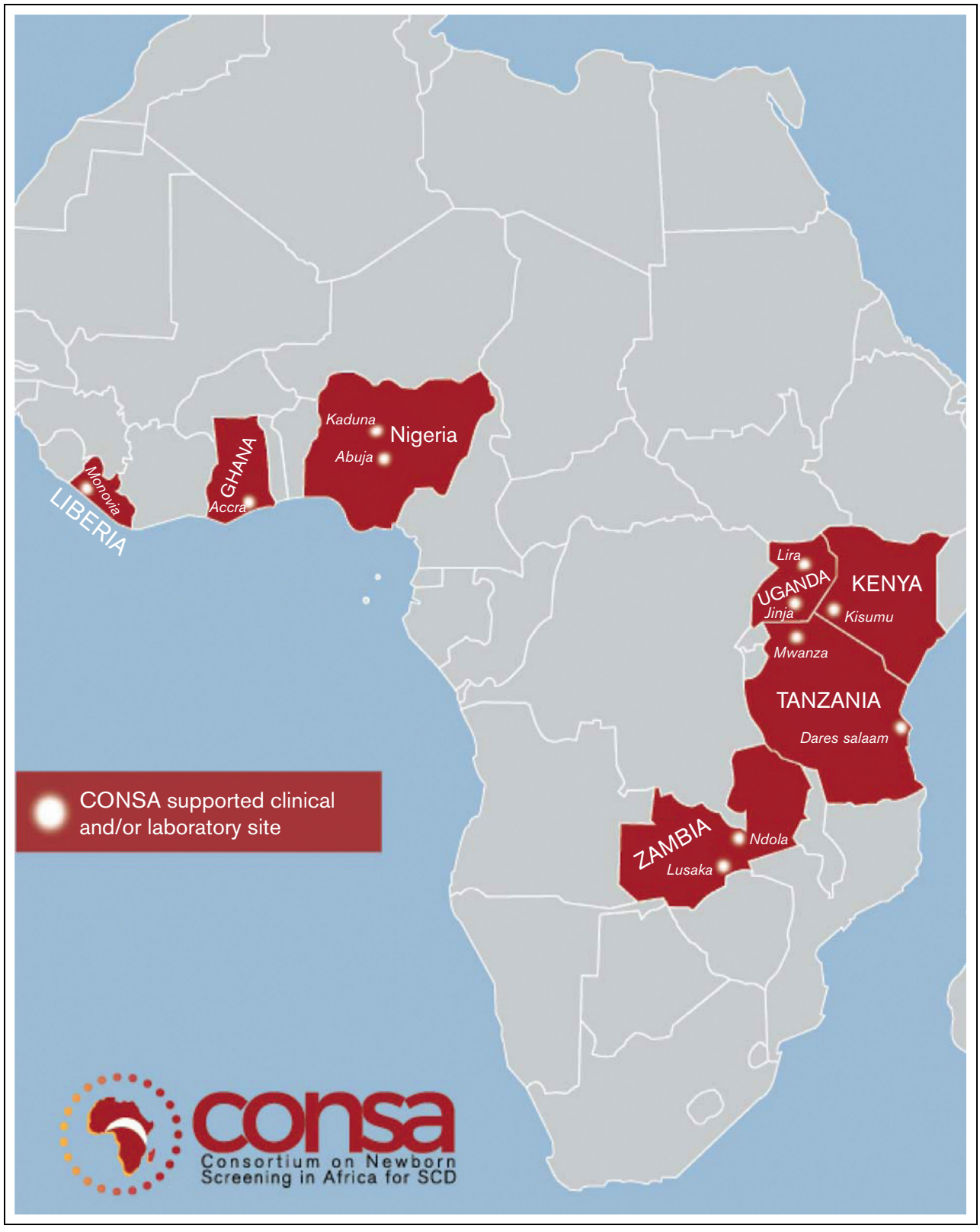

Figure 1. **Map of the 7 CONSA partner sites, by country.**

Table 3. Main elements of each of the 7 CONSA partner sites

Country Screening launch date	National coordinator(s)	Lead site for sampling and clinical care	Lead site for laboratory diagnosis	Supporting sites for sampling and/or clinical care	Catchment area, total annual target number of babies to be screened
Ghana Launch date: December 2020	K.O.-F.*	Greater Accra Regional Referral Hospital 37 military hospitals	Noguchi Memorial Institute for Medical Research	None	Accra 10 000
Kenya Launch date: December 2021	B.A.	Jaramogi Oginga Odinga Teaching and Referral Hospital	Jaramogi Oginga Odinga Teaching and Referral Hospital	Kisumu County Hospital and Lumumba Hospital	Kisumu 10 000
Liberia Launch date: September 2021	P.F.	John F. Kennedy Medical Center	John F. Kennedy Medical Center	James Davies Jr Memorial Hospital, Duport Road Clinic, C.H. Rennie Hospital, C.B. Dunbar Hospital, and Redemption Hospital	Greater Monrovia 10 000
Nigeria Launch date: November 2020	O.E.N.	Federal Capital Territory-University of Abuja Teaching Hospital Kaduna State - Barau Dikko Teaching Hospital - Kaduna State University Ahmadu Bello University Teaching Hospital	Federal Capital Territory - Centre of Excellence for Sickle Cell Disease Research and Training, University of Abuja Kaduna State -Sir Patrick Ibrahim Yakowa Memorial Hospital Reference NBS Lab, Kafanchan	Federal Capital Territory: University of Abuja Teaching Hospital, Gwagwalada Town Clinic; and Angwan Dodo, Dutse Makaranta, Dutse Alhaji, Kuje, Lugbe, Papei, Tungan Maje; and other primary health care centers Kaduna State: Yusuf Dantsoho Memorial Hospital; Gwamna Awan Memorial Hospital; Kawo General Hospital; Institute of Child Health, Banzazzau, Zaria; and Ahmadu Bello University Teaching Hospital	Federal Capital Territory Kaduna State 16 000
Tanzania Launch date: June 2021	L.C.	Muhimbili University of Health and Allied Sciences Bugando Medical Center	Muhimbili University of Health and Allied Sciences Bugando Medical Center	Temeke Regional Referral Hospital and Amana Hospital	Dar es Salaam Mwanza 10 000
Uganda Launch date: June 2021	C.K.	Jinja Regional Referral Hospital Lira Regional Referral Hospital	Ministry of Health - Central Public Health Laboratory	Immunization clinics	Jinja District Lira District 10 000
Zambia Launch date: April 2021	C.C.-L.	University Teaching Hospital - Children's Hospital Arthur Davidson Children's Hospital	University Teaching Hospital - Children's Hospital Arthur Davidson Children's Hospital	Immunization clinics, HIV-early infant diagnosis units, outpatient units	Lusaka Ndola 10 000

A total of 18 screening sites and 11 clinical sites across the 7-country consortium were selected for conducting trial procedures.
*Deceased. Search for replacement is underway.

extent. Separating children into 2 cohorts will provide for ethical treatment for both cohorts while maintaining analytic rigor.

Clinical protocol

The complete protocol is in supplemental Appendix 1. The first clinical appointment for babies with confirmed SCD must be conducted within the first 3 months of the baby's life. This visit includes the following information, recorded in the database:

- Confirmatory IEF hemoglobinopathy test with results recorded in the patient record established at initial screening.
- Parental consent for participation in the trial registry.
- Confirmation of parental contact information.
- Initiation of penicillin prophylaxis.
- Initiation of folic acid supplementation.
- Recording of the baby's immunization history for *Pneumococcus* and Hib.
- Provision of malaria prevention: ITNs and/or standard chemoprophylaxis.
- Scheduling of the second clinical visit, to occur within 3 months following the first visit.

The second clinical visit should be conducted within 6 months of the baby's birth and includes:

- Review of the confirmatory hemoglobinopathy test with parents/caregivers.
- Parental counseling about SCD.
- Completion of the parental consent form, if not completed during the initial clinical visit.

- Blood testing: complete blood count with differential and reticulocyte count, and malaria smear and parasite density.

Schedule of subsequent routine clinical visits:

- Every 3 months until 2 years of age and every 4 to 6 months from 3 to 5 years of age.
- Complete blood count with differential and reticulocyte count, annually.
- Malaria smear and parasite density, every 6 months.

Unscheduled medical visits will also be recorded.

Family education and counseling

Information conveyed to families before screening includes the potential benefits to the child for early diagnosis of SCD. At the confirmation visit of babies with positive SCD, key messages for families include basic information about the disease: the need for preventive medical care; urgent attention to symptoms such as fever, cough or pallor; and encouragement about childhood survival. Additional discussion should address the potential stigma associated with SCD and disproportional stigmatization of the mother, so both parents (or mother and another supportive party) are encouraged to attend the confirmation visit. The requisite inheritance of a hemoglobinopathy trait from both father and mother, the reasons SCD may be absent in other family members, and the potential for SCD in other family members are critical elements of counseling. These messages will be adapted to local language, culture, and context by each site.

Data collection

The ASH Research Collaborative Data Hub supports the CONSA database by providing online data collection tools, expert services, and serving as the data repository. ASH staff and data management experts have provided ongoing training, tool development, and monitoring of the database to ensure accuracy in data collection and analysis. Data privacy requires that identifiable trial participant data are accessible only by the respective site's study personnel. A data manager for each site is supported by ASH and must comply with QA/QI requirements for data management training, troubleshooting, networking, and scheduled reviews of deidentified data.

Enrolled children are assigned a unique study identification number. Initial CONSA CRFs require demographic data collection (eg, name, date of birth, sex, site of sampling, birthweight, gestational age [<37 weeks], multiple gestation/birth defects, blood transfusion history, results of screening and clinical testing, and parental/caretaker data for locating the child [name, occupation, telephone numbers, places of residence, workplace, and worship]). Initial clinical visit data include confirmatory results, review of protocol, education, and counseling points discussed with parents/caregivers, home management, acute care issues, spleen palpation, information on social support, and/or advocacy groups. Visit data include vital signs, prophylaxis and immunization history, clinical test results, medical events, and next appointment date. Additional data collected for babies with positive screens are caretaker(s) relationship to the child, name, and occupation. A CRF covers loss to follow-up and/or death. Cause of death, if known, will be reviewed by the data subcommittee as related/possibly related to SCD or unrelated, for example, trauma.

Assessment of trial outcomes

Population-based incidence of sickle trait and SCD among screened babies will be obtained for each county and for the birth cohort overall. Death under age 5 years of life is the primary end point for children with SCD enrolled in the CONSA trial. Estimated 2019 rate of overall childhood U5M in the region was almost 8% of live births, including risks not directly related to SCD.[34] For these reasons, and for discerning loss to follow-up for nonfatal reasons, the process for capturing information about missed clinical visits will include strenuous attempts to contact the child's parent/guardian/family members (at least 2 attempts) and hospital staff, in case of hospital admission or death. Data will be collected about family intent for trial continuation or cause(s) of death. There will be limited ability to determine precise cause of death, especially for events occurring outside of a medical facility.[35] CONSA will seek to (1) confirm deaths through contact with parents/families of enrolled children and (2) determine cause of death as probably/possibly SCD-related compared with unrelated (eg, occurrence before age 3 months, congenital anomaly, or accident/trauma/maternal mortality).

Surveys of participating families and other evaluative tools will be utilized to assess success and barriers to implementation of the CONSA trial and enhanced research capacity of the program staff. The steering committee will evaluate the outcomes, focusing on newborn screening, establishing SCD patient registry, implementation of interventions, delivery of standardized care, and health policy to enhance sustainability.

Biostatistical analyses

Sample size for each partner country was determined from 2 considerations: (1) estimated allele frequency of hemoglobin S (HbS) and HbC traits for predicting number of SCD diagnoses and (2) capacity for program conduct. For those reasons, 6 countries will screen 10 000 infants annually, with Nigeria to screen 16 000 annually.

SCD birth prevalence will be estimated for each site and the consortium overall using the HbS and HbC allele prevalence identified across screened infants. Let $p_S(j)$ be the HbS allele prevalence at site j [calculated out of $2n(j)$ alleles], then the estimated HbSS prevalence is $p_S(j)$.[2] Analogous estimates will be made for the compound heterozygous genotype HbSC as $2p_S(j)\,p_C(j)$. Confidence intervals will be estimated at the allele level using standard binomial formulas, then transformed to prevalence scale. Assuming SCD birth site prevalence of 0.5% to 2%, we expect to identify 250 to 1000 affected infants per site, with 800 to 1200 infants in Nigeria's larger sample. We will test for Hardy-Weinberg genetic equilibrium using χ^2 tests to examine evidence for either assortative mating or excess prescreening mortality among infants with SCD. In sites with noncontiguous catchment areas, estimates will be made separately for each area and for the entire site. In sites with complete information regarding rural and urban residence, subgroup analyses will be carried out for each type of residence.

Entries with missing genotype will be excluded; entries with genotype but missing subgroup data (eg, area of origin or

urban/rural) will be tallied and analyzed under an "other or missing" category for the missing variable(s). The number and proportion of missing entries will be reported in all analyses. For survival analysis, children with missing survival entries at follow-up end will be censored at the most recent date with data. Sensitivity analyses will exclude these children altogether or assume that they died immediately after loss to follow-up. Missing covariates will be imputed using Demographic and Health Surveys' standard "hot-deck" approach when relevant.[36]

At study end, U5M will be calculated for each site via the synthetic cohort life-table method used in standard Demographic and Health Surveys.[37] Subgroup analyses by SCD genotype, catchment area, and other key demographic categories will be performed. Some neonatal and early infant mortality will be missed owing to infant deaths before screening sample access.

Country site(s) responsibilities and accountability

Partner countries of CONSA must fulfill all the protocol requirements listed in Table 4.

Technical training for partner country's program staff

Training CONSA laboratory/clinical/data management staff has been a key aspect of program initiation and QA/QI. Training courses are available on the CONSA website and cover database entry and use, clinical care for young children with SCD, procedures to support follow-up from screening and clinical care, and laboratory procedures. Because country rollout occurred in successive waves, laboratory training sessions were held at different times and locations. In 2019, laboratory technicians from Ghana, Kenya, Liberia, Tanzania, and Zambia participated in a 2-day PerkinElmer (Waltham, MA) workshop held in Johannesburg, South Africa. PerkinElmer has contributed to the training of technical staff in installation of IEF equipment, running samples, and technical QA/QI. Because of the COVID-19 pandemic, some of the later training sessions were performed virtually. Site visits were conducted by both cochairs of the Laboratory and Diagnostics subcommittee (supplemental Appendix 2).

For training clinical staff, each participating site developed its own training processes, including tailored materials for staff and for

Table 4. Treatment, laboratory, and data collection requirements for CONSA

Standard clinical care	Program site requirements for clinical care
Medication use	Prompt availability and ability to administer/prescribe the principal drugs scheduled in the protocol, including penicillin and folic acid, once diagnosis of SCD is confirmed.
Immunization standard	An established Essential Programme on Immunization (EPI) must include administration of 2 vaccinations: pneumococcal (PCV-10 and PCV-13) or PPV-23, if the other pneumococcal vaccines are not available; and Hib.
Immunization requirement	CONSA participants from countries that do not operate EPI or have an EPI, which does not include the required vaccines identified in the requirement above, must demonstrate capacity to ensure that all patients will receive all required vaccinations within the appropriate timeline by an alternate mechanism.
Data system requirement	Ability to participate in the consortium's data reporting system with a designated data manager and reliable Internet capabilities onsite.
National approvals for human participant research and other regulatory authorities	Approval by the institutional ethics committee (eg, institutional review board) and other local/national authorities (if necessary) to capture patient data in the consortium's data reporting system and enroll patients into the registry trial.
Clinical care program	Established clinical care program for children with SCD that includes at least 1 pediatric SCD clinic or pediatric hematology clinic per week with personnel dedicated to the care of pediatric patients with SCD.
Catchment area	All CONSA participants must establish a proposed catchment area under the protocol and provide a plan to screen all babies within the designated area. CONSA participants must describe how they plan to enroll all babies with SCD into the protocol and patient registry.
Malaria prophylaxis	Malaria prophylaxis in the form of ITNs and/or standard recommended chemoprophylaxis must be provided to new or expectant mothers free-of-charge by the public health system of the country of the CONSA participant. If this is not ensured by the national public health system, the CONSA participant must show that ITNs and/or antimalarial chemoprophylaxis can be provided for free to families of all patients.
Laboratory and sampling	**Screening, laboratory, and diagnostic requirements**
Personnel compliance	Personnel at the referral laboratory must be in compliance with national regulations regarding laboratory certification and be willing to participate in the consortium-approved QA program.
Staffing for sample collection	Personnel must be trained to gather blood spots via filter paper cards from newborns in accordance with the protocol guidelines (supplemental Appendix 1).
Sample collection	Blood sample collection via heel prick should be obtained by 6 weeks of life, either in hospital when the baby is born or at the first neonatal care visit following birth (ie, first vaccination appointment).
Sample collection and laboratory materials	Logistics (availability of filter paper cards, gloves, lancets, shipping methods, etc) necessary for timely collection and shipment of screening samples to the referral laboratory.
Laboratory capacity for screening and diagnosis	A referral laboratory that can perform the initial screening test and confirmation tests via IEF and report results to the referring institution within 2 weeks of receipt of blood samples.
	Additional requirements
Family education and counseling	Each CONSA participant must have adequate family education and counseling services for families of babies enrolled in the consortium protocol.
Database requirements	Completion of the CRF for each clinical visit in the consortium database shortly after each visit.

parents/caregivers of affected infants, with support from ASH staff. This approach is concordant with an implementation research framework.[30] Training consisted of an overview of CONSA and project goals; newborn screening; data collection, entry, management and analyses; as well as standardized clinical care and genetic counseling on SCD for parents/caregivers of affected babies.

QA/QI

Regular and rigorous QA/QI is an essential aspect of the CONSA program to ensure accuracy of the data and to build capacity at each site. CONSA program leadership will perform periodic site visits to assess all aspects of program implementations. Site visits will be virtual or in person, depending on travel safety related to the COVID-19 pandemic. Three QA/quality control topics are described here in detail: data collection, laboratory performance, and clinical care, with centralized oversight from the respective CONSA subcommittees.

Data collection includes management of QA and data analyses. Each site has data clerks for manual database entry of contact information, demographics, screening and clinical results, and clinical follow-up. Data managers at each site oversee data entry and quality spot checks, do regular data review, and support clinical data entry. ASH staff provide training and technical assistance to site staff, monitor the database to ensure quality and completeness of data, and undertake remediation as needed, for example, for missing data.

QA/QI for hemoglobinopathy laboratory assays at each site are under direct oversight of the Laboratory and Diagnostic subcommittee and include (1) use of standardized PerkinElmer Migele IEF equipment and Resolve kits; (2) compliance with CONSA standard operating procedures for performing IEF and interpreting results; (3) photographs of all IEF gels and worksheets, uploaded on a weekly basis to an ASH Google drive folder for each country; (4) regular technical quality review of the IEF gels and accuracy of result interpretation; (5) regular virtual meetings with laboratory staff at each site for troubleshooting and retraining, as needed; (6) mandatory confirmatory IEF test for each baby with SCD enrolled in the CONSA clinical care program; and (7) collaboration with the United Kingdom National External Quality Assessment Service to regularly assess the quality of results from each site.

QA/QI for clinical care and follow-up is supported by monitoring clinical sites to ensure compliance with CONSA requirements as outlined in Tables 2 and 4. Oversight is provided by hematologists and/or pediatricians experienced in hematology and management of acute childhood illnesses and clinical SCD complications. Regular CONSA review for QA will include the completeness of submitted CRF data, medication distribution and adherence (eg, penicillin and malaria prophylaxis), management of acute clinical complications, elapsed times between screening and confirmatory tests, family education and counseling, initiation and continuity of standard care, excess participant loss owing to follow-up or deaths, and other barriers to program implementation. As needed, assistance will be provided by CONSA, potentially in concert with other regional SCD networks, for example, Sickle Cell Pan-African Research Consortium.[27,38]

Sustainability

Sustainability of the CONSA program requires continued partnerships with key local/regional/national stakeholders, including Ministries of Health, health care providers, and consumer advocates; alignment of program goals with local/national health policies; training of program staff in key functions; and ongoing standardized QA procedures for maintaining implementation. CONSA places strong emphasis on the need to engage each country's national health care leadership and existing infrastructure to sustain consortium activities through development of policy for expansion into a screening program. These strategies vary across countries owing to heterogeneity of the existing support and health care landscape in each region.

Strategies being adopted include (1) sensitization of the public via mass media to enhance awareness and reduce disease-associated stigma, (2) educational activities for health care authorities and practitioners focusing on the care of children with SCD, (3) local and national advocacy to expand SCD care and designate it as a covered entity under national health insurance schemes; one important component of these efforts is advocating for inclusion of hydroxyurea among the essential drug list in each country, (4) development of national standard operating procedures for newborn screening and new/updated SCD treatment guidelines that align across participating countries, (5) establishment of hematology technical working groups that prioritize SCD within the health ministries, and (6) advocacy for embedding newborn SCD screening and standard early intervention within existing primary health care centers and linkages to other concurrent SCD-focused sub-Saharan programs, for example, SickleInAfrica and Sickle Cell Pan-African Research Consortium.[27,29,39]

Ongoing public-private partnerships in each country have provided equipment, materials, and training for laboratory staff for screening infants, as well as an electronic application developed by the Ghana SCD screening program. The application improves linkage of electronic documentation and communication from SCD screening to clinical follow-up and is being offered to each CONSA country. These additional resources will help support program success and sustainability.

Discussion

CONSA represents a unique opportunity to assess outcomes of newborn screening for SCD and early intervention in low-resource settings where SCD is a prevalent condition associated with high, but heretofore undocumented impact, on early childhood survival. This implementation trial is an unprecedented effort to determine U5 morbidity and mortality in a registry-based SCD cohort using a standardized protocol and shared database in 7 countries in sub-Saharan Africa. Other key aspects of partner collaboration include (1) local and/or national public health outreach and other mechanisms of program support; (2) uniform data requirements within the data collection system; (3) cross-consortium collaborations and guidance; and (4) a shared approach for training, program maturation, data analyses, and dissemination.

ASH provides ongoing support by convening CONSA members at regular meetings, facilitating training of data managers and other key personnel (eg, nurses), procurement of required consumables, and providing content of materials for family education in the care

of young children with SCD. All 7 partner countries have successfully launched their programs. Collaborations with ASH and between partner country leadership are intended to deepen over time to accomplish the CONSA goals and enhance sustainability through governmental support and potential public-private partnerships.[21]

Challenges encountered early in program implementation included the following local and regional barriers: (1) logistical challenges for program launching at each site, for example, public participation of local and/or national health leadership; (2) infrastructure limitations such as space and suitable equipment, along with maintenance plans; and (3) delays in the acquisition and establishment of a stable source of consumable materials for screening and other program processes. Future challenges to impact may include reluctance of community and family engagement, competing public health priorities, and resource limitations for program sustainability.[38,39]

The impact of the global COVID-19 pandemic, starting in 2020, generated additional challenges[15] and imposed burdens on already strained local and/or national health resources and socioeconomic well-being. This shifted attention away from SCD and toward pandemic-related health care, reducing mobility and access because of population lockdowns as containment strategies to limit pandemic contagion, as well as reduced access to standard required pediatric vaccines owing to disruption of supply chains.

Despite these challenges, the resolve and collective wisdom of the CONSA partnership led by ASH, and the rising societal awareness in sub-Saharan Africa of the importance of the study goals, are continuing to drive progress and build momentum, as demonstrated by the successful establishment of the program in all partner countries. In addition to trial goals, consortium strengths also include capacity building at each site that may evolve toward country-led expansion in newborn screening, laboratory, and clinical programs for SCD.

CONSA is modeled after the International Consortium on Acute Promyelocytic Leukaemia (IC-APL), the first international multinational collaborative led by ASH in 6 Latin American countries.[40] IC-APL, like CONSA, adapted successful strategies employed in high-income countries to assess the impact on disease survival through the use of standardized diagnosis and treatment adapted to low- and middle-income countries. Analogous to CONSA's focus on reducing U5M from SCD, the IC-APL goal was to improve survival through early diagnosis and structured therapy for APL. Despite some challenges, IC-APL efforts successfully resulted in substantially reduced mortality compared with historical controls and development of enhanced capacity for leukemia treatment and research in participating countries in Latin America. The success of IC-APL augurs well for CONSA, notwithstanding the notable differences in geographical setting and scope.

Ultimately, newborn screening and early interventions for SCD are a compelling public health priority that should be implemented at the national level. The hope and spirit of CONSA is to catalyze progress toward this goal by demonstrating the high neonatal burden of SCD in the participating countries and the effectiveness of early intervention in reducing mortality by establishing a robust network of local experts and far-reaching public, foundation, and industry partnerships. Moreover, successful implementation of CONSA will provide a model and impetus for similar programs within and beyond the region where high disease burden and resource constraints may exist.[7]

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Authorship

Contribution: N.B., E.M.N., T.L.C., A.A.T., K.O.-F., B.A., V.N.T., O.E.N., C.C.-L., C.K., and L.C. (Steering Committee) designed the overall study, with significant contributions from B.P.D.I., R.E.W., I.O., A.P.O., C.W., and N.S.G.; O.E.N., P.F., V.N.T., L.C., C.K., C.C.-L., B.A., K.O.-F., I.O., E.E.A., and L.G.D. established the study, led the study sites, and provided data; N.S.G., A.Z., T.L.C., E.M.N., and O.E.N. led the manuscript writing, and editing (Publications Committee and American Society of Hematology staff); and all authors wrote, reviewed, and approved the manuscript before submission.

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