STROKE TRAINING, RESEARCH, AND EDUCATION TOWARD CAPACITY WITH HYDROXYUREA (STRETCH)

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DEDICATION

Dedicated to Luke, Andy, and Jude, with love and gratitude for the journey and adventure of being your mom.

ACKNOWLEDGMENTS

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ABSTRACT

Background and Purpose

Sickle cell anemia (SCA) is an inherited hematological disease characterized by chronic pain, susceptibility to infections, and significant morbidity and mortality, particularly among children living in resource-limited settings. Stroke is a complication of SCA that can be prevented through transcranial Doppler (TCD) ultrasonography, a screening tool that identifies children at risk, and treatment with hydroxyurea. This study will inform how public health leaders can mitigate stroke risk among children with SCA in sub-Saharan Africa and how TCD screening fits into a larger context of providing safe, effective care.

Methods

Stroke Training, Research, and Education Toward Capacity with Hydroxyurea (STRETCH) utilized a qualitative design that included semi-structured interviews with TCD examiners and stakeholders. There were 17 interviews with TCD examiners who participated in a training and supervision program, TCD trainers, and clinical care providers from 6 countries across sub-Saharan Africa. Interviews were coded and analyzed for themes that were used to identify effective training and program strategies, and to develop a capacity-building model for resource-limited settings.

Results

Participants reported satisfaction with the training program, noting that in-person training with sub-Saharan Africa-based examiners was preferable to initial training using a web-based platform, and that ongoing training, supervision, and technical support through collaboration between US-based and Africa-based teams was conducive to skill

development. Participants described the major clinical and socioeconomic impact of SCA on children, families and communities and emphasized the role of hydroxyurea in preventing complications and decreasing burden on health systems. Results indicate a call to action for improved education for clinicians, families, and community leaders and stakeholder support for health policy to facilitate access to hydroxyurea.

Conclusion

The complexities of healthcare infrastructure and the morbidity and mortality associated with SCA in resource-limited settings warrant a multifaceted approach to capacity building. The STRETCH model integrates education, policy development, and access to hydroxyurea as a holistic approach that leverages geographical partnerships and builds on existing resources in sub-Saharan Africa. By simultaneously addressing education, policy, and access barriers, public health leaders can work collaboratively toward building sustainable capacity that improves outcomes for children with SCA in these settings.

Katarzyna Czabanowska, PhD, Chair

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ABBREVIATION	
CCHMC	Cincinnati Children's Hospital Medical Center
MTD	Maximum Tolerated Dose
SCA	Sickle cell anemia
STRETCH	Stroke Training, Research and Education Toward Capacity Building with Hydroxyurea
TCD	Transcranial Doppler
TAMV	Time-averaged mean velocity

CHAPTER 1: INTRODUCTION

Problem statement

Sickle cell anemia (SCA) is an inherited hematological disease characterized by severe anemia, susceptibility to infections, recurrent painful events, and progressive organ failure. SCA is associated with increased morbidity and mortality, particularly in children under the age of 5 years, and most significantly impacts resource-limited settings where the capacity for diagnosis, screening for complications, and provision of care to these at-risk patients is limited. The recent Global Burden of Disease Study (2023) found that during 2000-2021, births of babies with SCA increased globally by 13.7%, and that mortality due to SCA was 11 times higher than that of all-cause mortality. The mortality burden of SCA is highest in children, particularly in countries with the highest under-five mortality rates, with SCA ranking in the top 20 causes of death in sub-Saharan Africa as compared to 76 -137th in respective high-income countries.

Stroke is one of the most severe acute complications of SCA and has devastating consequences for patients and their families. Stroke also represents a risk that can be mitigated with appropriate screening and preventive treatment. Transcranial Doppler (TCD) is a non-invasive screening tool using ultrasonography, that has been shown to be highly effective in identifying children with SCA who are at increased risk for stroke (Adams et al., 1992). Early identification allows for interventional treatment to mitigate the risk of stroke (Adams et al., 1998). Currently, TCD screening is extremely limited in sub-Saharan Africa, and its lack of utilization represents a capacity gap in a part of the world where the disease burden of SCA is greatest. The design and implementation of a well-structured training program, which includes ongoing supervision, retraining, and

informatics-based methodology for the review and scoring of TCD exams, represents an example of high impact capacity-building in low-resource settings with the greatest need.

To effectively perform high-quality TCD exams within the context of clinical research protocols and provide a framework for broader use in clinical settings, TCD screening must be implemented in a structured manner, involving a multi-tiered approach that includes validation and provision of equipment and technology, training local personnel, and building leadership and technical expertise on the continent of sub-Saharan Africa. Establishing a US-based coordinating center to support TCD examination and centrally score exams is insufficient for filling capacity gaps within local contexts and would limit the ability to provide a model for addressing broader educational gaps within these settings in a sustainable manner.

In 2015, Cincinnati Children's Hospital Medical Center (CCHMC) in Cincinnati, Ohio USA, initiated the first stages of a TCD screening and supervision program which evolved over the course of the next eight years to include TCD examiners from eight research sites in seven countries within sub-Saharan Africa, who now perform TCD exams under the supervision of a coordinating center at CCHMC in partnership with two expert super-examiners in Tanzania and Uganda. This novel approach that leverages expertise from the US and supports transfer of technology, capacity, and leadership skills into resource-limited settings can be used as a model for change at the local policy and practice levels in sub-Saharan Africa and will avoid unintentionally developing systems that involve perpetual reliance on external support. Partnering with research sites in sub-Saharan Africa involves cultural, linguistic, and operational challenges that require skilled leadership, shared vision, flexibility, and communication. This project will

describe capacity building efforts through the introduction of TCD technology, refining of TCD skills among examiners, and development of leadership and organizational skills within the super-examiner group and provide a scalable framework for stroke prevention through screening for risk and facilitating increased accessibility of treatment with hydroxyurea within local settings in sub-Saharan Africa.

Research Aims

Primary Research Objective

The primary objective of Stroke Training, Research, and Education Toward Capacity with Hydroxyurea (STRETCH) is to describe how public health leaders can mitigate stroke risk among children with SCA in sub-Saharan Africa using a feasible, effective, and sustainable Transcranial Doppler screening, training, and supervision program.

Secondary Objectives

- Describe the operational and systemic factors which influence the training and implementation of TCD screening in sub-Saharan African settings;
- Explore the role public health leaders have in the development of contextualized leadership skills within resource-limited settings providing clinical care to children with SCA;
- Assess and describe the role of technology and knowledge transfer as a key driver of stroke screening and prevention in the defined population; and
- Provide recommendations regarding how TCD screening for stroke risk in SCA in pediatric settings fits into the larger organizational context of providing safe, effective, and culturally-appropriate care.

Background and Significance

Sickle cell anemia (SCA) is among the world's most common forms of inherited hemolytic anemia, and results in significant morbidity and early mortality. SCA is most prevalent in Africa, with as many as 300,000 babies born annually, representing up to 2% of newborns in some sub-Saharan countries (Weatherall et al., 2005). Assuming that many of these babies die early in childhood, the World Health Organization (2010) estimates that SCA causes 6-16% of under-five mortality for many African countries, and this burden is projected to further increase substantially in the future. SCA is associated with high morbidity and mortality, particularly in children under five years of age. Acute complications of SCA include increased susceptibility to pneumococcal infections, vaso-occlusive painful crises, splenic sequestration, acute chest syndrome, stroke, and priapism with chronic complications including cerebrovascular damage, kidney disease, avascular necrosis, and gallstones (Mburu and Odame, 2019).

Blood transfusions are the main treatment for many life-threatening complications of SCA, including severe anemia due to hyperhemolysis or aplastic crisis, acute chest syndrome, splenic sequestration, and stroke; in Africa, malaria infections represent an additional reason for transfusions. Transfusions have risks including the transmission of blood-borne infections, transfusion reactions, and iron overload. Further, in sub-Saharan Africa blood transfusions represent a scarce resource within health systems. For example, in the Republic of Uganda in 2019, only 65% of blood transfusions requested were administered due to scarcity within the local blood supply, which was further exacerbated by the 2020 COVID-19 pandemic (Loua et al., 2021). The World Health Organization (2017) found that the majority of countries in Africa were unable to sustain adequate

volumes of blood needed to supply the per capita recommendation and had limited capabilities to maintain the safety of that supply. An alternative to transfusions, therefore, is needed to help manage SCA complications in sub-Saharan Africa.

Hydroxyurea is a simple but potent disease-modifying medication for SCA that increases fetal hemoglobin (HbF), inhibits intracellular sickling, limits vaso-occlusion, and decreases hemolysis and inflammation (Ware, 2010). Through induction of fetal hemoglobin (HbF), hydroxyurea has been shown to be a safe, accessible, and effective once-daily oral therapy that improves clinical outcomes in sub-Saharan Africa (Tshilolo et al., 2019, John et al., 2020). Its utilization is minimal in most pediatric settings in sub-Saharan Africa, and conventional strategies to achieve an appropriate, optimal dose require frequent clinic visits and laboratory monitoring, which present feasibility challenges in resource-limited settings.

Stroke is a common complication of SCA, occurring as young as 2 years old. Publications from the era before routine stroke screening and treatment provide natural history data regarding the frequency and severity of stroke. Children between the ages of five and nine years old have the highest incidence, and by the age of 20 years, the cumulative incidence of primary stroke is 11%, with devastating clinical consequences and up to one-third of patients die as a result (Powars et al., 1978, Ohene-Frempong et al., 1998). For those who survive their first stroke, a variety of neurocognitive disabilities persist, and recurrent stroke is common, especially in the first three years immediately following the initial incident (Powars et al., 1978). The substantial morbidity and mortality associated with stroke in this population necessitates the implementation of

locally feasible screening methods that allow children at increased risk to be identified and appropriate life-saving preventive treatment initiated.

TCD ultrasonography measures cerebral blood flow velocity in the major intracranial arteries. TCD uses ultrasound waves to measure the rate and direction of blood flow in the vessels within the Circle of Willis at the base of the brain and identifies vessels with high arterial flow by recording the time-averaged maximum velocity (TAMV). Normal velocities (<170 cm/sec) are associated with the lowest stroke risk, while conditional velocities (170 to 199 cm/sec) and abnormal TCD velocities (≥ 200 cm/sec) are associated with moderate risk and highest risk, respectively (Adams et al, 1992). TCD is a standard screening tool used in the United States and Europe, however its use in resource-limited settings where it has substantial opportunity to change clinical outcomes for children with SCA is limited based on lack of experienced examiners and limited use of hydroxyurea for stroke prevention.

In addition to morbidity and mortality associated with SCA, complications of SCA negatively impact individual and family quality of life and increase healthcare utilization and burden resource-limited healthcare systems. Mburu and Odame (2019) noted that in sub-Saharan Africa, the disease burden is exacerbated by inadequate healthcare infrastructure, poor nutrition, and infectious comorbidities including malaria, tuberculosis, and HIV. The outlook for children with SCA in sub-Saharan Africa, however, is not entirely bleak. Ambrose et al. (2023) in an open-label, Phase 2 trial found that TCD screening plus hydroxyurea at maximum tolerated dose (MTD) was an effective stroke prevention strategy in an African setting, demonstrating the crucial need to fill this capacity gap. Public health leaders implementing TCD screening training,

education, and screening programs to identify children at increased risk for stroke in conjunction with improvements in the accessibility of hydroxyurea is therefore an opportunity to both improve outcomes for children with SCA in these settings and build capacity within local healthcare settings through structured education sessions and ongoing supervision.

Leadership Change Management: Theoretical Frameworks

Public health leaders can respond to opportunities to effect change within public health settings through the identification of tools that are feasible and appropriate within local contexts, planning for change utilizing public health and leadership change models appropriate for the focus and setting, and then implementing them in a manner that enhances their uptake and optimizes their impact on patients, families, and communities. The RE-AIM framework (Glasgow et al, 1999) is a model used in public health settings to evaluate the impact and sustainability of interventions. The model consists of five key dimensions: Reach, Efficacy, Adoption, Implementation, and Maintenance, and will be used to describe change management activities and public health recommendations associated with TCD screening programs. This is of particular relevance in resource-limited settings where assessment of short-term objectives as well as broader impact within the local context are key to understanding long-term viability of interventions.

TCD screening is a significant opportunity to effect change within public health systems in resource-limited settings, and fits into a broader context of the need to build capacity for diagnosis and treatment of affected individuals as well as to strengthen the healthcare workforce providing care to this at-risk, underserved population. The Collective Impact Model (Kania and Kramer, 2011) will be used to describe the

implementation of TCD training, education, and screening programs in conjunction with recommendations for increased accessibility to disease-modifying therapy. The Collective Impact Model facilitates description and understanding of how multiple players may change their behaviors to solve complex public health problems and a context to understand how long-term change can be achieved in these settings. Clinical settings are traditionally characterized by a hierarchical leadership structure, and the Collective Impact Model will provide an alternative lens through which responsibilities can be shared, distributed, and/or rotated among team members, thus strengthening the healthcare workforce at the organizational level in settings where this represents a significant capacity gap.

Rationale for This Study

Leadership behaviors, strategies, and qualities represent one of the most fundamental factors of healthcare workforce development (De Brun et al., 2019), which is particularly relevant within resource limited settings where leadership change management is needed at multiple levels within health systems. The qualitative design of this study, which includes an integrative literature review and data collection through semi-structured interviews with individuals who can provide specific, contextual insights into TCD training and supervision methods as well as systemic, operational, workforce, and educational factors within their local settings, allows for thematic analysis to provide crucial information to fill the existing knowledge gaps and inform future directions for international research collaborations. STRETCH represents an opportunity to describe an evolving TCD examiner program from the perspectives of examiners, trainers, and stakeholders and to provide informed recommendations for policy and healthcare

workforce capacity-building best practices within health systems caring for children with SCA in sub-Saharan Africa.

CHAPTER 2: LITERATURE REVIEW

Introduction

An integrative literature review was performed with the objective of providing crucial context for how public health leaders best implement a high-quality, effective multidisciplinary TCD screening program to identify children with sickle cell anemia (SCA) who are at increased risk for stroke in resource-limited settings in sub-Saharan Africa. This review aimed to 1) understand the magnitude of the problem; 2) gain further insight into TCD as an effective, feasible mechanism to identify children at risk for stroke; and 3) understand the operational and systemic factors which impact the training and implementation of TCD screening in a resource-limited setting. Secondary review focused on where children with SCA seek care, including healthcare infrastructure, cultural issues, and technology transfer and how public health change models can be applied to understand and define a pathway for change.

Literature Review Design

An integrative literature review is a structured method which incorporates diverse research methodologies to capture the full context of a chosen subject (Whittemore and Knafl, 2005). This method involves defining a problem or question, searching literature, evaluating, and coding results into themes or categories, which can then be used to synthesize evidence into conclusions. While early iterations of this design were criticized as lacking the rigor associated with a systematic review, the updated methodology has more structure, inclusion/exclusion criteria, and methods to enhance data collection and analysis to provide the necessary rigor of a robust review while allowing for the flexibility to include a variety of research designs. Integrative design was chosen for this

review as it provides structure while allowing for a comprehensive description of the existing knowledge and gaps from a variety of perspectives to facilitate a more in-depth understanding of the complex and inter-related themes. An integrative literature review structure is further suited for this topic in that it incorporates multiple purposes, including reviewing existing literature regarding the morbidity and mortality of SCA, use of TCD and training methodology as a screening tool, public health policy, healthcare workforce issues, and leadership model concepts which collectively provide a comprehensive assessment of the existing knowledge and associated knowledge gaps.

Literature Review Methods

Given that care for children with SCA in resource-limited settings and TCD screening for stroke within this context has been studied within multiple disciplines including medical, scientific, public health, and international public health contexts, a semi-systemic, integrative strategy was employed to review qualitative and quantitative research and reach comprehensive, reliable conclusions. Peer-reviewed journal articles were the primary source of literature to provide background, significance, and overall context for the project. A broad literature review included background information on SCA; its clinical characteristics, course, and outcomes with and without treatment; available treatment options; and social, economic, and political factors influencing access to care in resource-limited settings.

Consideration was given to data from the US as compared to sub-Saharan Africa, and a focused review of available sources of literature specific to healthcare settings within sub-Saharan Africa was performed. Further contextual information was included in the literature review to provide appropriate background on TCD as a clinical screening

tool, healthcare infrastructure within the identified settings, capacity gaps, and leadership change models relevant to the research objectives and context. Manuscripts published in peer-reviewed journals, such as *Lancet*, *Lancet Global Health*, *New England Journal of Medicine*, *Blood*, and *British Journal of Haematology*, were referenced, however impact factor was considered secondary to content, robustness of findings, and relevance to the population and locations identified.

Table 2.1. Literature Sources

Data Sources	Search	Type
Medline Full Text (EBSCO)	Sickle cell disease OR sickle cell anemia AND hydroxyurea; sickle cell disease AND morbidity OR mortality, sickle cell anemia AND transcranial Doppler OR hydroxyurea	Peer-reviewed journal articles
Medline (PubMed)	Same as above	Peer-reviewed journal articles
Google Scholar	Sickle cell disease AND [Uganda, Ghana, Tanzania, Angola, Kenya or DRC], hemoglobinopathies, sickle cell disease AND sub-Saharan Africa AND healthcare capacity gaps; change management AND sub-Saharan Africa AND Re-Aim OR Collective Impact Model OR technology transfer	Peer-reviewed journal articles, policy statements
World Health Organization	Prevalence of sickle cell disease and [Uganda, Ghana, Tanzania, Angola, Kenya or DRC] AND public health AND sickle cell disease	Dataset, reports, policy statements/directives
IAHO (Integrative African Health Observatory)	Healthcare, pediatrics, sickle cell disease	Datasets

Keywords & Terms

Keyword searches using data sources (Table 2.1) relied on the main concepts identified relevant to the primary and secondary research questions and utilized common synonyms and terminology to broaden the scope of possible results. Results were reviewed to further refine search criteria to access the most relevant literature to provide

context and support for the project. Keyword searches included relevant terms in both the American and British English languages, such as anemia/anaemia and hemoglobin/haemoglobin, given the common use of both spelling formats in the project settings.

Table 2.2 Sample Keywords and Search Terms

Concept	Synonyms or Related Terms
Sickle cell disease	Sickle cell anemia, sickle cell anaemia, HbSS, Hemoglobin S disease, drepanocytosis
Hydroxyurea	Hydroxycarbamide, Siklos®, Hydrea®, Droxia®
Pediatric	Children, adolescents, paediatric
Transcranial Doppler	TCD, ultrasound screening for stroke
Hemoglobinopathy	Red cell disorders, inherited hemoglobinopathy
Prevalence	Incidence, disease burden, cumulative incidence
Capacity building	Training, grassroots efforts, development, education, healthcare infrastructure development, workforce development, North-South partnerships
Leadership	Leaders, stakeholders, decision-making, authority
Treatment	Therapies, interventions, supportive care, preventative care, prophylaxis (as penicillin, immunizations, etc.).
Morbidity and mortality	Death, clinical complications, clinical outcomes
Feasibility	Suitability, viability
Barriers	Obstacles, limitations

Inclusion and Exclusion Criteria

Table 2.3 Studies inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria

• Peer-Reviewed journal articles OR official policy statements from WHO, Ministry of Health, or similar agencies
• Publications from January 1990 to present
• Primary focus on sickle cell anemia
• Both quantitative and qualitative research
  ○ Quantitative studies will include phase 1-4 interventional clinical trials, epidemiologic studies, prospective cohort studies, and ancillary studies
  ○ Qualitative research will include survey studies, interviews, and in-person observations
• Preference will be given to clinical trials conducted in sub-Saharan Africa for greater relevance to the population of focus
• Editorials and media coverage only if directly related to the research questions
	• Publications from before 1990
	• Studies with participants over the age of 18 years at enrollment

The Mixed Methods Appraisal Tool methodology (Hong et al., 2018) was employed, which was relevant to much of the literature reviewed with the exception of editorials, public health policy documents, and media coverage, the latter of which were used only for supporting analysis of identified themes. This system was chosen as it was designed for use in appraising research of varying designs, includes assessment criteria for both qualitative and quantitative research and provides clear guidelines for employing the method effectively.

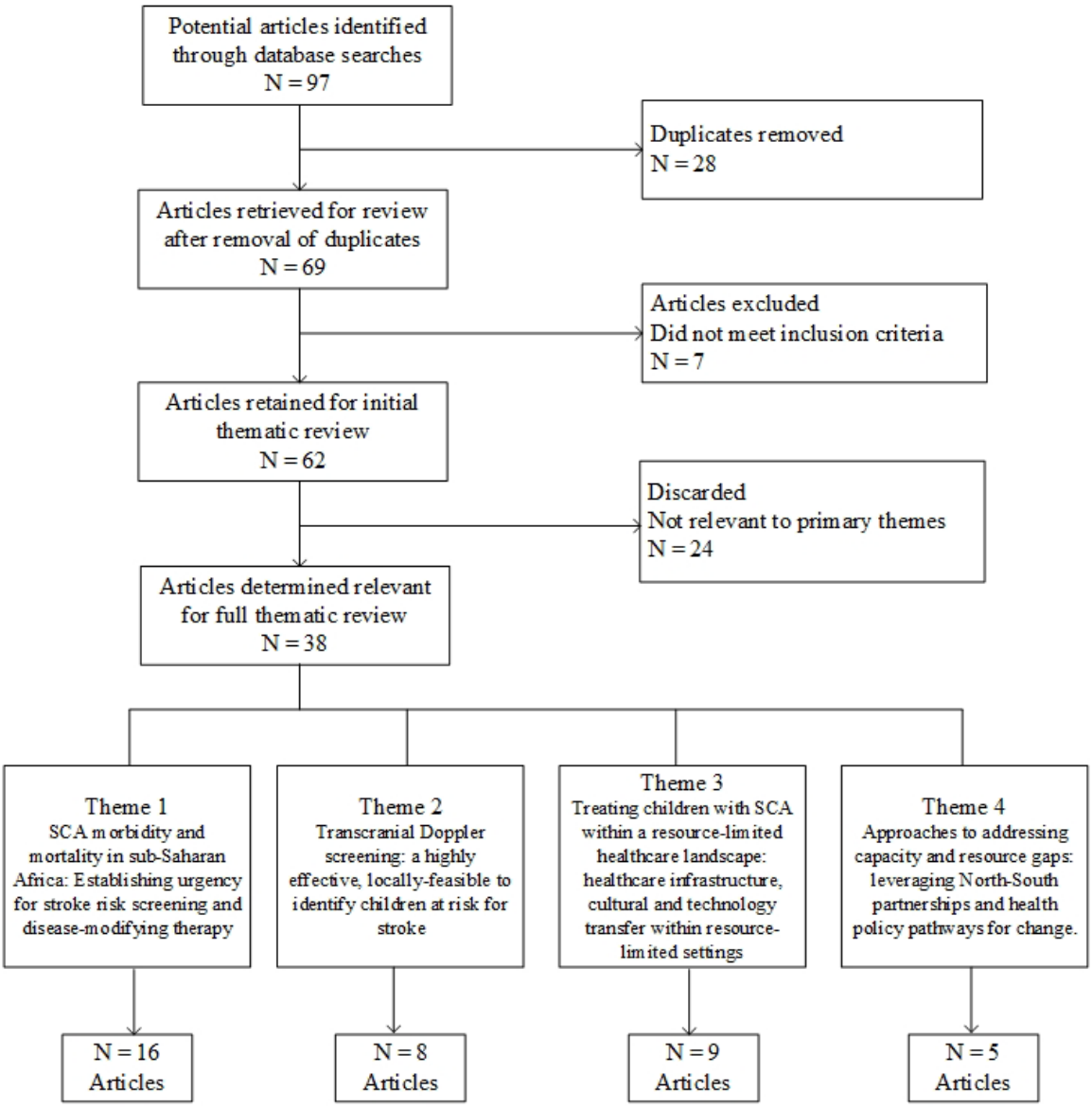
Literature Review Results

Initial searches returned a total of more than 90 manuscripts. This list was further refined to 38 publications that were categorized into four main themes, which were then analyzed into relevant secondary themes as shown in Table 2.4, below.

Table 2.4 Classification of Major Themes

Theme	Relevant Secondary Themes
1. SCA morbidity and mortality in sub-Saharan Africa: Establishing urgency for stroke risk screening and disease-modifying therapy	Background: Diagnosis, newborn screening Stroke in SCA: epidemiology, morbidity and mortality Treatment options in the US vs. sub-Saharan Africa Capacity and resource gaps in sub-Saharan Africa Access to basic treatment/preventative measures Access to therapies Healthcare resource limitations
2. Transcranial Doppler screening: a highly effective, locally-feasible to identify children at risk for stroke	Overview: background, use, interpretation Training program/Training methodology for TCD: US and in resource-limited settings Context for scale-up based on effective vs. ineffective training methods and program structure
3. Treating children with SCA within a resource-limited healthcare landscape: healthcare infrastructure, cultural and technology transfer within resource-limited settings	Capacity and resource gaps in sub-Saharan Africa Lack of education Costs of screening vs. treatment – economic reasons for screening; influence on policy makers Healthcare infrastructure, eHealth, need for operationalizing/building capacity within systems using evidence-based research
4. Approaches to addressing capacity and resource gaps: leveraging North-South partnerships and health policy pathways for change	North-South partnerships and resource-limited settings Re-AIM Model Collective Impact Model Workforce gaps and development opportunities

*Figure 2.1 Literature Review CONSORT Diagram**



*Developed by author

Table 2.4 Extraction Table with Associated Themes

Full Citation	Theme	Relevant Secondary Theme	Theme	Relevant Secondary Theme
Adams, R., McKie, V., Nichols, F., Carl, E., Zhang, D. L., McKie, K., Figueroa, R., Litaker, M., Thompson, W., & Hess, D. (1992). The use of transcranial ultrasonography to predict stroke in sickle cell disease. *The New England Journal of Medicine, 326*(9), 605610. PMID: 1734251. https://doi.org/10.1056/NEJM199202273260905	2. Transcranial Doppler screening: a highly effective, locally-feasible to identify children at risk for stroke	Overview: background, use, interpretation	1. SCA morbidity and mortality in sub-Saharan Africa: Establishing urgency for stroke risk screening and disease-modifying therapy	Stroke in SCA: epidemiology, morbidity and mortality, Treatment options in the US vs Africa
Adams, R. J., McKie, V. C., Hsu, L., Files, B., Vichinsky, E., Pegelow, C., Abboud, M., Gallagher, D., Kutlar, A., Nichols, F. T., Bonds, D. R., Brambilla, D., Woods, G., Olivieri, N., Driscoll, C., Miller, S., Wang, W., Hurlett, A., Scher, C., Berman, B., Carl, E., Jones, A. M., Roach, E. S., Wright, E., Zimmerman, R. A., & Waclawiw, M. (1998). Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *The New England Journal of Medicine, 339*(1), 5–11. PMID: 9647873. https://doi.org/10.1056/NEJM199807023390102	2. Transcranial Doppler screening: a highly effective, locally-feasible to identify children at risk for stroke	Overview: background, use, interpretation	1. SCA morbidity and mortality in sub-Saharan Africa: Establishing urgency for stroke risk screening and disease-modifying therapy	Stroke in SCA: epidemiology, morbidity and mortality, Treatment options in the US vs Africa
Ali, S. B., Moosang, M., King, L., Knight-Madden, J. & Reid, M. (2011). Stroke recurrence in children with sickle cell disease treated with hydroxyurea following first clinical stroke. *American Journal of Hematology, 86*(10), 846–850. PMID: 21898530. https://doi.org/10.1002/ajh.22142	1. SCA morbidity and mortality in sub-Saharan Africa: Establishing urgency for stroke risk screening and disease-modifying therapy	Stroke in SCA: epidemiology, morbidity and mortality, Access to basic treatments/preventative measures, Access to therapies, Healthcare resource limitations		

Full Citation	Theme	Relevant Secondary Theme	Theme	Relevant Secondary Theme
Ambrose, E. E., Latham, T. S., Songoro, P., Charles, M., Lane, A. C., Stuber, S. E., Makubi, A. N., Ware, R. E., & Smart, L. R. (2023). Hydroxyurea with dose escalation for primary stroke risk reduction in children with sickle cell anaemia in Tanzania (SPHERE): An open-label, phase 2 trial. *The Lancet Haematology*, *10*(4), e261–e271. PMID: 36870358. PMCID: PMC10132280. https://doi.org/10.1016/S2352-3026(22)00405-7	2. Transcranial Doppler screening: a highly effective, locally-feasible to identify children at risk for stroke	Overview: background, use, interpretation, Training program/Training methodology for TCD: US and in resource-limited settings, Context for scale-up based on effective vs ineffective training methods and program structure	1. SCA morbidity and mortality in sub-Saharan Africa: Establishing urgency for stroke risk screening and disease-modifying therapy	Stroke in SCA: epidemiology, morbidity and mortality, Treatment options in the US vs Africa
Aygun, B., Lane, A., Smart, L. R., Santos, B., Tshilolo, L., Williams, T. N., Olupot-Olupot, P., Stuber, S. E., Tomlinson, G., Latham, T., Ware, R. E., & REACH Investigators (2024). Hydroxyurea dose optimisation for children with sickle cell anaemia in sub-Saharan Africa (REACH): extended follow-up of a multicentre, open-label, phase 1/2 trial. *The Lancet Haematology, S2352-3026*(24)00078-4. Advance online publication. https://doi.org/10.1016/S2352-3026(24)00078-4	1. SCA morbidity and mortality in sub-Saharan Africa: Establishing urgency for stroke risk screening and disease-modifying therapy	Capacity and resource gaps, Access to therapies, Healthcare resource limitations		
Bhuiyan, M. R., Deb, S., Mitchell, R. A., Teddy, P. J., & Drummond, K. J. (2012). The effect of formal training on the clinical utility of transcranial Doppler ultrasound monitoring in patients with aneurysmal subarachnoid haemorrhage. *Journal of Clinical Neuroscience, 19*(9), 1255–1260. PMID: 22727749. https://doi.org/10.1016/j.jocn.2012.02.001	2. Transcranial Doppler screening: a highly effective, locally-feasible to identify children at risk for stroke	Overview: background, use, interpretation, Training program/Training methodology for TCD: US and in resource-limited settings Context for scale-up based on effective vs ineffective training methods and program structure		

Full Citation	Theme	Relevant Secondary Theme	Theme	Relevant Secondary Theme
Brambilla, D. J., Miller, S. T., & Adams, R. J. (2007). Intra-individual variation in blood flow velocities in cerebral arteries of children with sickle cell disease. *Pediatric Blood & Cancer, 49*(3), 318–322. PMID: 17243135. PMCID: PMC2867598. https://doi.org/10.1002/pbc.21142	2. Transcranial Doppler screening: a highly effective, locally-feasible to identify children at risk for stroke	Training program/Training methodology for TCD: US and in resource-limited settings, Context for scale-up based on effective vs ineffective training methods and program structure		
Egesa, W. I., Nakalema, G., Waibi, W. M., Turyasiima, M., Amuje, E., Kiconco, G., Odoch, S., Kumbakulu, P.K., Abdirashid, S., & Asiimwe, D. Sickle cell disease in children and adolescents: A review of the historical, clinical, and public health perspective of sub-Saharan Africa and beyond. *International Journal of Pediatrics, 2022.* PMID: 36254264. PMCID: PMC9569228. https://doi.org/10.1155/2022/3885979.	3. Treating children with SCA within a resource-limited healthcare landscape: healthcare infrastructure, cultural and technology transfer within resource-limited settings	Capacity and resource gaps in sub-Saharan Africa, Lack of education	1. SCA morbidity and mortality in sub-Saharan Africa: Establishing urgency for stroke risk screening and disease-modifying therapy	Capacity and resource gaps, Access to therapies, Healthcare resource limitations
Esoh, K., Wonkam-Tingang, E., & Wonkam, A. (2021). Sickle cell disease in sub-Saharan Africa: Transferable strategies for prevention and care. *The Lancet Haematology, 8*(10), e744–e755. PMID: 34481550. https://doi.org/10.1016/S2352-3026(21)00191-5	1. SCA morbidity and mortality in sub-Saharan Africa: Establishing urgency for stroke risk screening and disease-modifying therapy	Capacity and resource gaps, Access to therapies, Healthcare resource limitations		

Full Citation	Theme	Relevant Secondary Theme	Theme	Relevant Secondary Theme
Frenk, J., Chen, L., Bhutta, Z. A., Cohen, J., Crisp, N., Evans, T., Fineberg, H., Garcia, P., Ke, Y., Kelley, P., Kistnasamy, B., Meleis, A., Naylor, D., Pablos-Mendez, A., Reddy, S., Scrimshaw, S., Sepulveda, J., Serwadda, D., & Zurayk, H. (2010). Health professionals for a new century: Transforming education to strengthen health systems in an interdependent world. *The Lancet, 376*(9756), 1923–1958. PMID: 21112623. https://doi.org/10.1016/S0140-6736(10)61854-5	3. Treating children with SCA within a resource-limited healthcare landscape: healthcare infrastructure, cultural and technology transfer within resource-limited settings	Capacity and resource gaps in sub-Saharan Africa, Lack of education, need for operationalizing/ building capacity within systems using evidence-based research	2. Transcranial Doppler screening: a highly effective, locally-feasible to identify children at risk for stroke	Context for scale-up based on effective vs ineffective training methods and program structure
Glasgow, R. E,, Vogt, T.M., & Boles, S.M. (1999). Evaluating the public health impact of health promotion interventions: The RE-AIM framework. *American Journal of Public Health, 89*(9), 1322–6. PMID: 10474547. PMCID: PMC1508772. https://doi.org/10.2105/AJPH.89.9.1322	4. Approaches to addressing capacity and resource gaps: leveraging North-South partnerships and health policy pathways for change	Re-AIM Model	3. Treating children with SCA within a resource-limited healthcare landscape: healthcare infrastructure, cultural and technology transfer within resource-limited settings	Need for operationalizing/ building capacity within systems using evidence-based research
Glasgow, R. E., & Estabrooks, P. E. (2018). Pragmatic applications of RE-AIM for health care initiatives in community and clinical settings. *Preventing Chronic Disease, 15,* E02. PMID: 29300695. PMCID: PMC5757385. https://doi.org/10.5888/pcd15.170271	4. Approaches to addressing capacity and resource gaps: leveraging North-South partnerships and health policy pathways for change	Re-AIM Model		

Full Citation	Theme	Relevant Secondary Theme	Theme	Relevant Secondary Theme
Global Burden of Disease 2021 Sickle Cell Disease Collaborators. Global, regional, and national prevalence and mortality burden of sickle cell disease, 2000-2021: a systematic analysis from the global burden of disease study 2021. *The Lancet Haematology, 10*(8), e585–e599. PMID: 37331373. PMCID: PMC10390339. https://doi.org/10.1016/S2352-3026(23)00118-7	1. SCA morbidity and mortality in sub-Saharan Africa: Establishing urgency for stroke risk screening and disease-modifying therapy	Background: Diagnosis, newborn screening, morbidity and mortality, Treatment options in the US vs Africa		
Inusa, B. P. D., Sainati, L., MacMahon, C., Colombatti, R., Casale, M., Perrotta, S., Rampazzo, P., Hemmaway, C., & Padayachee, S. T. (2019). An educational study promoting the delivery of transcranial Doppler ultrasound screening in paediatric sickle cell disease: A European multi-centre perspective. *Journal of Clinical Medicine*, *9*(1), 44. PMID: 31878188. PMCID: PMC7019609. https://doi.org/10.3390/jcm9010044	2. Transcranial Doppler screening: a highly effective, locally-feasible to identify children at risk for stroke	Training program/Training methodology for TCD: US and in resource-limited settings, Context for scale-up based on effective vs ineffective training methods and program structure		
John, C. C., Opoka, R. O., Latham, T. S., Hume, H. A., Nabaggala, C., Kasirye, P., Ndugwa, C. M., Lane, A. & Ware, R. E. (2020). Hydroxyurea dose escalation for sickle cell anemia in sub-Saharan Africa. *The New England Journal of Medicine, 382*(26), 2524–2533. PMID: 32579813. https://doi.org/10.1056/nejmoa2000146	1. SCA morbidity and mortality in sub-Saharan Africa: Establishing urgency for stroke risk screening and disease-modifying therapy	Treatment options in the US vs Africa, Access to basic treatments/preventative measures		
Kania, J. & Kramer, M. (2011) Collective Impact. *Stanford Social Innovation Review, 9*(1), 36–41. https://doi.org/10.48558/5900-KN19	4. Approaches to addressing capacity and resource gaps: leveraging North-South partnerships and health policy pathways for change	Collective Impact Model	3. Treating children with SCA within a resource-limited healthcare landscape: healthcare infrastructure,	Need for operationalizing/ building capacity within systems using evidence-based research

Full Citation	Theme	Relevant Secondary Theme	Theme	Relevant Secondary Theme
			cultural and technology transfer within resource-limited settings	
Kania, J., Hanleybrown, F., & Juster, J. S. (2013). Essential mindset shifts for collective impact. *Stanford Social Innovation Review, 12*(4), A2–A5. https://doi.org/10.48558/VV1R-C414	4. Approaches to addressing capacity and resource gaps: leveraging North-South partnerships and health policy pathways for change	Collective Impact Model	3. Treating children with SCA within a resource-limited healthcare landscape: healthcare infrastructure, cultural and technology transfer within resource-limited settings	Need for operationalizing/ building capacity within systems using evidence-based research
Lobo, C., Hankins, J. S., Moura, P., & Pinto, J.C. (2010). Hydroxyurea therapy reduces mortality among children with sickle cell disease. *Blood, 116*(21), 843–843. https://doi.org/10.1182/blood.V116.21.843.843	1. SCA morbidity and mortality in sub-Saharan Africa: Establishing urgency for stroke risk screening and disease-modifying therapy			
Marks L. J., Munube, D., Kasirye, P., Mupere, E., Jin, Z., LaRussa, P., Idro, R., & Green, N. S. Stroke prevalence in children with sickle cell disease in sub-Saharan Africa: A systematic review and meta-analysis. *Global Pediatric Health, 2018*(5). PMID: 29785408; PMCID: PMC5954575. https://doi.org/10.1177/2333794X18774970.	1. SCA morbidity and mortality in sub-Saharan Africa: Establishing urgency for stroke risk screening and disease-modifying therapy	Stroke in SCA: epidemiology, morbidity and mortality, Treatment options in the US vs Africa, Access to basic treatments/preventative measures, Access to therapies	2. Transcranial Doppler screening: a highly effective, locally-feasible to identify children at risk for stroke	Overview: background, use, interpretation, Context for scale-up based on effective vs ineffective training methods and program structure

Full Citation	Theme	Relevant Secondary Theme	Theme	Relevant Secondary Theme
Mburu, J., & Odame, I. (2019). Sickle cell disease: Reducing the global disease burden. *International Journal of Laboratory Hematology, 41*(S1), 82–88. PMID: 31069977. https://doi.org/10.1111/ijlh.13023	3. Treating children with SCA within a resource-limited healthcare landscape: healthcare infrastructure, cultural and technology transfer within resource-limited settings	Capacity and resource gaps in sub-Saharan Africa, Costs of screening vs treatment - economic reasons for screening: influences on policy makers, Healthcare infrastructure		
McGann, P. T., Hernandez, A. G., & Ware, R. E. (2017). Sickle cell anemia in sub-Saharan Africa: Advancing the clinical paradigm through partnerships and research. Blood, 129(2), 155–161. PMID: 27821508. PMCID: PMC5234214. https://doi.org/10.1182/blood-2016-09-702324	1. SCA morbidity and mortality in sub-Saharan Africa: Establishing urgency for stroke risk screening and disease-modifying therapy	Capacity and resource gaps, Access to therapies, Healthcare resource limitations		
Moodley, K., Rennie, S., Behets, F., Obasa, A. E., Yemesi, R., Ravez, L., Kayembe, P., Makindu, D., Mwinga, A., & Jaoko, W. Allocation of scarce resources in Africa during COVID-19: Utility and justice for the bottom of the pyramid? *Developing World Bioethics, 21*(1), 36–43. PMID: 32845575. PMCID: PMC7461286. https://doi.org/10.1111/dewb.12280	1. SCA morbidity and mortality in sub-Saharan Africa: Establishing urgency for stroke risk screening and disease-modifying therapy	Access to basic treatments/preventative measures, Healthcare resource limitations	3. Treating children with SCA within a resource-limited healthcare landscape: healthcare infrastructure, cultural and technology transfer within resource-limited settings	Capacity and resource gaps in sub-Saharan Africa, Lack of education, need for operationalizing/ building capacity within systems using evidence-based research

Full Citation	Theme	Relevant Secondary Theme	Theme	Relevant Secondary Theme
McGann, P. T., Nero, A. C., & Ware, R. E. (2017). Clinical features of β-thalassemia and sickle cell disease. In P. Malik & J. Tisdale (Eds.), *Gene and cell therapies for beta-globinopathies* (Advances in Experimental Medicine and Biology, volume 1013). Springer. https://doi.org/10.1007/978-1-4939-7299-9	1. SCA morbidity and mortality in sub-Saharan Africa: Establishing urgency for stroke risk screening and disease-modifying therapy	Background: Diagnosis, newborn screening		
Ndeezi, G, Kiyaga, C., Hernandez, A. G., Manube, D., Howard, T. A., Ssewanyana, A., Nsungwa, J., Kiguli, S., Nudgwa, C. M., Ware, R. E., & Aceng, J. R. (2016). Burden of sickle cell trait and disease in the Uganda sickle surveillance study (US3): A cross-sectional study. *The Lancet Global Health, 4*(3), e195–200. PMID: 26833239. https://doi.org/10.1016/S2214-109X(15)00288-0	1. SCA morbidity and mortality in sub-Saharan Africa: Establishing urgency for stroke risk screening and disease-modifying therapy	Background: Diagnosis, newborn screening, Access to basic treatments/preventative measures		
Nichols, F. T., Jones, A. M., & Adams, R. J. (2001). Stroke prevention in sickle cell disease (STOP) study guidelines for transcranial Doppler testing. *Journal of Neuroimaging, 11*(4), 354–362. PMID: 11677874. https://doi.org/10.1111/j.1552-6569.2001.tb00063.x	2. Transcranial Doppler screening: a highly effective, locally-feasible to identify children at risk for stroke	Overview: background, use, interpretation, Training program/Training methodology for TCD: US and in resource-limited settings		
Olupot-Olupot, P., Wabwire, H., Ndila, C., Adong, R., Ochen, L, Abondo, G., Amorut, D., Okalebo, C., Akello, S. R., Oketcho, J. B., Okiror, W., Asio, S., Odiit, A., Alaroker, F., Nyutu, G., Maitland, K. M. & Williams, T. N. (2020). Characterizing demographics, knowledge, practices and clinical care among patients attending sickle cell disease clinics in Eastern Uganda. *Wellcome Open Research, 5*(87). PMID: 32802962. PMCID: PMC7406951. https://doi.org/10.12688/wellcomeopenres.15847.2	3. Treating children with SCA within a resource-limited healthcare landscape: healthcare infrastructure, cultural and technology transfer within resource-limited settings			

Full Citation	Theme	Relevant Secondary Theme	Theme	Relevant Secondary Theme
Power-Hays, A., Tomlinson, G. A., Santos, B., Williams, T. N., Olupot-Olupot, P., McGann, P. T., Aygun, B., Lane, A., Stuber, S. E., Latham, T. & Ware, R. E., Hydroxyurea reduces the transfusion burden in children with sickle cell anemia: The reach experience. *Blood, 138*(S1), 11. https://doi.org/10.1182/blood-2021-146632	3. Treating children with SCA within a resource-limited healthcare landscape: healthcare infrastructure, cultural and technology transfer within resource-limited settings			
Power-Hays, A., Tomlinson, G. A., Tshilolo, L., Santos, B., Williams, T. N., Olupot-Olupot, P., Smart, L. R., Aygun, B., Lane, A., Stuber, S. E., Latham, T., & Ware, R. E. (2024). Reducing transfusion utilization for children with sickle cell anemia in sub-Saharan Africa with hydroxyurea: Analysis from the phase I/II REACH trial. *American Journal of Hematology*, 99(4), 625–632. Advance online publication. PMID: 38332651. https://doi.org/10.1002/ajh.27244	3. Treating children with SCA within a resource-limited healthcare landscape: healthcare infrastructure, cultural and technology transfer within resource-limited settings			
Quinn, C. T., Rogers, Z. R., McCavit, T. L., & Buchanan, G. R. (2010). Improved survival of children and adolescents with sickle cell disease. *Blood, 115*(17), 3447–3452. PMID: 20194819. PMCID: PMC2867259. https://doi.org/10.1182/blood-2009-07-233700	1. SCA morbidity and mortality in sub-Saharan Africa: Establishing urgency for stroke risk screening and disease-modifying therapy	Background: Diagnosis, newborn screening Capacity and resource gaps, Access to basic treatments/preventative measures, Healthcare resource limitations		

Full Citation	Theme	Relevant Secondary Theme	Theme	Relevant Secondary Theme
Rankine-Mullings, A, Reid, M, Soares, D, Taylor-Brian, C, Wisdom-Phipps, M, Aldred, K., Latham, T., Schultz, W., Knight-Madden, J., Badaloo, A., Lane, A., Adams, R., & Ware, R. E. (2021). Hydroxycarbamide treatment reduces transcranial Doppler velocity in the absence of transfusion support in children with sickle cell anaemia, elevated transcranial Doppler velocity, and cerebral vasculopathy: the EXTEND trial. *British Journal of Haematology, 195*(4), 612–520. PMID: 34291449. https://doi.org/10.1111/bjh.17698	2. Transcranial Doppler screening: a highly effective, locally-feasible to identify children at risk for stroke	Context for scale-up based on effective vs ineffective training methods and program structure	3. Treating children with SCA within a resource-limited healthcare landscape: healthcare infrastructure, cultural and technology transfer within resource-limited settings	Costs of screening vs treatment - economic reasons for screening: need for operationalizing/ building capacity within systems using evidence-based research
Ranque, B., Kitenge, R., Ndiaye, D. D., Ba, M. D., Adjoumani, L., Traore, H., Coulibaly, C., Guindo, A., Boidy, K., Mbuyi, D., Ly, I. D., Offredo, L., Diallo, D. A., Tolo, A., Kafando, E., Tshilolo, L., & Diagne, I. (2022). Estimating the risk of child mortality attributable to sickle cell anaemia in sub-Saharan Africa: A retrospective, multicentre, case-control study. *The Lancet Haematology, 9*(3), e208–e216. PMID: 35240076. https://doi.org/10.1016/S2352-3026(22)00004-7	1. SCA morbid ity and mortality in sub-Saharan Africa: Establishing urgency for stroke risk screening and disease-modifying therapy	Background: Diagnosis, newborn screening; morbidity and mortality		
Seargeant, G.R., & Ndugwa, C. N. (2003). Sickle cell disease in Uganda: A time for action. *East African Medical Journal, 80*(7), 384–387. PMID: 16167756. https://doi.org/10.4314/eamj.v80i7.8724	3. Treating children with SCA within a resource-limited healthcare landscape: healthcare infrastructure, cultural and technology transfer within resource-limited settings			

Full Citation	Theme	Relevant Secondary Theme	Theme	Relevant Secondary Theme
Steinberg, M.H., Barton, F., Castro, O., Pegelow, C. H., Ballas, S. K., Kutlar, A., Orringer, E., Bellevue, R., Olivieri, N., Eckman, J., Varma, M., Ramirez, G., Adler, B., Smith, W., Carlos, T., Ataga, K., DeCastro, L., Bigelow, C., Saunthararajah, Y., Telfer, M., Vichinsky, E., Claster, S., Shurin, S., Bridges, K., Waclawiw, M., Bonds, D., & Terrin, M. (2003). Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: Risks and benefits up to 9 years of treatment. *Journal of the American Medical Association, 289*(13),1645–1651. PMID: 12672732. https://doi.org/10.1001/jama.289.13.1645	3. Treating children with SCA within a resource-limited healthcare landscape: healthcare infrastructure, cultural and technology transfer within resource-limited settings			
Tshilolo, L,, Tomlinson, G., Williams, T. N., Santos, B., Olupot-Olupot, P., Lane, A., Aygun, B., Stuber, S. E., Latham, T. S., McGann, P. T., & Ware, R. E. (2019) Hydroxyurea for children with sickle cell anemia in sub-Saharan Africa (2019). *The New England Journal of Medicine, 380*(2), 121–131. PMID: 30501550. PMCID: PMC6454575. https://doi.org/10.1056/NEJMoa1813598	1. SCA morbidity and mortality in sub-Saharan Africa: Establishing urgency for stroke risk screening and disease-modifying therapy	Treatment options in the US vs Africa, access to basic treatments/preventative measures,		
Wang, W. C., Ware, R. E., Miller, S. T., Iyer, R. V., Casella, J. F., Minniti, C. P., Rana, S., Thornburg, C. D., Roger, Z. R., Kalpatthi, R. V., Barredo, J. C., Brown, R. C., Sarnaik, S. A., Howard, T. H., Wynn, L. W., Kutlar, A., Armstrong, F. D., Files, B. A., Goldsmith, J. C., Waclawiw, M. A., Huang, X., & Thompson, B. W. (2011). Hydroxycarbamide in very young children with sickle-cell anaemia: A multicentre, randomised, controlled trial (BABY HUG). *The Lancet, 377*(9778), 1663–1672. PMID: 21571150. PMCID: PMC3133619. https://doi.org/10.1016/S0140-6736(11)60355-3	3. Treating children with SCA within a resource-limited healthcare landscape: healthcare infrastructure, cultural and technology transfer within resource-limited settings			

Full Citation	Theme	Relevant Secondary Theme	Theme	Relevant Secondary Theme
Ware, R. E., de Montalembert, M., Tshilolo, L., & Abboud, M. R. (2017). Sickle cell disease. *The Lancet, 390*(10091), 311–23. PMID: 28159390. https://doi.org/10.1016/S0140-6736(17)30193-9	1. SCA morbidity and mortality in sub-Saharan Africa: Establishing urgency for stroke risk screening and disease-modifying therapy	Stroke in SCA: epidemiology, morbidity and mortality, Treatment options in the US vs Africa, Capacity and resource gaps, Access to basic treatments/preventative measures, Access to therapies, Healthcare resource limitations		
Weatherall, D., Hofman, K., Rogers, G., Ruffin, J., & Hrynkow, S. (2005). A case for developing north–south partnerships for research in sickle cell disease. *Blood, 105*(3), 921–923. PMID: 15466925. https://doi.org/10.1182/blood-2004-06-2404	4. Approaches to addressing capacity and resource gaps: leveraging North-South partnerships and health policy pathways for change	Workforce gaps and development opportunities		
World Health Organization: Regional Office for Africa. (2010). *Sickle-cell disease: A strategy for the WHO African region.* https://www.afro.who.int/sites/default/files/2017-06/afr_rc60_8.pdf	1. SCA morbidity and mortality in sub-Saharan Africa: Establishing urgency for stroke risk screening and disease-modifying therapy	Background: Diagnosis, newborn screening		

The results of this review indicate substantial morbidity and mortality associated with SCA in sub-Saharan Africa, establishing an urgency for stroke risk screening and accessibility to treatment in this population. The morbidity and mortality associated with SCA in sub-Saharan Africa is crucial to providing context for the magnitude of the problem and to establish urgency regarding the overall need for improved diagnosis, screening for complications and treatment for affected children. The background of TCD screening was then explored, including review of research which validated its use as a screening tool within the population of children with SCA in the United States and the gaps that exist in training methodology outside of the global North.

The role of TCD as a screening tool in SCA necessitates a description of available treatments with a specific focus on resource-limited settings, including the relationship between healthcare infrastructure, cultural issues, technology, and knowledge transfer. Lastly, approaches to addressing capacity and resource gaps: leveraging North-South partnerships and health policy pathways for change was identified as a fourth theme in order to assess available literature on methods for implementing change to build capacity within healthcare systems in resource-limited settings, utilizing public health leadership models and strategies to facilitate sustainable policy and system change.

Theme 1: SCA Morbidity and Mortality in sub-Saharan Africa: Establishing Urgency for Stroke Risk Screening and Disease-Modifying Therapy

SCA is a common and life-threatening hematological condition that affects the development of red blood cells and results in significant clinical morbidity and mortality. Ware et al. (2017) described a wide range of severe clinical complications which reflect the complex pathophysiology of the condition, including vaso-occlusive painful crises,

infection, anemia, and catastrophic organ damage, noting that these are rarely fatal in well-resourced countries. Outcomes are significantly more dire in resource-limited settings where healthcare infrastructure is limited, and barriers include lack of clinical knowledge, delayed diagnosis, limited access to preventative care such as immunizations, penicillin prophylaxis and malaria prophylaxis, scare and/or unsafe blood supplies, and limited access to disease-modifying therapy.

McGann et al. (2017) noted that SCA affects nearly every organ in the body, with a long list of acute and chronic disease manifestations due to the critical role of hemoglobin in delivering oxygen to all organs. In the US, mortality of children (under five years of age) with SCA has decreased significantly due to diagnosis through universal newborn screening programs and interventions such as penicillin prophylaxis and pneumococcal vaccinations (Quinn et al., 2010). McGann et al. (2017) expanded on the clinical impact of SCA in resource-limited settings, noting that therapeutic options are limited primarily to packed erythrocyte or exchange blood transfusions. In sub-Saharan Africa, transfusion use is limited by major challenges including inadequate blood supply, a high risk of transfusion-transmitted infections, and the risk of hemolytic transfusion reactions (Esoh et al., 2021).

The WHO (2010) provided context for the disease burden in sub-Saharan Africa, noting that in many African countries an estimated 10–40% of the population carries the sickle cell gene resulting in estimated disease prevalence of at least one to two percent. In a multicenter, retrospective case control study, Ranque et al. (2022) found mortality rates for children with SCA of 15.6% in those younger than one year of age, 36.4% in children under 5 years, and 43.3% in children less than 10 years of age. The 2021 Global Burden

of Disease analysis documented that SCA contributes significantly to all-cause mortality in pediatric populations and underscored the importance of surveillance efforts as well as research to inform the deployment of evidence-based prevention and treatment of SCA (GBD Sickle Cell Disease Collaborators, 2023).

Uganda was one of the first countries in Africa with a documented significant SCA disease burden. Ndeezi et al. (2016) completed a surveillance study of infants born to HIV-positive mothers throughout Uganda whose blood had been collected at birth through the country's Early Infant Diagnosis program. Following analysis by hemoglobin electrophoresis through isoelectric focusing, the investigators confirmed the high prevalence of sickle cell trait and SCA in Uganda, with notable variation between regions and districts. These data informed further research and national strategies within Uganda and other sub-Saharan African countries for SCA, including neonatal screening, clinical screening, and treatment interventions in targeted high-risk areas.

Stroke in SCA

Stroke is one of the most severe acute complications of SCA and has devastating consequences for patients and their families as well as a significant burden on healthcare systems in resource-limited settings that are poorly equipped to manage them. In a systematic review, Marks et al. (2017) found the prevalence of stroke in children with SCA living in sub-Saharan Africa to be 2.9 – 16.9%, with disease mortality, inaccurate diagnosis and regional variability limiting more precise estimates. The authors argued that high disease and stroke-related mortality likely led to an underestimation of the number of children affected by stroke. Stroke in SCA occurs primarily in childhood, with sudden onset of neurological dysfunction due to restricted or fully obstructed blood flow

which inhibits delivery of oxygen to the intracranial arteries, necessitating immediate intervention through exchange transfusion (Ware et al., 2017). Clinical consequences of neurological complications in children with SCA include death, lifelong physical and cognitive disabilities, special education needs, and increased risk for recurrent stroke, which Ali et al. (2011) note that these complications are far more difficult to manage in resource-limited settings, emphasizing the importance of screening tools such as TCD to identify children at risk and utilization of hydroxyurea at an optimized dose to prevent stroke in this population.

Egesa et al. (2022) described multi-layer capacity gaps that lead to a lack of understanding at the provider and patient/family level about SCA in sub-Saharan Africa and result in decreased access to screening, diagnosis, and life-saving care. These include misconceptions about SCA, cost of screening and treatment, and inadequate healthcare infrastructure to provide continuity of care throughout the lifespan. The authors emphasized the importance of Ministry of Health involvement to continually sensitize the public regarding facts about SCA to mitigate the effects of these misconceptions which limit health-seeking behavior among patients and families. As access to basic care and treatment increases for children with SCA in the United States and Europe, the increasingly broadening gap in sub-Saharan Africa represents a major health disparity which can be mitigated through effective implementation of locally feasible tools such as TCD, which can be appropriately scaled and aligned with increased availability of treatment options through health policy support and stakeholder engagement to drive change and improve outcomes in this underserved population.

Theme 2: Transcranial Doppler (TCD): A feasible, effective method to identify children at risk for stroke

Stroke in SCA represents a risk that can be mitigated with appropriate screening and preventive treatment. TCD is a screening method which uses non-invasive ultrasonography at the point of care to measure the velocity of blood in the intracranial arteries and detects stenosis by identifying vessels with high arterial flow velocities (Adams et al., 1992). The highest time-averaged mean velocity (TAMV) measured in three major cerebral arteries has become the standard TCD value reported and used to inform clinical decision-making in children with SCA (Nichols et al., 2001). Adams et al. (1992) in a landmark study demonstrated that TCD could be effectively used to screen children with SCA for primary stroke risk. The study showed that a relative risk of stroke was more than 40 times greater among children with a TAMV of ≥ 200cm/sec and was the basis for a subsequent prospective randomized clinical trial which treated children with high risk for stroke with blood transfusions, after which many pediatric sickle cell centers in the United States and Europe initiated TCD screening to identify and treat children with SCA at high risk for development of primary stroke (Adams et al., 1998).

TCD is a particularly attractive tool for use in resource-limited settings due to its relative ease of performance, lack of the necessity for sedation, and lack of radiation exposure. It is non-invasive, painless, portable, and its results can be reproduced if performed and scored using appropriate standards. Due to intra-individual variation in TCD velocities over time, serial TCD measurements are typically performed as part of a TCD clinical screening program (Brambilla et al., 2007) which underscores the importance of defined standard operating procedures, training methodology, and

examination review in order to minimize variability and improve reliability, validity, and clinical decision-making based on TCD results.

TCD screening is highly relevant in settings where universal access to disease-modifying therapy is limited due to cost, availability or other factors. Identifying children at highest risk in a safe, feasible, and non-invasive manner and facilitating access to treatment has the potential to drastically improve clinical outcomes in this high-risk group while also decreasing long-term burden on families and healthcare systems. Ambrose et al. (2022) showed that TCD screening in a cohort of children with SCA in Tanzania identified a subset with elevated velocities who were then treated with hydroxyurea with escalation to MTD. A rapid, substantial, and sustained reduction in TCD velocities and therefore lower associated stroke risk was observed in the study population along with improved laboratory and clinical outcomes.

A major barrier across clinical settings is a lack of skilled personnel trained in administering TCD exams. Without adequate technical training and oversight, the reliability and validity of TCD results is limited in terms of clinical relevance at the patient care level. There is poor inter-rater reliability between untrained TCD examiners and those who have undergone structured training programs, with higher velocities identified in untrained examiners and greater sensitivity in TCD results among trained operators (Bhuyian et al., 2012). Inusa et al. (2020) demonstrated in a multi-center assessment of TCD training in Europe that this obstacle can be mitigated through the implementation of a standardized and reproducible training program which utilizes competency validation. The authors found that the use of imaging TCD was superior to non-imaging TCD and required less training to reach competency, however non-imaging

TCD may represent a more cost-effective and logistically sound option in resource-limited settings in sub-Saharan Africa. The latter will be the focus of the STRETCH project, and the nuances associated with training this method will be examined as they represent a gap in the literature.

Ambrose et al. (2023) demonstrated that building local capacity with clinical training, research infrastructure resources, and high-quality transcranial Doppler performance is feasible in resource-limited settings, which in conjunction with access to hydroxyurea can significantly decrease primary stroke risk. The lack of TCD screening programs represents a capacity gap across sub-Saharan Africa where the disease burden of SCA is greatest, and the design and implementation of a well-structured training program that includes ongoing supervision, retraining, and informatics-based methodology for the review and scoring of non-imaging TCD exams represents an example of high impact capacity-building in low-resource settings with the greatest need.

Theme 3: Treating children with SCA within a resource-limited healthcare landscape: healthcare infrastructure, cultural and technology transfer within resource-limited settings

SCA Treatment: Trends and Capacity Gaps

In addition to the morbidity and mortality resulting from complications of SCA, the disease negatively impacts individual and family quality of life, increases healthcare utilization and burdens resource-limited healthcare systems. Mburu and Odame (2019) noted that in sub-Saharan Africa, the disease burden is exacerbated by inadequate healthcare infrastructure, poor nutrition and infectious comorbidities including malaria, tuberculosis, and HIV. Research on SCA disease burden as well as safe and effective

disease-modifying treatment options within sub-Saharan Africa suggests that with the appropriate public health policy and improved education among patients, providers and communities, the outcomes of children with SCA in these settings have the potential to improve substantially. Olupot-Olupot et al. (2020) found in a survey study of 1,829 participants with SCA in eastern Uganda that approximately half of the participants knew that SCA was inherited from both parents, but a substantial proportion did not know how the disease was transmitted, many of whom believed that SCA is transmitted through blood transfusion. Further, less than 10% were taking hydroxyurea, 20% reported feeling stigmatized, and 80% reported hospital admission for sickle cell-related complications in the past year, all underscoring the need for improved care for sickle cell patients in Uganda.

If TCD can be effectively implemented within these settings to screen for stroke risk, clinicians must then have available treatment options for at-risk patients and policymakers must support health systems addressing the multiple knowledge gaps which exist in this area. Hydroxyurea has been shown to be a safe, accessible, and effective disease-modifying therapy which improves clinical outcomes in children with SCA (Wang et al., 2011, Lobo et al., 2013, Tshilolo et al., 2019). Its utilization is limited in most pediatric settings in sub-Saharan Africa, and conventional strategies to achieve an appropriate, optimal dose require frequent clinic visits and laboratory monitoring, which present feasibility challenges in resource-limited settings. Recently, escalation of hydroxyurea to MTD was proven to be superior for reducing complications of SCA than a lower, fixed dose (John et al., 2020, Aygun et al., 2024) and reduced the incidence of

blood transfusions within affected patients (Power-Hays et al., 2021, Power-Hays et al., 2024).

Hydroxyurea has a relatively narrow therapeutic index and works best at an optimal dose. The optimal dose differs by individual although most require more than the traditional 20 mg/kg/day. While escalation to higher optimal doses has been shown to be safe and effective, multiple barriers exist to achieving optimal dosing via standard dose escalation outside of clinical trials. Dose escalation is a resource-intensive process that takes 6-12 months and requires frequent clinic visits to make dose adjustments and accurate laboratory monitoring to avoid dose-limiting toxicities. In order to balance achieving maximal efficacy and limiting toxicity, this process often must be supervised by a trained hematologist or pediatrician who are limited by lack of trained providers, which suggests opportunities for systematic improvement in dosing strategies from an educational, systemic, or technology transfer perspective to make the treatment more accessible in local healthcare settings.

With regard to neurological protection and mitigation of the morbidity and mortality associated with primary and recurrent stroke risk, Rankine-Mullings et al., (2021) showed in a prospective phase 2 open-label trial involving children with SCA and documented cerebral vasculopathy living in a low-resource Caribbean setting that hydroxyurea treatment escalated to MTD significantly reduced TCD velocities, provided laboratory and clinical benefits, and offered primary stroke prevention. With evidence of decreased stroke risk statistically evident, the fact that the treatment was also found to be safe between risk groups further supports the potential benefits of its utilization,

particularly in resource-limited settings where access to a consistent and safe blood supply for transfusion is limited.

Healthcare Workforce Limitations in Resource-Limited Settings

Human resources limitations within healthcare settings, exacerbated by limited healthcare infrastructure and insufficient health policy to prioritize limited resources towards areas of high-impact are a major challenge in Africa. There are inequities in access to healthcare services at all levels of care following the COVID-19 pandemic (Moodley et al., 2020). Healthcare providers may have limited clinical education and evidence-based knowledge which magnifies existing challenges in screening and treatment, which presents an opportunity for capacity-building and knowledge transfer in a meaningful, sustainable manner from well-resourced to resource-limited settings. Frenck et al. (2010) supported this barrier of "collective failure" in the equitable transfer of healthcare advances and scientific learning between well-resourced and resource-limited settings. TCD training is an example of an opportunity to improve clinical skillsets and implement clinical decision-making tools via distance and in-person education as a realistic step to facilitate change in this area.

Theme 4: Approaches to addressing capacity and resource gaps: leveraging North-South partnerships and health policy pathways for change.

The efficacy of TCD screening and benefits of hydroxyurea use for children with SCA living in sub-Saharan Africa have been clearly documented, however prospective research is needed to identify and implement effective, accessible methods for TCD screening in local settings. More broadly, the literature demonstrates the safety and efficacy of hydroxyurea as a disease-modifying therapy for SCA which directly impacts

stroke risk when dosed optimally, however, there is a major gap which exists between the implementation of TCD screening and the accessibility of hydroxyurea within a broader population of patients. Therefore, it is necessary to understand the factors which underlie these gaps as well as potential mechanisms to mitigate them. This relatively broad theme is inclusive of the local context, as well as specific medical, technological and public health-related opportunities that can be explored to improve hydroxyurea utilization, and the role of leadership and change management to support capacity building through expansion of research and other programmatic partnerships between the US and sub-Saharan African countries.

North-South Partnerships: Utilizing Leadership Models to Plan for Change

Weatherall et al. (2005) argued that the goal of furthering research and improving clinical care globally necessitates the development of long-term partnerships between research groups working on this disease in well-resourced and resource-limited countries. These partnerships, facilitate transfer of knowledge and technology toward the improvement of local healthcare infrastructure and development of the healthcare workforce and represent an opportunity for implementing lasting change beyond research settings when local context is considered. Use of leadership change models to understand the local context and to establish structured methodology for change through North-South partnerships is an effective strategy which utilizes the strengths and resources of involved parties toward a common set of goals. The Re-AIM and Collective Impact leadership change models are relevant to understanding the complex issues associated with implementing change within healthcare systems and informing policy in resource-limited settings.

The Re-AIM model (Glasgow et al., 1999) was developed to assist in planning and evaluation of clinician and community-based projects and can be used as a tool in the translation of research into practice. The model utilizes a multi-dimensional approach which includes reach, efficacy, adoption, implementation, and maintenance to support a structured and measurable approach to change management relevant to public health programming and policy. This model translates well into international practice due to its use of core dimensions which allow for a multi-faceted understanding of implications within real world settings and provides a useful lens through which programming such as TCD screening and training can be defined within local contexts.

The Collective Impact Model (Kania & Kramer, 2011) calls for individuals, organizations, and entities to abandon individual agendas in favor of a single, common agenda, requiring all participants to develop a common understanding of a health system problem and mutual agreement to solve it. This is particularly relevant to public health leadership change management given the multiple stakeholders, roles and disciplines involved in international health systems which all need to change behaviors to solve a complex public health problem. Shifting from isolation within and among groups to viewing work within the context of a broader system has direct and indirect impact on how practitioners design and implement work processes, how funders incentivize and engage with workers and program teams, and how policymakers bring solutions to a broader scale (Kania et al., 2013).

Discussion

Limitations

There are two notable limitations that impact the interpretation of findings within

this literature review. The review focused primarily on published clinical trial data and is therefore limited to qualitative research that might influence the public health context and associated implementation strategies within sub-Saharan Africa. Secondly, the focus on hydroxyurea as a therapeutic option did not include a comparative analysis of literature on other possible treatment options such as bone marrow transplant or gene therapy which may be of interest to the affected population, however, this was not a focused goal of this review.

Conclusions

The complex landscape of SCA within the sub-Saharan African context is clearly described through this literature review, indicating that SCA represents a significant public health challenge in Africa. Despite advancements in diagnosis and management of SCA, multiple barriers to optimal clinical care exist, including well-defined screening programs, limited availability and access to hydroxyurea, and knowledge gaps among the healthcare workforce which necessitate a multi-faceted approach to building capacity in resource-limited settings. While working to improve care within a healthcare and research context in these settings involves inherent challenges, it also provides an opportunity for collaboration with local communities to identify and operationalize the change management strategies that are most likely to achieve their goals. By engaging in a research partnership with local medical and public health leaders as well as government agencies, community groups, and other key stakeholders, the change management steps from Glasgow et al. (1999) and Kania and Kramer (2011) can be enacted in an approach that is locally relevant, culturally appropriate, and scientifically sound. The literature supporting the four themes identified within this integrative literature search

demonstrates the significant disease burden of SCA in this population and the extensive impact that research partnerships can have to improve outcomes for this underserved, at-risk population.

CHAPTER 3: METHODS

Study Design

STRETCH utilizes a qualitative design which includes semi-structured interviews with TCD examiners and stakeholders with thematic analysis to answer the primary and secondary research questions. Interviews were conducted with TCD examiners who participated in the training and supervision program at various stages, TCD super-trainers, and local clinical care providers. All methods and materials used in this study were approved by the Indiana University Institutional Review Board (protocol approval number 21156) and CCHMC Institutional Review Board (protocol approval number 2023-0655).

Study Population

The population for this study includes TCD examiners working in sub-Saharan Africa previously trained in the CCHMC International Sickle Cell research program between 2015 - 2023 and the primary stakeholders identified from each working location at the sites listed in Table 3.1. Participating sites included three rural sites in Uganda, Tanzania, and Kenya and four urban sites in Angola, Democratic Republic of Congo and Uganda, all of which serve as regional referral facilities where many patients often travel long distances for medical care that they cannot obtain close to their homes. All sites participate in therapeutic trials for children with SCA, through which they gained access to the TCD training and supervision program.

Table 3.1 Recruitment Sites

Site Number	Site Name	Location	Setting	Number of Participants
01	Mulago Hospital Sickle Cell Clinic	Kampala, Uganda	Urban	2
02	Mbale Clinical Research Institute	Mbale, Uganda	Rural	4
03	Bugando Medical Centre	Mwanza, Tanzania	Rural	2
04	Centre Hospitalier Mère-Enfant Monkole	Kinshasa, Democratic Republic of Congo	Urban	1
05	KEMRI Wellcome Trust Kilifi District Hospital	Kilifi, Kenya	Rural	4
06	Hospital Pediatrico David Bernardino	Luanda, Angola	Urban	2
07	Korle Bu Teaching Hospital	Accra, Ghana	Urban	2

Figure 3.1 Map of Participating Sites

Recruitment

After IRB approval, the project was presented to potential participants during monthly team teleconferences with an invitation to participate if interested. Participants were asked to complete an interview via phone, Zoom, or in person depending on availability and individual preference. During the interview, trained interviewers performed a semi-structured interview which included questions about the participant's knowledge of SCA, their experiences with TCD training, the role TCD screening plays in their general practice, and their approach to working with children with SCA in their respective settings in an effort to describe how public health leaders can mitigate stroke

risk among children with SCA in sub-Saharan Africa using an effective, sustainable and feasible TCD screening, training and supervision program. Interviewers also inquired about participants' insights regarding challenges their organizations face in providing care for children with SCA and how capacity can be best built within their settings. Interviews took an average of 60 minutes to complete.

Informed Consent

Study investigators requested a waiver of written documentation of consent/authorization because participating in the interview process is an activity that would not otherwise require consent outside of a research setting. The STRETCH study presented no more than minimal risk to the privacy of individuals, since participants would only be sharing their experiences and opinions in a confined group and all data collected was de-identified. As this is a qualitative study during which no identifying information was used and no biological samples were obtained for research, both IRBs approved the request for a waiver of written consent. Participants provided verbal consent to proceed with the semi-structured, recorded interview at the beginning of the interview session after the research aims and activities were described, were informed that participation was entirely voluntary and that the interviews could be stopped at any time should the participant feel any level of discomfort or wish to end the dialogue. All interviews were completed in entirety with no report of discomfort during or after interview completion.

Potential Benefits

Participants were informed during the verbal consent process that there was no direct benefit from or payment for their participation in the research interviews. They

were informed that they would have the opportunity to provide their observations, experiences, and insights to describe the TCD training and supervision program to date, and towards the continued improvement and expansion of the program within resource-limited settings. Additional benefits included informing the ideal training methods for learning new skills and competencies as part of a community of learners as well as participating in a learning network focused on evidence-based care for patients with SCA. Possible additional benefits included increased knowledge about SCA screening and treatment and improved TCD training methods. Participants were informed of the potential for this study to impact future sickle cell clinical care and research as the information that is learned may be used in future provider education and that no compensation would be provided for participation.

Potential Risks

The risks for participation were minimal and consisted mainly of unintentional disclosure of personal information to members outside of the research team and the risk of participants feeling uncomfortable completing interview questions. No unanticipated problems occurred during the study. All interview responses were de-identified after coding and before being added to the manuscript as representative quotes to avoid any indication of interviewer identify beyond the interviewer's role as TCD examiner, super-examiner, or stakeholder.

Privacy and Confidentiality

The informed consent process addressed various aspects of participant privacy including the level of control over the circumstances and extent of sharing one's personal information. At the time of verbal consent, the potential participant could1) decline to

participate or 2) agree to participate with the understanding that they may withdraw at any time, giving the participant control over the circumstances of sharing their personal information. Raw interview data will not be available to anyone not directly associated with the study during or after study completion. All study personnel were trained in privacy and confidentiality and minimizing risks related to loss of privacy and confidentiality. The performance of research personnel was monitored by the investigators to ensure the strictest standards for protection of confidentiality.

Interview Guide Development

A semi-structured interview guide was developed to obtain an overall description of the TCD program from the perspective of the super-examiners and trainees over the course of 2015 - 2023 and to describe participants' experiences to glean insight into how public health leaders can implement a high-quality TCD screening program and how those learnings fit more broadly into public health factors involved in care for children with SCA. A similar interview guide was developed for use with local stakeholders in the clinical settings where the TCD screening program was run. The interview guides were organized based on the themes identified in the literature review with flexibility to allow for participants to provide additional information as needed with the intent of elucidating additional themes or sub-themes if appropriate during thematic coding.

TCD Examiner Interview

The TCD examiner interview consisted of 52 questions categorized into sections. See Appendix A for the complete TCD Examiner Interview Guide.

Table 3.2 TCD Examiner Interview Sections and Associated Content

Section	Summary of Content/Questions
General/Background	• Level of experience in healthcare • Description of TCD training received to date • Experience with performing TCD exams in general
Overview of Healthcare Facility/Site	• Description of setting (hospital, outpatient clinic, etc.) • Description of community (rural, urban), • Local SCA patient population size.
Transcranial Doppler Training	• Knowledge about TCD before training • Description of the TCD training received as a new trainee • Description of ongoing training and supervision • Challenges experienced • Description and comments regarding various formats used, • Experience during and after certification process
TCD in Practice	• Current practices post-certification with TCD practice • Consultation opportunities with colleagues • Communication and use of results within clinical practice • Access and barriers to TCD locally • Local impact, capacity built • Goals for the next 2 years
SCA Knowledge	• General knowledge regarding SCA • Clinical implications and risk • Diagnosis of SCA and sickle cell trait • Screening and treatment costs • Education and capacity gaps.

Stakeholder Interview Guide

A stakeholder interview guide was developed to ascertain insights from local clinicians who care for SCA patients. The TCD Examiner Guide was adapted for use with stakeholders who may not have direct access to TCD training based on their role but engage with the TCD screening program and have insight into its role within the local context. See Appendix B for the complete Stakeholder Interview Guide.

Table 3.3 Stakeholder Interview Guide Sections and Associated Content

Section	Summary of Content/Questions
General/Background	• Level of experience in healthcare • Background in healthcare/training • TCD training received, if any • Experience with performing TCD exams in general
Overview of Healthcare Facility/Site	• Description of setting (hospital, outpatient clinic, etc.) • Description of community (rural, urban) • Local SCA patient population size
Local Context	• Existing stroke screening protocols in place locally • Financial and logistical burdens associated with screening protocols • Consequences and health outcomes of stroke in pediatric SCA patients • Socioeconomic burden of stroke in SCA patients
Transcranial Doppler Screening	• Impact of current TCD screening program • Potential impact of expanded screening • Overall impression of TCD screening program • Opportunities for examiner improvement • Effective and ineffective training methodology
TCD in Practice	• Communication and use of results within clinical practice • Access and barriers to TCD locally • Local impact, capacity built • Ethical considerations and cultural factors associated with TCD screening • Key stakeholders and community partners who should be involved in TCD screening program implementation • Potential long-term benefits of TCD screening programs • Risks associated with not implementing expanded screening • Additional comments regarding capacity building and technology transfer within local setting
SCA Knowledge	• General knowledge regarding SCA • Clinical implications and risk • Diagnosis of SCA and trait • Screening and treatment costs • Education and capacity gaps.

Interview Process

Data collection via semi-structured interviews with TCD examiners and clinical care stakeholders occurred during 20 November through 13 December 2023. Participants provided verbal consent to participate in the interview and for digital recordings of the

discussions. Names were removed and replaced with identification numbers. Interviews were recorded on Zoom using auto-transcription software, saved, and cleaned by the interviewer after transcription, within 24 hours of completion of the interview. In instances where Zoom failed to transcribe the interview accurately Rev.com software was used to transcribe.

Data Management and Analysis

A coding system was created to aid in coding focus group transcripts. Data analysis was conducted utilizing the Grounded Theory method (Glaser, 1967, Strauss and Corbin, 1990) following a three-step coding framework of open, axial, and selective coding. The Grounded Theory method provides a mechanism through which theories can be generated through the iterative process of constant comparison. Data are analyzed as they are collected and as similarities and differences among the codes are conceptualized, a coding scheme reflecting themes is further refined by clustering codes together to make categories and sub-categories. A combination of the open coding method Glaser (1967, 1978) and the later-refined addition of Axial and Selective Coding methods (Strauss and Corbin, 1990) was used in order to allow for a broad review and collection of themes across interviews followed by an iterative process determining where the themes intersect categorically.

The Grounded Theory open, axial and selecting coding model was chosen for analysis of the qualitative data collected during the examiner and stakeholder interviews for several key reasons. First, the model provides the necessary structure for a robust coding process, analysis and generating of results while allowing for flexibility and not relying on pre-conceived theories or constructs. Secondly, the iterative process allows for

continuous analysis of findings in a cyclical manner, allowing researchers to refine their understanding of the phenomenon as the datasets are built. Lastly, Grounded Theory is sensitive to context, enabling researchers to focus on contextual factors such as socioeconomic conditions, cultural norms, resource gaps and/or infrastructure limitations which are of particular relevance in resource-limited settings.

These factors are of particular importance given that the research questions and setting represent a significant knowledge gap which is needed to inform public health policy and practice in these areas. This renders the emergence of themes and patterns directly from the data generated of critical importance to answering the research questions in a manner that both informs the development of feasible and realistic methods and health policy to support them, and documents key capacity and education gaps for future research. Utilizing a methodology that limits the emergence of themes or relies too heavily on preconceived theoretical models would introduce risk into an area where an accurate assessment of local context and factors is a key component to the current research questions and from where the future directions will follow.

Open Coding

Open coding is the first step in the iterative Grounded Theory methodology and involves identifying concepts and categories from data collecting during qualitative research. This is an important step in that it allows for themes to emerge from the data itself and does not attempt to force them into a predetermined set of themes without providing flexibility for new themes to emerge. The first step of open coding occurred during cleaning of interviews within 24 hours of completion, where interviewers created a set of notes during the process of cleaning. These notes and the full transcripts were

provided to set group of trained coders who performed a full review of the transcripts and prepared a comprehensive set of codes and themes, noting which interview generated each response.

Axial Coding

Axial coding follows the open coding process within the Grounded Theory model under the Strauss method. Once open codes were generated and initial set of main themes identified, the codes were examined in order to identify relationships between them and to generate an initial set of sub-categories which provide further insight into the concepts being studied within the research questions. New, emergent themes or sub-themes are identified through this iterative process which allows the researcher to gain a more in-depth understanding of the data. Interviews were coded in the sequence in which they were performed, using a constant comparison process in order to return to prior interviews to ensure that insights related to emerging themes which were identified later in the process are captured in entirety. This process continues until thematic saturation is reached, with no new themes or categories emerging from the data. Axial coding was performed by a trained member of the research team in conjunction with the researcher, and a quality control review occurred at the end of the axial process to ensure that no major themes, sub-themes, or key examples were missed in the coding process.

Selective Coding and Analysis

The goal of selecting coding is to integrate the different categories identified during the open and axial coding processes into one cohesive theory informed by the data as a whole (Strauss, 1998). During this final step in the coding process which follows thematic situation, core relationships were identified between the major themes,

subthemes and categories and carried out into a more abstract level which allows for development of a grounded theory supported by the data. The researcher performed the selecting coding steps with review and quality control checks from two members of the research team. The results were then used to prepare a final code book with CONSORT diagrams demonstrating the coding process, themes, sub-themes, and categories identified, and a set of sample quotes identified which most closely supported each area. These were used to inform the results of the research questions as and directions for future research.

Code Book

A code book was developed to facilitate the organization of participant responses from 20 hours of interviews and categorize them into themes and sub-themes. Seven main categories were identified, with 36 sub-themes and 48 initial codes which emerged during analysis of the participant responses (Appendix C). The coding analysis was verified by two independent study team members and the author to ensure consistency. Interview quotes which support results and inform the application and development of theoretical models for change were included in the results, with a more comprehensive listing of representative quotes included in table format in the supplemental appendix (Appendix D).

CHAPTER 4 RESULTS

Overview

The interviews generated a rich volume of data from nine TCD examiners, including two examiners who received additional training to become trainers ("super examiners") and eight stakeholders with direct involvement in the TCD training and supervision program, local health facilities, and population of children and families affects by SCA. Six main thematic categories and 32 subcategories were identified during thematic analysis of 755 coded responses and 744 confirmed codes after removal of duplicates. These themes and subcategories have several important intersections, which collectively underscore the importance of sustainable and scalable training methodologies and improved pathways for access to care for patients with SCA in sub-Saharan Africa.

Interviewees provided extensive context regarding the impact of SCA within their settings, broad gaps in education and training among healthcare providers, and major healthcare system infrastructure barriers related to hydroxyurea access which could be improved significantly through a combination of organizational program, process improvements, and health policy support. The importance of key stakeholder engagement, particularly among Ministries of Health and policymakers was a theme across multiple interviews, specifically when discussing the barriers and facilitators to expanded TCD screening and improving access to hydroxyurea.

Participants described the impact of stroke in SCA and the clinical effects of SCA from a socioeconomic perspective and how this message must be emphasized to public health leaders, especially Ministry of Health policymakers, in order to effect lasting change. The analysis includes a summary of interview results by category, theme and

number of coded responses is included in Table 4.1 which are further elaborated upon within each category and theme with representative quotations. These were then analyzed to identify intersections within the themes and categories which informed a comprehensive theoretical model which integrates the results into a manner which can be used to inform health system infrastructure and policy changes within sub-Saharan African settings.

Table 4.1 Coded Statements by Category

Category	Code Description	Coded Statements
SCA burden and clinical features	Background, diagnosis, newborn screening	60
	The burden of sickle cell anemia on the community	23
	The burden of sickle cell anemia on the healthcare system	24
	Treatment options in the US vs. sub-Saharan Africa	1
	Access to basic treatment/preventative measures	37
	Access to therapies (hydroxyurea, transfusion)	10
	Total	**155**
Stroke in SCA	Stroke in SCA: epidemiology, morbidity, and mortality	15
	Impact of stroke: family, community, and healthcare system	6
	Total	**21**
Transcranial Doppler Screening: methods, use, training	Overview: background, use, interpretation	45
	Training program/Training methodology for TCD: US and in resource-limited settings	125
	Context for scale-up based on effective vs. ineffective training methods and program structure	17
	The need for TCD in sub-Saharan Africa	27
	Challenges of TCD	20
	Desire to expand TCD use	41
	TCD Training frustrations	9
	Total	**284**
Healthcare infrastructure, workforce knowledge and technology transfer in resource-limited settings	Volume of patients vs healthcare capacity	15
	Hospital resources - Capacity and resource gaps in sub-Saharan Africa	17
	Staffing limitations - Capacity and resource gaps in sub-Saharan Africa	21
	Healthcare infrastructure, eHealth, need for operationalizing/building capacity within systems using evidence-based research	8
	Barriers to TCD expansion	20

Category	Code Description	Coded Statements
	Training/background of healthcare workers	6
	Total	**86**
Social determinants of health	Capacity and resource gaps in sub-Saharan Africa: the cost of SCA care	44
	Capacity and resource gaps in sub-Saharan Africa: patients travel for care	13
	Health literacy	28
	Costs of screening vs. treatment – economic reasons for screening; influence on policy makers	20
	Lack of education	39
	Cultural considerations	9
	Local context	23
	Total	**176**
Public health leadership change management, leadership change models and implementation	Stakeholder engagement	6
	Organizational structure/change management	3
	Workforce gaps and development opportunities	1
	Health policy opportunities	6
	North-South partnerships	6
	Total	**22**

Transcranial Doppler Screening: Methods, Use and Training

Program Description and Context

The results of STRETCH provide valuable insights into how public health leaders can mitigate stroke risk among children with SCA in sub-Saharan Africa using an effective, sustainable, and feasible Transcranial Doppler screening, training and supervision program. Interviewees described their experiences during training as well as operational and systemic factors which influence the training and implementation of TCD screening in sub-Saharan African settings. Six TCD examiners who participated, including the two super-examiners, were involved from the early phases of the program, rendering them uniquely poised to speak to its evolution over the last six years, while three examiners were trained after the program was in place for 3-4 years. Describing the current TCD program and its evolution to date provides several key insights which answer this question and inform how education and training gaps for SCA can be most effectively mitigated within clinical settings in sub-Saharan Africa using a theoretical model appropriate for these settings and their inherent strengths and challenges.

The Cincinnati Children's Hospital Medical Center (CCHMC) Division of Hematology international TCD screening program began in 2015 with the initial training of the first African TCD examiner. The project leadership team hired an experienced US-based TCD super-examiner and trainer experienced in TCD methodology from the US-based STOP trial to train one examiner in Kampala, Uganda. The original problems that the program was intended to address included (1) introduction of technical TCD skill training into sub-Saharan Africa; (2) provide equipment and ongoing technical support to perform high-quality TCD examinations; and (3) fill the operational support capacity gap to allow TCD findings to be utilized for the purpose of research questions as well as to inform hydroxyurea dosing. Prior to the introduction

of this program, there was no structured TCD screening program with operational oversight from the US in sub-Saharan Africa, without which TCD results are of limited value in the clinical or research contexts.

TCD examiner training was implemented using a combination of in-person and remote training. Trainers initially were US-based, which later transitioned to Africa-based trainer/super-examiners with oversight from the CCHMC sickle cell research team. Leadership training and mentorship is provided to TCD trainers to further develop sub-Saharan Africa-based program leadership. Table 4.2 lists current program elements which have been implemented in the last four years, all described by interview participants as key aspects of the program.

Table 4.2 Current TCD Training and Supervision Program Components

TCD Program Component	Strategies Employed
Implementation of ongoing supervision program	Monthly formal TCD examiner calls are conducted, which include ongoing training topics, skill review, training on new hardware/software, troubleshooting and ongoing skill-building
TCD leadership team	Two Africa-based trainers and a US-based team leader are available 24/7 for examiner support via a shared WhatsApp group that allows all examiners to communicate and learn from each other, specifically related to challenges and learnings relevant to all sites.
In-Person training	On-site for initial examiner training (3-5 days) when possible, annual in-person training for a sub-group of examiners
Central review and scoring	All TCDs are uploaded by examiners into a central database and scored by TCD leadership team to ensure accuracy and appropriate clinical follow-up for elevated exam results.
Clinical follow-up: Increasing capacity within local sites for stroke prevention	Prioritization of highest risk population for treatment accessibility: children identified to be at risk for stroke are prioritized for hydroxyurea treatment and/or dose optimization if currently treated in order to mitigate stroke risk.
Technical support	Provided by CCHMC team

TCD Training: Experience and Examiner Impression of Methods

Objectives of the existing TCD program have evolved over time, and challenges experienced during various stages of the program have informed improvements over time which can also be used to inform strategic planning of broader scale-up. Challenges included the initial use of a US-based super-examiner/trainer only, which limited the success of examiner training due to cultural and linguistic differences. This was compounded by existing difficulties with communication, examiner learning pace and basic skill needs regarding use of the TCD equipment and associated technology. Following implementation of a new operational leadership team which included a US-based lead from the CCHMC Data Coordinating Center and two African TCD super-examiners, goals included 1) develop a stronger communication platform by establishing monthly training and oversight calls with all examiners; 2) identification, purchase, validation and deployment of new equipment; 3) creation of a process for central scoring of TCDs and communication to clinical staff for treatment optimization; and 4) documentation of a technology transfer plan which can be used to inform policy pertaining to scaling use of TCD in local site settings.

Key findings from a training methodology perspective included participants' preference of a hybrid program structure which emphasizes in-person training that is supported by online/distance learning and support. There was a trend across examiners that the length of time in person/onsite was generally too brief, particularly when translation was needed. Examiners preferred learning TCD examination skills on patients with SCA in lieu of other patients in clinic, because children without SCA have lower velocities which can be more difficult to optimize using the TCD equipment.

A super-examiner noted the importance of initial time spent training in-person followed by ongoing, remote training and supervision, noting challenges associated with attempting initial TCD training remotely:

> *"The only thing that I found challenging of these on this list is if you're training the skill for the first time and someone is on Zoom. That is very, very hard; trying to train and learn a practical skill online. The time you use to explain something 6 times, the one who is there physically could just touch the hand and put it where it's supposed to be. But one week or 2 weeks of the physical training, then the online forums are very effective because you can continue polishing. Without being grounded in the actual skill within the first one or 2 weeks, Zoom is not very effective, if you've not had any prior training. But after training, it can be another very good way of reinforcing what you studied earlier on."*

A TCD examiner further noted:

> *"I think this one from African based trainers, I think it worked well. Open forum discussion meetings, zoom. In person practice session with sickle cell disease patients. In person practice sessions with the demo, I think all of those were most effective."*

Interview participants noted that written training materials, standard operating procedures and manuals of operations were helpful in support of the interactive methods, but that they were less likely to seek them out if not prompted to do so by team leaders. Real-time support from US for technology challenges was highlighted by many as key to facilitating progress, and examiners appreciated the accessibility of the US-based team despite time and location differences, thus underscoring the importance of communication and relationship building within international teams to facilitate open dialogue and problem-solving when inevitable challenges arise.

Shifting to sub-Saharan Africa-based trainers was a positive change in the program for several reasons: facilitating communication as interviewees stated that they experienced less hesitancy to raise questions in a setting where asking questions is as perceived as challenging a team member in a leadership role. Examiners also spoke of the value of the program format which facilitated interaction between examiners and not solely between examiners and the coordinating center. Monthly interactive calls plus an online text group allowed examiners to

troubleshoot issues and learn about common challenges and strengths among them. These calls remain ongoing after all examiners are certified, which allows for continued team building and collaboration across sites/countries, further strengthens the organizational and leadership skills both of the TCD super examiners and exposes examiners to these skills, which builds capacity within their TCD practice and more broadly within their roles at their respective sites. Speaking about the monthly calls, a TCD examiner noted:

> *"Usually, the examiners get a chance to see what their problems are. Then either the trainers or fellow examiners give a solution. It's two-way, yes, it's open, the trainer says things, and the examiner also says things. And maybe for an examiner that is not bold enough to say what their problem is, but they are usually given a chance to express their problems. And then on the call, we can brainstorm together."*

Stakeholders' impressions of the training and supervision program were overwhelmingly favorable particularly with regard to the program structure and elements, emphasizing the value of knowledge and technology transfer via collaboration between the examiner sites and the Cincinnati Children's team. Stakeholder respondents described their desire to see TCD screening expand beyond the research context and be made available to other patients, while maintaining the high-quality examination results. They acknowledged the costs associated with such an expansion as well as the critical need for improved pathways for accessing hydroxyurea in this patient population, which constitute gaps that can be addressed through healthcare infrastructure improvements and health policy to support the costs of the screening assessments and treatment

Program Challenges

There were several challenges during the initial program rollout related to equipment functionality and technical difficulties associated with early skill development among the examiner group. Interview participants described challenges with their early skill development, when they had very limited exposure to TCD and were learning the concepts. The equipment was new to the examiners, and their experience and comfort with troubleshooting technical

issues was extremely limited. Training was initially provided by a US-based examiner, and the addition of sub-Saharan Africa-based super-examiners strengthened the program significantly from the perspective of interviewees.

The program includes English and non-English speaking examiners (French and Portuguese), which has required creative solutions to ensure that all content is delivered consistently, and adequate support is provided for those who do not read or speak English. One of the super-trainers spoke to the importance of considering the in-person training format and time needed for trainees to have time to learn onsite with a trainer when translation is needed.

> *"The barrier is with difference in language. Let's say you're an English speaker, and you're training French speaking or Portuguese speaking. If it's the same language English to English, one week is enough. But if it's a different language, English to French, English to Portuguese, I think you need 2 weeks. Because that first week, just trying to get to speak a common language thus, for to understand you, and you to understand them. But with them English speaking, you just go directly into the content. So, when you'd need more time for a difference in the languages being speak spoken may be English to French, English to Portuguese, or vice versa, I'd recommend 2 weeks. But if it's English to English, one week is surely sufficient for a physical training."*

All examiners, with the exception of one, were trained initially using Sonara/tek non-imaging TCD equipment, which was commonly used in the United States and Europe the time that the program began. There were a variety of equipment and IT-related challenges which required ongoing, real-time support from the US-based team. Examiners and super-trainers consistently reported appreciation for the US-based coordinating center team's willingness to work with examiners remotely despite time differences, and their use of creative solutions to communicate such as WhatsApp and Facetime, using multiple computers and phones to allow for real-time viewing before Zoom-based screen sharing technology was available. An examiner noted:

> *"The other thing that has been going well is with troubleshooting. We are working with machines and sometimes the machines jam or get a problem. I would like to commend the Cincinnati Children's side for trying to work to brainstorm and troubleshoot to resolve*

any problems in real time. If you have a problem with your machine and you request help, and it took you 2 months, then that would be a problem. But as soon as you raise a problem, they will organize a meeting, then the problem will be addressed. I think that's a strength, that in case of any mechanical, any technical issues in terms of the machine they are usually solved immediately. And then those open forum calls in case a site has more problems than the other, then a separate site call from the rest of the examiners is usually organized with just that sight to address that problem, which I think is such a good thing."

In 2022, new technology was introduced which involved a system validation of the Dolphin ID non-imaging TCD system and a structured equipment distribution process, training and re-certification of the examiners. New equipment was deployed over a six-month period and the coordinating center team used the monthly teleconference schedule as a forum to train examiners on system basics as well as for demonstration how to use the new equipment. French translation was provided during the sessions, and all training sessions were recorded, transcribed, and translated into French and Portuguese along with all written training materials. Recordings, demonstrations, and training documents are disseminated to the group via a secure study website to ensure version control. Two in-person training courses with interactive practice sessions were provided during annual investigator meetings. The examiners' experience was overwhelmingly positive, they reported learning a great deal and quickly, and troubleshooting the technology was far smoother than in the initial Sonara/tek rollout. Interviewees credited the updated training program format at the time, the well-established relationships among the participants and the solid foundation of skills and knowledge that they had built by that point through their early practice.

Despite early challenges, linguistic differences, and new equipment deployment, the program has successfully trained and certified 14 TCD examiners, performed over 5,000 high-quality TCDs and screened more than 1,700 children with SCA for stroke risk. There have been four successful international training meetings as well as individual on-site visits at all sites, and

monthly operations and training calls continue along with ongoing review of exams on a rolling basis. TCD results are communicated to sites on a quarterly basis, with all elevated exams reported expeditiously so that clinicians can review cases and act accordingly to mitigate stroke risk.

Expansion of TCD within sub-Saharan Africa for SCA: Context for scale-up based on program elements and structure

TCD has been shown to be a highly useful tool for identification of stroke risk in children with SCA, and the current training and supervision model is, in the opinion of interview participants, highly effective. However, the CCHMC international TCD program is currently in use within clinical research settings only, and there is great interest and need for expansion without a clear path forward. Interview participants spoke about the need for and interest in TCD in their settings, but also shared concerns about the cost of the procedure and the limitations among providers in knowledge of appropriate action steps to mitigate risk of stroke for patients. Further, cost of treatment in the form of hydroxyurea or transfusions is prohibitive to many families without national insurance or Ministry of Health subsidy of hydroxyurea.

A stakeholder commented:

> *"I think the problem is about the cost, adding more cost to the patients. I would propose, if possible, that if we get this technology at subsidized costs, that will be a plus. Then we have a common protocol but can be applicable for almost all the settings. Currently, no one knows how to do it. They just think, 'Today's the TCD exam, let's do it.' But we don't do it. They forget about it. There are no tracking tools. So, I would say, is to develop a package, a training package. Then of course there is the need for subsidizing costs."*

An examiner further noted:

> *"The barriers have always been financially and also some of them have the fear of being told that their child is prone to getting stroke, with nothing to do for them."*

Overall, however, the interest in expansion of TCD beyond the clinical research setting is significant, with a clear sense of the need and how impactful the screening tool can be if

implemented in a strategic, sustainable manner appropriate within local settings. One of the super-examiners stated:

> *"I'd love to spread that TCD gospel, even if it's like extending the information in the training schools trying to work with the Ministry to see how they can put these TCDs, at least at regional referral hospitals. It has proved beneficial in the research setting. Now can we get it out of the research settings and put it on a higher level, on the country level? Regional referral hospitals, like many people, don't even know about TCDs. My goal would be to spread that TCD gospel to as many people as you can, and then try to see if we can work out a way of like getting it past the research setting so that even the other patients can benefit."*

An examiner further noted:

> *"I think CCHMC has done a good job in the particular research that we are doing. Out of [all the studies], is there's a way can work together with CCHMC to spread it to other facilities? I know, maybe that's a long stretch, but it has done well in the research setting. Is there room to extend it to others? Or is it asking too much?"*

The TCD examiners and stakeholders identified several program elements as highly effective, including modifications which included the implementation of super-examiners, improved capacity for web-based training and real-time communication, and establishment of the examiner group for collaboration and problem-solving. The group has formed a cohesive team who now see their abilities and potential with TCD and all of whom have goals which include expanding their knowledge and skillsets. There are significant gaps which exist from a resource perspective, as well as pathways which need to be established within healthcare systems to better utilize TCD results to mitigate the devastating morbidity and mortality associated with stroke and SCA.

Stroke in Sickle Cell Anemia

Stroke was categorized as a standalone theme during analysis to gain more in-depth insight into the depth and breadth of its impact. Interview respondents discussed at length the effects of stroke on individuals with SCA, their families, communities and the health systems

that provide their care. The morbidity and mortality associated with stroke in this population were well known to interviewees, and many interviewees described the level of frustration that they feel knowing that TCD is available as a screening tool but that they cannot use it outside of study populations currently.

Interview participants noted that it is common among caregivers of children with SCA to perceive stroke as an abstract risk, thinking it is unlikely to happen to their child, and then when a stroke occurs it is both shocking and devastating to the child and family, suggesting that increased awareness and education is needed among caregivers. Further, TCD examiners and stakeholders felt that in general, providers are ill-equipped to prevent stroke using hydroxyurea due to availability and cost issues, and transfusion is similarly challenging due to cost and blood supply limitations. From an economic perspective, stroke affects the entire family as parents are unable to continue to work when ongoing care and physical or occupational therapy is needed for a child, and this level of supportive care is often cost-prohibitive to families. Many children with SCA affected by stroke are unable to progress in school at the same rate as their peers, and without treatment with hydroxyurea or transfusion, the effects of secondary stroke can be even more devastating. Appendix C, Table C.2 lists representative quotes from TCD super-examiners, examiners and stakeholders regarding the extent and gravity of these issues.

Sickle Cell Anemia: Screening, Diagnosis, Burden, and Clinical Features

Interview respondents discussed the clinical features of SCA, the extent to which screening and diagnosis is available within their settings, and the treatments that patients need and/or receive. Examiners and stakeholders noted that diagnosis of SCA via newborn screening remains variable in their countries, particularly in peripheral areas, leaving a large population of affected children and their caregivers unaware of their SCA status until they experience

complications requiring intervention or die from an infection or other complication of the disease without knowing that they were at risk.

In general, there is some awareness among families about the possibility of SCA, however in many settings it remains understood as an illness of pain or bones, and not a hematological condition until proper diagnosis has occurred and ongoing care is initiated. Interview respondents spoke of the burden of SCA within their settings, noting that families often are unprepared for the diagnosis and ill-equipped to financially, logistically and/or socio-economically manage the child's ongoing needs. An examiner, discussing the diagnostic process and conversations that clinical teams have with families about the diagnosis of SCA and family history noted the following:

> *"We ask [about family history] because, sickle cell here in Swahili called 'Selimondo.' In their localities, they are using the word 'ugonjwa wa mifupa,' or sickness of the bones. This word has been going around and if that thing happens to their community. Sometimes we ask them 'this condition your child has, is it similar to any anyone in your family, whether on you on your husband's side or your side?' Sometimes they tell you. 'Oh, yeah, there's an aunt had something like this.' You narrow down this information, then you give out the genetic history about this thing. Sometimes, if you probe more, they even get to understand where this thing is coming from. Generally, most of them claim they have no clue. And they tell you 'I don't know anything. This is the first time you're telling me, and you're telling me my son is sick and I don't know anything.'"*

A consistent theme across interviews was the role that hydroxyurea plays in improving clinical outcomes for children with SCA, and the need for improved awareness and education among healthcare providers to utilize it optimally, and the challenges families have in accessing it, primarily due to cost and availability. Respondents noted that it is very clear in clinic which children are taking hydroxyurea, and how different their clinical course and outcomes are, particularly those who started treatment at young ages. The introduction of TCD and expansion of its use in these settings must be done in consideration of ethical issues which arise when

identifying a child who is at risk for stroke without having direct access to the necessary treatment to mitigate that risk.

A stakeholder noted:

> *"As a clinic, we are not only seeing the [study] participants. It's a special clinic for sickle cell disease. Maybe we conduct a TCD exam, and we give them that they are at a higher risk of getting stroke. Then we do the same thing and need [to] talk to them, talk to their parents for the ones who are not on hydroxyurea. Then we will have to talk to their parents to ensure that they get hydroxyurea as soon as possible because of the beneficial effects that hydroxyurea has to these patients."*

Another stakeholder commented:

> *"When introducing [TCD screening] means we have to make sure hydroxyurea is available. You cannot just do TCD and it's high and you leave somebody. Or if you don't use hydroxyurea, then other means of treatment have to be there, like transfusions. Though in our area, we don't even do extended cross match which is really a risk to our patients. We have automated machines that the hospital has bought but when we introduce this to a majority of people have to have the alternative of treating them when you find the TCD is elevated. I think the best thing we can say is you have to make sure hydroxyurea is available widely."*

Interview responses included discussion of the use of blood transfusions within the SCA population, noting that transfusions are often indicated when a child is at risk from stroke and due to other clinical diagnoses, such as cases of malaria or acute chest syndrome. Participants indicated that these situations during which transfusions are often indicated can be prevented through treatment with hydroxyurea and expressed frustration when clinician knowledge and/or a family's inability to afford the medication prevent the use of what they know to be a possible life-saving treatment for the child affected. Interviewees further commented on blood scarcity issues which are common in their settings, underscoring the importance of prevention through use of hydroxyurea.

Healthcare Infrastructure, Workforce Knowledge, and Technology Transfer in Resource-Limited Settings

Assessment of the role of technology and knowledge transfer as a key driver of stroke screening and prevention as well as more broadly within the SCA treatment context in these settings is crucial to informing organizational change and policy which would support effective implementation of TCD programs and improved access to hydroxyurea treatment. To that end, participants were asked to describe their local settings, volume of patients as compared to overall healthcare resource capacity and staffing limitations.

Hospital resources: Capacity and gaps

Interview respondents consistently reported resource limitations and burden on the healthcare system as barriers to diagnosis and care in children with SCA. Clinic patient volumes at referral centers are significant, and respondents noted that inadequate staffing resources are compounded by lack of education and knowledge among healthcare providers about the management of SCA, specifically with hydroxyurea. The creation of a model which includes strengthening of the healthcare system from an education as well as efficiency perspective will be key to improving the capacity of healthcare providers to manage volumes and pay necessary attention to the clinical issues associated with management of SCA. An examiner noted:

> *"You can have one health care provider having a line of like 150 patients to see that day, so unless the symptoms you're talking about are in line with sickle cell, they may ask. But if their general symptoms with the large listed with a patient load, patient burden outside, waiting for the regular care, this may be something that is easy to miss because of the large number of patients, the large volumes of patients, except if you have the cardinal features of sickle cell. You're trained to ask for it, but truth, you may not ask for it because of the patient volumes."*

Healthcare infrastructure, eHealth and capacity building within systems

Documentation of diagnostic results and communication of this information was a consistently reported limitation, due in large part to lack of medical records, limited communication pathways between facilities and technology-based healthcare infrastructure. This represents a significant gap that cannot be addressed solely through the implementation of a TCD training and supervision program and is an example of the need for more broad capacity building within the healthcare system to support such a program. One of the super-examiners stated:

> *"At my facility, there used to be a newborn screening with the Ministry. But many of those children did not get their results. The actual screening for sickle cell happens when someone gets all those cardinal features of sickle cell then the health provider will recommend a hemoglobin electrophoresis to see if they have sickle cell. That's when people get to know that they [have SCA]. After presenting with the vaso-occlusive crisis, anemia, acute chest syndrome, all those symptoms, and then they examine, and then the health care provider will query sickle cell, and they test it, and then they may find that's what they have."*

Interview participants also discussed the role of healthcare provider knowledge after TCD results are confirmed, specifically in case of results which indicate a high risk for stroke. The importance of generalized knowledge about hydroxyurea within these settings is crucial, as it is a lower-cost, arguably safer alternative to transfusions which also does not burden the local blood supply in the way that transfusion use among SCA patients does. An examiner noted:

> *"So even if you can afford the TCD screen, not in a research study, if it's [elevated] results, then it's going to be even more expensive to protect the patient. In the first place, the person who's going to afford a TCD will have some money. So, this health worker can just decide how you can just do exchange transfusion. Even if they would have done simpler things like ensuring the patient has a maximum tolerable dose of hydroxyurea and a chronic transfusion. They might recommend, the exchange transfusion."*

These provider knowledge gaps represent a major opportunity for capacity building through educational efforts via North-South partnerships which can effect change by optimizing knowledge within the existing healthcare system instead of solely adding staff without adequate training.

Interview respondents consistently emphasized the vital role hydroxyurea plays in improving outcomes for children with SCA. While the TCD training program itself was found to be effective in identifying children at risk for stroke, the potential for broadening its use in sub-Saharan African settings brings to the forefront gaps in provider knowledge about treating SCA and more specifically about hydroxyurea as well as gaps within the healthcare system which render hydroxyurea inaccessible to the majority of affected children in sub-Saharan Africa. Social Determinants of Health, or the contexts in which individuals are born, grow and live, including the social, political, and economic structures which affect healthcare systems and access to care (World Health Organization, 2007), are an important lens through which these knowledge and access gaps can be understood.

There was consensus regarding the disease burden of SCA within the local settings for those who are diagnosed, as respondents discussed the high volumes of patients with SCA, many of whom do not live in close proximity to a national referral hospital and who must travel long distances for care, as well as those who live in urban centers in closer proximity to clinics but cannot afford care. Historical mistrust of the healthcare system, poverty and illiteracy are other barriers which interview respondents noted as impacting patients' ability to seek and access care for SCA. A stakeholder stated:

> *"There is a lot of poverty in the community. There are people who may not have resources. They don't have the funds or the finances to be able to access healthcare, even though the health facilities are available [in my setting]. There are also fairly high levels of illiteracy, and that illiteracy does perpetuate some cultural and social myths and beliefs surrounding healthcare. Even for those who have the funds, they may not actually seek health care in a health facility at the onset of an illness, because they may believe that it's due to other things. They seek alternative care before they come to hospital. Most of it is "this isn't an illness for the hospital. It's cared for elsewhere" whether it's in a church or prayer convoy, or a traditional healer, some other providers other than people who are within the hospital."*

The interviews further demonstrated that education is necessary among not only healthcare providers and communities but also among policymakers and ministries of health regarding the importance of hydroxyurea to prevent complications of SCA resulting from stroke as other clinical morbidities. The overall cost and burden on the healthcare system to manage complications of SCA can be mitigated through the comparatively low cost of hydroxyurea. A stakeholder noted:

> *"[SCA] is actually the one of the biggest burdens within the setting. Sickle cell and its complications is what fills the pediatric ward. About 70% of the of the ward is made up of the patients, children living with sickle cell with its related complications. If you remove them from the picture with education and proper screening and care, then our wards actually will be almost empty. But it's just getting the education out there of how to learn if you have it, how to [manage] it."*

Another, stakeholder noted:

> *"When you optimize the dose of hydroxyurea because of stroke, you also prevent other complications that you did not intentionally plan to prevent. For example, they will have less acute chest syndrome, less pain. Overall, the screening program can trigger other benefits which are not stroke related, also fewer strokes will happen. Patients will have more money to spend in other things as opposed to going for physical therapy, also lost wages, because it's [used] up to take care of these children."*

Pathways Forward: the STRETCH Model

A well-defined, optimized training and supervision program for TCD examiners is feasible within sub-Saharan African settings, and there are resource gaps as well as opportunities to mitigate them evident through the interviews performed. When asked what the path forward should be to prevent stroke and improve outcomes for children with SCA within their local settings, capacity building, stakeholder engagement and health policy were a consistent response. Several interview respondents noted stakeholder engagement as a critical factor for both expansion of a TCD screening program and for broader support of healthcare infrastructure improvements and accessibility of hydroxyurea to patients with SCA. All respondents emphasized the role of ministries of health to appropriately prioritize these issues within

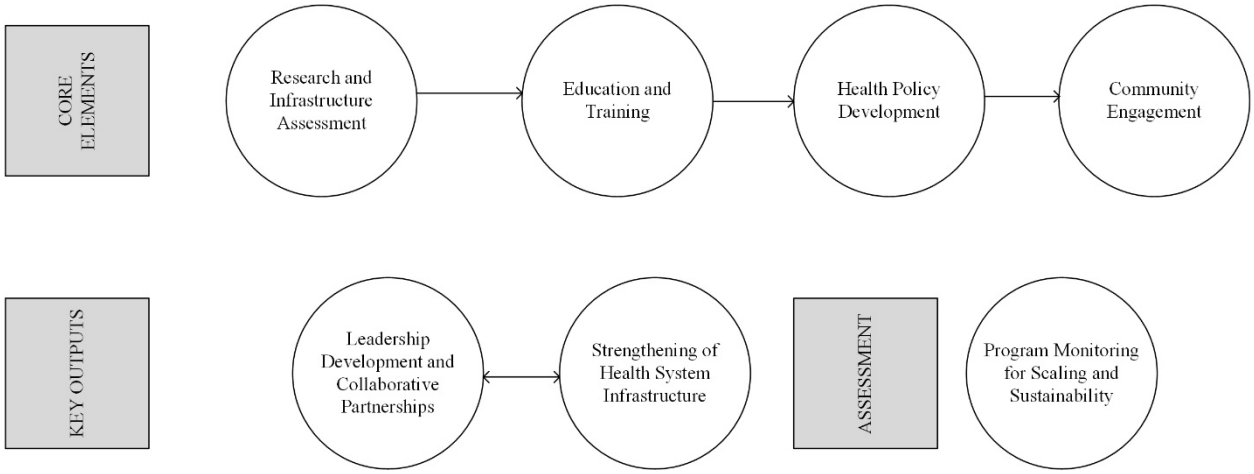
healthcare system and enact policy to allocate necessary resources to implement and sustain change.

The impact of North-South partnerships and the collaboration between the US-based CCHMC team and the sites in sub-Saharan Africa was also identified by interview participants as a key driver of capacity building not only related to the TCD technical skills and concepts but more broadly in the investment in the site teams' development of computer and organizational skills, clinical documentation, communication and problem-solving. A combination of these partnerships are crucial to developing skillsets and knowledge in resource-limited settings with policy and resource allocation and could facilitate significant change in outcomes for children with SCA living in sub-Saharan Africa. A stakeholder summarized this by noting:

> *I think this STRETCH program that you are developing is a plus, and the TCD trainings in Africa—if you pull it across I think it's a fantastic opportunity for capacity building. Especially for people who are going to start the clinics. Now that hydroxyurea is part of the essential drug lists, WHO essential drug lists, and more and more African countries are taking up sickle cell management seriously, more [children living longer], TCD appearing. But there needs to be more support for it, I think. The innovation in training with fantastic people, even our people, is important. So I'm happy that you also decided to put all of their experiences together and make a team, there are fantastic results from it. We should keep going and do more.*

A significant volume of interview responses and analysis of their content and themes was used to develop a STRETCH model which includes key findings from the analysis. While the primary aim of the research was to determine the most effective training and implementation methods for TCD screening to mitigate stroke risk in sub-Saharan Africa, analysis of the interviews suggests that a more comprehensive theme of capacity building inclusive of the primary aim as well as strengthening the healthcare workforce through education and informing health policy towards improving accessibility for hydroxyurea in children with SCA is more fully aligned with the frequency and depth of the themes.

Figure 4.1 STRETCH Model*



* Developed by author

The core elements of the model emphasize key areas of focus needed to build a foundation upon which change can be implemented in a sustainable way. Research and infrastructure assessment will include thorough observation of existing processes, infrastructure, and policy as well as currently available resources which can be leveraged in new and innovative ways. Education program development is a crucial next core element, which must have multi-directional targets including healthcare professionals, patients and families, community leaders and policymakers. These educational programs can be implemented through support of North-South collaborative partnerships to build capacity which can be further scaled over time to meet evolving needs as skills and knowledge bases become more advanced. Advocacy for health policy to include hydroxyurea at MTD along with facilitating importation of hydroxyurea at an affordable cost will be critical to the inclusion of hydroxyurea at MTD within SCA care guidelines, which will align with educational efforts to raise awareness within health systems and the community. Community engagement is the fourth core element of the model and will involve building stakeholder engagement and empowering community leaders to develop partnerships and build a shared agenda regarding the need to improve outcomes for children with SCA.

Communication of the impact of poor outcomes for SCA on individuals, families, communities, and the health system will be an important focus such that the effect of change can be observed and built upon over time.

Leadership development and collaborative partnerships is the first of two key outputs of the model and will be evidenced through building local capacity for effective leadership through formal and informal training as well as collaborative relationships with international partners will strengthen local leaders' ability to structure and lead healthcare providers within local settings. Integrating capacity building efforts within the existing healthcare systems and structures through incremental changes supported by key stakeholders and local leaders will facilitate sustainability of change which can be further scaled. The second output, strengthening of the health system infrastructure, involves investment in capacity for newborn screening, improving access to hydroxyurea through strengthening supply chain systems to support availability and investment in healthcare facilities and systems, including eHealth infrastructure and information sharing of medical record documentation between facilities to improve continuity of care.

Due to the complexities of healthcare infrastructure landscape and the significant morbidity and mortality associated with SCA in resource-limited settings, a multifaceted approach is needed for effective capacity building. Through a comprehensive analysis of results, the STRETCH model integrates dimensions of education, policy development, and access to hydroxyurea as a holistic, collaborative approach which leverages North-South partnerships and builds upon existing resources to implement change in public health settings in sub-Saharan Africa. By addressing education, policy, and access barriers simultaneously, public health leaders can work collaboratively towards building sustainable capacity that supports continued

improvement within healthcare systems, supports patients and families and improves outcomes for children with SCA in these settings.

CHAPTER 5 IMPLEMENTATION AND PLAN FOR CHANGE

Overview

In addition to the significant morbidity and mortality resulting from complications of SCA in affected children, these complications negatively impact individual and family quality of life, increase healthcare utilization and burden resource-limited healthcare systems. Public health leaders have an opportunity to improve outcomes for children with SCA in sub-Saharan Africa and build capacity within local healthcare systems. The development of well-structured TCD screening programs, increased accessibility to hydroxyurea and knowledge and technology transfer efforts to expand provider knowledge about SCA together represent the multiple dimensions for implementing and sustaining change in resource-limited settings. Utilizing key learnings from STRETCH TCD examiner, super-trainer and stakeholder interviews and themes from an analysis of relevant literature, a two-tiered implementation plan for change was developed.

The proposed plan incorporates North-South partnerships with consideration of local context to ensure its feasibility and sustainability within resource-limited settings. The first tier includes an implementation plan for the current structure of the TCD training and supervision program using the RE-AIM framework (Glasgow et al., 1999) followed by a broader implementation plan which utilizes the Collective Impact Model (Kania and Kramer, 2011) to describe the multi-faceted nature of improving care for children with SCA in sub-Saharan Africa through a combination of knowledge and technology transfer to support optimal TCD screening in conjunction with capacity building among the healthcare system from an educational perspective and pathways for improved accessibility of hydroxyurea through stakeholder engagement and health policy.

TCD Training and Supervision Program Structure and Scalability: Assessment Using the RE-AIM Framework

The RE-AIM framework was developed by Glasgow et al. (1999) to evaluate public health and community interventions through five dimensions, reach, efficacy, adoption, implementation, and maintenance, which occur at individual, clinic/organization, and community levels and interact to determine the public health-based impact of a program or policy. This framework is particularly useful in resource-limited settings where complex relationships exist between these dimensions which, if improperly defined or understood, can lead to wasted resources and constitute a threat to the sustainability and scalability of changes implemented. The model further helps to prioritize key outcomes in settings where limited resources are available and a scaled approach is needed to move tools and interventions from clinical research into broader clinical settings within healthcare systems (Glasgow and Estabrooks, 2018).

The RE-AIM framework encourages planning strategies that can reach the most people affected by health disparities, be widely adopted in diverse settings and by diverse staff with a range of expertise and be implemented and sustained at a reasonable cost (Glasgow and Estabrooks, 2018). In the first phase, the TCD training and supervision program was designed to directly serve research participants enrolled at partner sites. Over the course of a 7-year period, the program evolved and multiple strategies were implemented to facilitate improved knowledge transfer and examiner retention of information which directly translated to improved quality of TCDs the results of which were directly relevant to clinical decision-making. The program now represents a structured methodology with the opportunity for further capacity building on a larger scale within the interview site countries as well as additional settings within sub-Saharan Africa.

Table 5.1 TCD Training and Supervision Program: Assessment and Considerations for Scaling through RE-AIM Framework

Dimension	Description/Elements	Application to Current TCD Program	Plan for Change: Implications for scale-up in sub-Saharan Africa
Reach	Target population: who is intended to benefit, how they can be reached. Target participants may be identified at multiple levels. Who participates in and/or is exposed to the intervention?	TCD super-examiners and examiners at defined sites	Target populations must be defined in health settings to include multi-disciplinary healthcare providers and leaders within healthcare systems or organizations.
Effectiveness	Most important benefits to be achieved	TCD examiner fluency with equipment and process; establish foundation of knowledge about TCD; consistency in quality and accuracy of examinations; build collaborative teams who can help each other, which facilitates sustainability and problem-solving.	Well-defined training model which includes in-person training with super-examiner; metrics regarding expected time in training and practice examinations with feedback provided to enhance examiner skill development. Expand super-examiner group to 3-4 to increase capacity for in-person training; prepare training content for expansion within 2-3 existing partner countries.
	Likelihood of negative outcomes	Inconsistency was likely in the early phase of the program due to sub-optimally managed language differences, complex concepts trained too quickly and without necessary repetition; technological/equipment challenges at all sites.	Consideration of unintended consequences of the program is needed, including identifying children at risk for stroke without adequate access to hydroxyurea or transfusion, challenges associated with poor record-keeping at site and communication gaps between providers.
	Measured by change on key outcomes and consistency across groups	Examiner adherence to TCD protocols, quality of exams (adequate vs. inadequate); attendance rate at training and supervision sessions.	Scale up data management systems to track metrics in real-time for assessment of key outcomes. Documentation of training and supervision sessions will be key to demonstrate adherence over time. Eventually, the number of children screened and

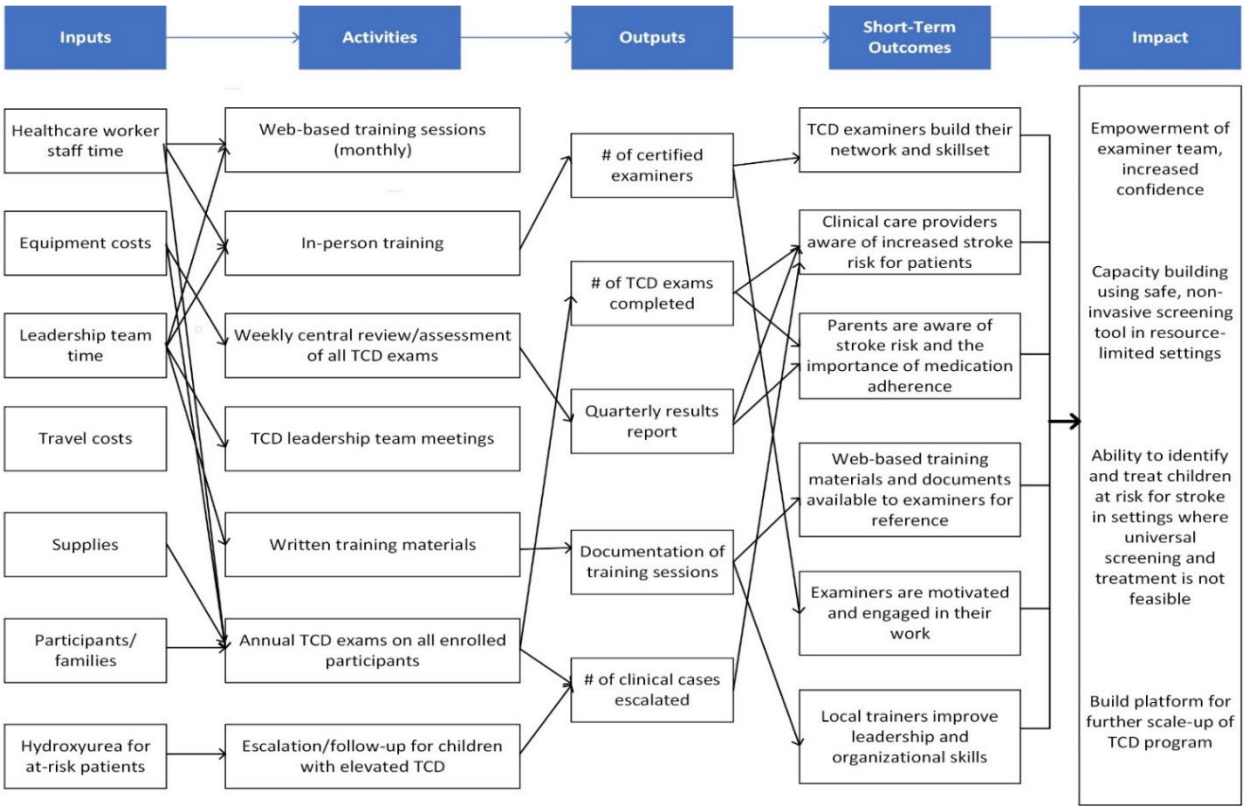
Dimension	Description/Elements	Application to Current TCD Program	Plan for Change: Implications for scale-up in sub-Saharan Africa
			identified to be at-risk and the subset who can access hydroxyurea will be a key longer-term programmatic metric.
Adoption	The absolute number, proportion, and representativeness of settings	Number of examiners and super-examiners trained and certified in initial group.	Phased approach to include scale-up over time as program builds momentum.
Implementation	Consistency in program delivery, adaptations done or planned, cost and results	Remote training in the early stages needed to be adapted due to inconsistent examiner performance; adaptations included addition of super-examiners to support in-person training efforts and to build capacity within sub-Saharan Africa, consistent feedback provided to examiners which was repeated multiple times and translated to aid in examiner understanding. Results at the time of the program review were exceptional in terms of exam consistency and examiner and super-examiner performance.	Training curriculum must be well-documented and structured, recordings of sessions may be monitored to assess fidelity to the program standards. Examiner support and additional super-examiner support will continue from US-based team, with ongoing assessment of opportunities to shift responsibilities to Africa-based teams for ongoing sustainability. Costs include staff and trainer time, equipment, and space needs within local clinics, as well as some provision for hydroxyurea in the event of an elevated result.
Maintenance	Longevity of effects and program sustainability	Initiative took one year for initial examiner certification, with improved consistency of performance as evidenced by high-quality exams after program updates were made over the course of the next two years.	Sustainability of program elements and target outputs will require stakeholder engagement and support at organizational and ministry of health levels; change management strategies will be needed to implement structured programming within healthcare settings with limited infrastructure. North-South partnerships can be leveraged in support of this objective and overall program strategy with development of local leaders as a core facet.

Using the RE-AIM framework and considering the feedback from TCD examiners and stakeholders, actions for implementing change specifically related to TCD examiner programming include increasing the super-examiner team to include additional expert trainers who can provide a wider reach for in-person training early in examiners' exposure to the equipment, technology, and subject matter. Site visits and additional in-person time following training is also a key aspects of ongoing program success and participant engagement. Remote communication via Zoom and WhatsApp cannot replace what can be learned when visiting a site, and this must be incorporated into program expansion planning and budget. This time spent in-person is crucial to establishing a solid foundation of knowledge and basic skills which can be supported through ongoing remote training. In-person time should be extended when translation is needed. This training model and its content can be replicated across settings with measurements of progress/fidelity to the program goals.

A secondary aim of STRETCH was to describe how public health leaders develop contextualized leadership skills within resource-limited settings providing clinical care to children with SCA. Public health leaders in this case include the TCD examiners, super-examiners, and stakeholders themselves as representative of the population of healthcare workers who are poised to benefit from programming such as this, in addition to public health policy leaders within these settings. Investment in their knowledge through engaging them in the development and maintenance of program standard operating procedures and training materials, organization and facilitation of group meetings, optimizing communication to build collaborative teams and support problem-solving, developing their clinical and programmatic writing skills and facilitating development of

IT-based skills will support the successful adoption and maintenance of the program through fostering buy-in at participant levels and help to ensure appropriateness within the local context for future scale-up.

*Figure 5.1 Logic Model for TCD Training and Supervision Programming**



* Developed by author

Collective Impact Model: Improving healthcare provider knowledge and accessibility to hydroxyurea

Research on SCA disease burden as well as safe and effective disease-modifying treatment options within sub-Saharan Africa suggests that with the appropriate public health policy and infrastructure within local contexts, the outcomes children with SCA in these settings have the potential to improve substantially. A combined effort to build capacity within the healthcare system through education supported by North-South

partnerships and health policy to support access to hydroxyurea for affected children is an ambitious yet reasonable and necessary solution. The Collective Impact Model (Kania and Kramer, 2011) is a powerful framework for addressing complex issues within healthcare systems which involve multiple stakeholders and are affected by social, political and economic factors. The framework, which is relevant to public health leadership and change management in its emphasis on multiple players and behavior change in order to solve a complex public health problem, is a lens through which the problem can be understood and mitigated within resource-limited settings in sub-Saharan Africa.

The first step in the Collective Impact Model is to understand the problem, which in this case involves an understanding of the disease burden, morbidity and mortality of SCA as well as social, cultural and economic barriers to care as well as gaps in the healthcare system infrastructure where children seek care. Formation of a common agenda is a crucial step during which stakeholders from multiple disciplines and areas come together to prioritize key objectives that they collectively see as important steps towards improving care which are feasible within the local context. Establishing shared measurement systems allow for consistent metrics to measure progress towards established goals. Early successes are an important aspect of sustaining change, and the framework emphasizes building mutually reinforcing activities as a key step, which in this case would involve building awareness about SCA, utilizing North-South partnerships to implement educational opportunities for healthcare providers and improving diagnostic and clinical screening, such as TCD.

Continuous communication channels must be established to facilitate information sharing and collaboration among involved parties and to coordinate among stakeholders. Multiple forums can be used, including web-based forums, regular meetings, structured and unstructured communication, and in-person meetings and conferences whenever logistically possible to reinforce collaboration and build relationships, which are needed to sustain change. Kania and Kramer note that implementation of "support backbone infrastructure" is needed, which involves a neutral party or parties who facilitate and coordinate efforts and help to continually align activities of stakeholders towards a common agenda. While a US-based coordinating group will be useful in this area, ultimately expertise and support infrastructure must exist within the local contexts in order for true capacity to be built.

Mobilization of resources from a financial and resource perspective will involve a combination of government funding, philanthropic grants and in-kind investment from partners. Support from ministries of health to allocate healthcare provider time for the purpose of education will be needed, given the significant patient volumes which interview respondents described and the difficulties healthcare workers experience with prioritizing their time for activities beyond patient care. Significant progress could be made through financial support from pharmaceutical companies who manufacture hydroxyurea if importation costs can be minimized and/or manufacturing is shifted to occur on the African continent, a true measure of capacity building in the long-term.

Continuous monitoring must occur in order to evaluate the progress of collective impact activities, with openness for adaptation and learning with transparent discussion regarding obstacles and/or failures that will occur. Strategies may need to be adjusted in

response to these assessments to achieve better outcomes. In addition to working towards the specific health policy, hydroxyurea accessibility and educational objectives of this initiative, the activities involved will help to foster continued growth within the healthcare system and create an environment which is open to change and sustainability of those changes over time.

Health Policy Recommendations

Green et al. (2016) in an assessment of system-based limitations to outcomes for SCA in Uganda note that post-screening, system limitations include lack of facilities, inadequate training of healthcare providers, lack of ongoing clinical and diagnostic analysis, lack of medications, and counseling as areas identified by healthcare providers. The interplay among resources, education of healthcare providers, and the ability of families to access hydroxyurea necessitates policy action to leverage change within the local context. There are direct, actionable steps that are possible in this context with the right policy-driven support.

Key policy decisions that need to be made involve the following:

1. Increase accessibility of hydroxyurea for SCA within local health systems with appropriate dosing to improve clinical outcomes through pharmaceutical cost-sharing for increased uptake.
2. Improve healthcare infrastructure to allow for transfer of information from diagnosis to local caregiver settings.
3. Educate and build capacity within the local healthcare system as it pertains to SCA diagnosis and treatment; supported by North-South partnerships using a structured, hybrid web-based and in-person format which can be replicated.

Summary and Policy Impact

The potential impact of policy-driven change to decrease cost and increase accessibility for hydroxyurea as a disease-modifying therapy for SCA in sub-Saharan Africa is significant. By leveraging existing infrastructure and critically assessing and implementing operational changes that are both logistical and feasible, the likelihood of successful implementation and long-term sustainability is higher. Leveraging findings from STRETCH interviews which define the most effective training and program methods as well as key capacity gaps within local contexts, the RE-AIM and Collective Impact models support a structured framework to plan for change in a manner which includes understanding of social, economic and political factors that are relevant in local settings and emphasizes continuous assessment, adaptation and communication as core elements to build capacity and sustain change in the long-term.

CHAPTER 6 DISCUSSION

STRETCH generated a significant amount of research data which describe how public health leaders can mitigate stroke risk among children with SCA in sub-Saharan Africa using an effective, sustainable and feasible Transcranial Doppler screening, training and supervision program. Over 740 individual responses from more than 20 hours of interviews were coded for thematic analysis. Interview participants included TCD examiners trained through the CCHMC Hematology International TCD program between 2015 and 2023, super-examiners who received additional training and supervision to centrally review TCD exams and provide oversight, and stakeholders providing clinical care to patients at the TCD sites.

Participants were from Angola, Democratic Republic of Congo, Ghana, Kenya, Tanzania, and Uganda who provided insights into the most effective programmatic and training tools which would facilitate expansion of TCD in sub-Saharan Africa. They further shared insights into the disease burden of SCA within their settings from a clinical, socioeconomic, and public health perspective, noting major areas of children's lives which are negatively affected by SCA and by stroke. Further data were provided regarding the role of knowledge and technology transfer through North-South partnerships using the current program as an example, emphasizing the need for investment in education about SCA and treatment with hydroxyurea among clinical care providers and health facility staff. The role of hydroxyurea was emphasized by interview participants, with consensus around the importance of improving accessibility of the treatment to children at a young age in order to prevent stroke, acute chest syndrome, complications of malaria and other infections and other effects of SCA which can be fatal

and/or result in significant morbidity and mortality which negatively impact life expectancy, quality of life and result in burden on resource-limited health systems.

Interpretation of Results

Training and Supervision Methodology

The primary aim of the research was to describe the most effective training and supervision methods to facilitate the execution of high-quality, clinically-relevant TCD exams in sub-Saharan Africa. Examiner feedback related to training methods indicated the importance of in-person training, particularly early on in the process, and the benefits of periodic site visits or in-person meetings, when possible, to facilitate ongoing collaboration and relationships among the examiner team. Examiners who were first trained remotely through web conference felt that they did not retain the key conceptual information as well as they did when provided with in-person training several months later. The majority of examiners were first trained in-person, and felt that while these interactions were productive, longer training sessions would have been preferable, particularly when translation was needed. Challenges identified included technological difficulties with the first set of Sonara/tek non-imaging equipment, linguistic differences which limited examiners' ability to understand content and terminology, and presentation methods which often included US-based examiners and program leads speaking too quickly and covering content too rapidly without adequate repetition.

There was a consensus among interview respondents that the introduction of trained super-examiners living in sub-Saharan Africa was a positive change in the program in that it allowed for improved communication due to cultural and linguistic similarities, strengthened the program by building more capacity for examination

reviews, feedback and supervision sessions, and leadership skills within the examiner team. The two super-examiners have become mentors to the group, the majority of whom are nurses or non-radiology medical techs, who all seek to emulate their professional growth and leadership development. Other positive aspects of the training and supervision program in its current state include frequent communications between the examiner group through monthly supervision conferences and troubleshooting discussions which occur in real-time with the super-examiners and US-based program lead using a group chat. The implementation of new TCD equipment in 2022 was relatively seamless, examiners and stakeholders felt, strengthened by a strong foundation of collaboration in the group, comfort-level with the content and examiners' ability to problem-solve through technical difficulties. All examiners and stakeholders felt that the program has had a positive effect on them as individuals and as a team, and that it is an important step toward building capacity in sub-Saharan Africa.

The need for expansion of TCD beyond the clinical research context was emphasized by all interview respondents, who spoke of being proud to represent such a uniquely skilled group, but who see major gaps in healthcare systems' ability to screen for stroke in this young population who is at risk for devastating complications or death. In consideration of the need to broaden TCD's reach within resource-limited settings, the TCD training and supervision program was analyzed using interview responses and the RE-AIM model (Glasgow et al., 1999). Through the framework dimensions of Reach, Effectiveness, Adoption, Implementation and Maintenance, early program successes along with crucial adaptations were described along with considerations for scale-up within sub-Saharan Africa.

The experiences of examiners during training and insights from stakeholders demonstrate that a well-designed, structured format for TCD exam performance and review and a system which documents results for follow up facilitates clinicians' ability to utilize results in a manner that supports improved care. The program structure and methods constitute a model which could perform favorably when scaled within sub-Saharan Africa for use with TCD and more broadly within the public health context to fill education and resource gaps. The evolution of the TCD training and supervision program further represents an example of the role of technology and knowledge transfer as a key driver of stroke screening and prevention in this population of at-risk children.

Over an eight-year period, examiners from CCHMC research partner sites in six sub-Saharan African countries (Angola, Democratic Republic of Congo, Ghana, Kenya, Tanzania and Uganda) received technical training in the execution and assessment of TCD exams along with training in research best practices, documentation and team development and dynamics. With an emphasis on communication and problem-solving, the team learned to creatively manage challenges as they arose, developed strong collaborations, and grew to be a cohesive group which represents a uniquely skilled team within sub-Saharan Africa that can be modeled after and/or scaled with appropriate consideration of local context.

SCA and Stroke: Burden and A Call for Change

Interview respondents spoke at length about the significant burden of SCA in their local settings, including limitations in screening which often result in delays in diagnosis until symptoms are apparent, the number of patients who need care as compared to the limited staffing capacity within healthcare systems, and the devastating consequences

that complications of SCA have, particularly stroke, on a child and their family. Examples were provided which spoke to the major social and economic impact that families experience after a child experiences a stroke, including lost wages, time away from work to provide ongoing care, and specialty therapy needs. Respondents noted that children with stroke who survive experience life-long cognitive and neurological effects which inhibit their ability to continue in school and significantly diminish their quality of life. A common statement at the end of each description was that examiners and stakeholders are aware that disease-modifying therapy in the form of hydroxyurea at MTD could play a major role in preventing these devastating complications, and a call to action was clear.

Pathways for Treatment with Hydroxyurea

A secondary aim of STRETCH was to describe how TCD screening for stroke risk in SCA within pediatric settings fits into the larger broader context of providing safe, effective care using hydroxyurea. There was a consensus among interview respondents that patient and families' access to hydroxyurea remains limited due to availability and cost, and that there is an ethical dilemma which exists when identifying a child to be at risk for stroke without the appropriate access to disease-modifying therapy. While transfusions are possible, and according to interview participants, they are a more widely understood treatment option in some settings, blood scarcity issues, safety of the blood supply and cost render transfusions a less attractive intervention than hydroxyurea which is comparatively lower in cost, simpler to administer and can prevent severe morbidity and mortality when dosed at MTD.

Healthcare workers' knowledge about SCA in general and how to use hydroxyurea to treat SCA were also noted as healthcare system-related limitations by interview respondents. Several respondents noted that outside of more advanced or referral hospital settings, clinicians' abilities to effectively treat children with SCA are limited. A combination of health policy-driven increased accessibility to hydroxyurea with education for healthcare workers facilitated by North-South partnerships would fill several critical gaps and have the potential to improve outcomes for children with SCA living in sub-Saharan Africa.

Research Implications

There are several important implications from TCD has been shown to be a safe, non-invasive, cost-effective screening tool that can be used to identify children with SCA at risk for stroke. TCD has demonstrated feasibility and useability for resource-limited settings where the transfusion therapy and hydroxyurea are not available to the entire population affected, therefore necessitating a screening tool to identify and prioritize those at greatest risk of stroke. TCD is of further value in settings where children are treated with hydroxyurea as it permits identification of those in need of dose optimization for optimal neurological protection. STRETCH describes the evolution of what is now a highly trained team of examiners who are supervised closely in order to maintain this technical skill is crucial to TCD being effectively implemented and clinically impactful in these settings.

The CCHMC Hematology International TCD program and its multi-level focus on education, use of informatics tools for tracking and scoring of exams and its ability to inform clinical follow-up at the local level is uniquely poised to effect change within

healthcare systems in sub-Saharan Africa, and therefore improving the lives of children with SCA. This qualitative study constitutes a crucial step in documenting the various program components, equipment and technology transfer, training interventions and communication strategies utilized over the past eight years. The STRETCH study results can inform the next phase of the program which will be directly targeted towards optimizing TCD screening and moving towards broader implementation of hydroxyurea for at-risk children with SCA in sub-Saharan Africa.

A full analysis of coded responses beyond TCD training methodology was performed using the Collective Impact Model (Kania and Kramer, 2011). This framework is suited to resource-limited settings and capable of addressing complex issues within healthcare systems which involve multiple stakeholders and are affected by social, political, and economic factors. Three main policy decisions are recommended as a result of this analysis: 1) Increased accessibility of hydroxyurea for SCA within local health systems with appropriate dosing to improve clinical outcomes through pharmaceutical cost-sharing for increased uptake; 2) Improvement in healthcare infrastructure to allow for transfer of information from diagnosis to local caregiver settings; and 3) Education and capacity-building within the local healthcare system as it pertains to SCA diagnosis and treatment; supported by North-South partnerships using a structured, hybrid web-based and in-person format which can be replicated and built upon over time.

Study Strengths

The qualitative design of this study, which included an integrative literature review and data collection through semi-structured interviews with individuals who can

provide specific, contextual insights into TCD training and supervision methods as well as systemic, operational, workforce, and educational factors within their local settings, allowed for a robust thematic analysis which included a rich set of codes that fill the existing knowledge gaps and inform future directions for international research collaborations. Interview participants were highly engaged and willing to provide extensive details about their experience with the TCD training and supervision program as well as the complexities of caring for children with SCA and the challenges they experience within their local settings. The study design is a robust methodology to achieve research aims and provided valuable insights which can inform future capacity building efforts and health policy and healthcare infrastructure improvements in resource-limited settings.

The semi-structured interview format provided consistent information which could be compared across disciplines and countries during thematic analysis which strengthened trend analysis while allowing for adequate flexibility to support probing for further relevant information when appropriate. Trained research team members with no prior direct exposure to the CCHMC International TCD training program or the examiners performed the interviews, allowing for minimal bias or preconceived notions about the strengths or weaknesses of the program and in an effort to avoid any social or generalizability bias associated with prior relationships or perceived power differentials between the interviewers and participants. Four trained research team members completed the open coding process, followed by two team members who performed the axial and selective coding, which allowed for a robust analysis with systemic quality control and validation for consistency.

Study Limitations

There are several limitations of the research worth noting. Firstly, logistical and availability limitations prevented all examiners from being interviewed. Two were on leave at the time of the project and one was unavailable due to scheduling constraints. While the majority (11/14) of the eligible interview respondents provided a substantial volume of information, given the small sample size, these gaps in data collection must be acknowledged as potential sampling bias which constitutes a threat to generalizability of the results. The data analysis plan included multiple coders and the use of open, axial and selective coding with independent coders, however there is a subjective nature to qualitative analysis which can affect the validity of the results.

Contribution to the Field

Through detailed literature review which identified key themes and sub-themes, semi-structured interviews performed with TCD examiners, super-examiners and stakeholders, and an analysis of capacity building and health policy opportunities using the RE-AIM and Collective Impact frameworks, STRETCH documents that poor clinical outcomes, including stroke, indicate capacity gaps for SCA screening, diagnosis, and treatment in resource-limited settings in sub-Saharan Africa. Literature to date has focused on clinical interventions and outcomes, and more work is needed in the area of capacity building to bring evidence-based screening tools such as TCD and interventions such as hydroxyurea to broader populations of affected children while strengthening the healthcare infrastructure.

These interventions can be implemented more effectively within resource-limited settings if analyzed with consideration of the local context to identify the most effective

training and programmatic strategies that will be sustainable over time. The STRETCH model synthesizes education, policy development, and access to hydroxyurea into a holistic, collaborative approach which leverages North-South partnerships and builds upon existing resources to implement change in public health settings in sub-Saharan Africa. Incorporating local context and leveraging strengths of existing resources within the model provides a strengths-based methodology for incremental change which builds upon early success and provides a foundation for strategic problem-solving and continuous improvement through capacity building.

Future Directions

STRETCH underscores the importance of North-South partnerships and the impact of education and technology transfer to build capacity in resource-limited settings. The value of collaboration through time spent in-person at local sites is crucial to establishing robust relationships which will facilitate development of common agendas and communication in the long-term. These relationships can be leveraged to utilize the strengths of experts in well-resourced settings while building capacity for leadership locally. Educational programming which utilizes the methods identified by interview respondents as effective while leveraging technology to support real-time communication between international partners can provide a robust foundation to build the knowledge base of healthcare providers about improved care for children with SCA and how hydroxyurea can be used to mitigate the risk of stroke and other complications of TCD.

Future research projects should further investigate these training and program methods when scaled beyond the stages described in this project. Specific focus should be placed on strategies for engaging stakeholders to drive policy change, which was a

theme emphasized by the interview respondents when asked about the most important steps needed to increase accessibility to hydroxyurea. More than one respondent spoke of knowledge as equally if not more important than additional staffing resources, representing a major opportunity for North-South partnerships to collaborate to effect long-term, sustainable change in these settings.

Conclusions

Children with SCA in sub-Saharan Africa represent an overlooked population with a life expectancy significantly less than those in the United States and Europe. In addition to the devastating morbidity and mortality associated with the disease, its effects are far-reaching, with broad social, economic and health system impact. TCD has been shown to be a safe and effective method to screen children with SCA for stroke risk, and with proper training and supervision is feasible, sustainable, and clinically useful in resource-limited settings. Interview respondents indicated consensus regarding major capacity gaps which exist within their healthcare systems, including education needs among healthcare workers and health policy to improve access to hydroxyurea. Told from the perspectives of a uniquely trained group and their respective stakeholders in six sub-Saharan African countries, STRETCH provides a unique and valuable lens through which researchers, public health leaders and policy makers can plan for the crucial actions needed to improve care, mitigate stroke risk, and improve outcomes for children with SCA in sub-Saharan Africa in a feasible and sustainable way.

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APPENDICES

APPENDIX A: TCD Examiner/Super-Examiner Interview Guide

Role of interview participant: *(i.e. nurse, medical officer, radiologist)* _____

1. What is your level of training in healthcare?

2. Please describe the TCD training that you have received to date.

3. When did this training occur?

4. How much experience do you have with TCD exams in total?

Overview of Healthcare Facility/Site:

5. What type of setting(s) do you work in? (*i.e Hospital, clinic, etc*)

6. How would you describe your healthcare setting?

7. Please describe the community that you live and work in.

8. How many patients at your facility have SCA? _____

9. How many people in your community are affected (diagnosed) by SCA? _____

10. What is the approximate percentage of patients in your clinic with SCA?

Transcranial Doppler (TCD) Training

11. How much did you know about TCD before you began training? Please describe your knowledge prior to starting training.

12. Please describe the TCD training that you received as a new trainee:
    Format:
    Content:
    Frequency:

13. Please describe the ongoing TCD supervision and training:

    Format:
    Content:
    Frequency:

14. How challenging did you find TCD training?

15. What did you find challenging specifically?

16. Please describe the practice that you performed prior to certification:

17. What were the most effective training methods used?
    - ☐ Power point presentations from US-based trainers
    - ☐ Power point presentations from Africa-based trainers

- ☐ Open-forum discussion meetings (in person)
- ☐ Open-forum discussion meetings (Zoom)
- ☐ In-person practice sessions with patients (children with SCA)
- ☐ In-person practice sessions with demo patients (non-SCA)
- ☐ Remote/Zoom or facetime practice sessions with patients (children with SCA)

18. Why? Please share your comments about effective methods.

19. What were the most ineffective training methods used? (select all that apply)
    - ☐ Power point presentations from US-based trainers
    - ☐ Power point presentations from US-based trainers
    - ☐ Open-forum discussion meetings (in person)
    - ☐ Open-forum discussion meetings (Zoom)
    - ☐ In-person practice sessions with patients (children with SCA)
    - ☐ In-person practice sessions with demo patients (non-SCA)
    - ☐ Remote/Zoom or facetime practice sessions with patients (children with SCA)

20. Why? Please share your comments about ineffective methods.

21. Do you find performing TCD exams challenging?

22. If so, what do you find most challenging about performing TCD exams?

23. What do you find to be easy about performing TCD exams?

24. How would you describe your comfort-level with performing TCDs independently?

25. Do you ever consult a colleague when performing TCDs? Under which circumstances do you do this, and is it helpful?

26. What areas would you like to improve in your TCD skills, if any?

27. If you could change three things about the TCD training process, what would they be? (Training, supervision, scoring, notifications, results, etc)

28. If you could change three things about the ongoing supervision for certified examiners, what would they be?

TCD in Practice

29. Who communicates TCD results to your patients and their families? Please describe the interactions in your clinic.

30. Do you think TCD screening has an impact on your patient population? If yes, please describe. If no, please describe why not.

31. What are the barriers to more patients being screened with TCD in your local setting?

32. If a patient is identified as being at increased risk for stroke in your setting, what clinical actions occur?

33. Has being a certified TCD examiner expanded your capacity as a local provider? If so, how?

34. What goals do you have for yourself as a TCD examiner in the next 2 years?

35. What goals do you have for the TCD examiner program in the next 2 years?

36. Is there anything else you would like to share about your experiences in TCD training and as an examiner? About the local population and your role?

Optional Questions

Sickle Knowledge Questions: (T/F)

1. Sickle cell disease only affects Africans	**True/False**
2. Sickle cell disease affects the red blood cells	**True/False**
3. Providers should be notified when the child has a temperature of 101 degrees	**True/False**
4. Children with SCA are not affected by hot or cold temperatures.	**True/False**
5. Ice can be used if the child injures themselves.	**True/False**
6. Sickle cell disease can cause pain anywhere in the body.	**True/False**
7. Children with SCA are at a higher risk of stroke than other people	**True/False**

How are patients screened for SCA in your setting?

Does your facility perform screening as part of a new patient examination?

- ☐ Blood screening for sickle cell trait/SCA
- ☐ Asking about medical history/symptoms on a medical history form
- ☐ Asking about family history for sickle cell trait

How much does a screening test cost per patient?

How is the testing funded?

Do you know approximately how many new patients are tested each year for sickle cell disease? If so, how many?

Of those that are tested, please estimate the number and percentage of new patients diagnosed by age:

0-1 year_____
2-3 years_____
3-5 years_____
6-10 years_____
10+ years _____

Do you feel sufficiently educated about SCD?

Do you feel sufficiently educated about SCD screening and diagnosis?

What other trainings do you feel would benefit you? Is there anything else you would like to share?

APPENDIX B: Stakeholder Interview Guide

Role of interview participant: *(i.e. nurse, medical officer, radiologist)* _____

1. Please describe your role at your local clinic/setting.

2. What is your level of training in healthcare?

3. Please describe the TCD training that you have received to date, if any.

4. When did this training occur?

5. How much experience do you have with TCD exams in total?

Overview of Healthcare Facility/Site:

6. What type of setting(s) do you work in? (*i.e Hospital, clinic, etc*)

7. How would you describe your healthcare setting?

8. Please describe the community that you live and work in.

9. How many patients at your facility have SCA? _____

10. How many people in your community are affected by SCA? _____

11. What is the approximate percentage of patients in your clinic with SCA?

Local Context

12. What screening techniques or protocols are in place in your setting for patients with SCA at risk for stroke?

13. What is the financial and logistical burden of these current screening techniques on the healthcare system and families?

14. What are the consequences of strokes in pediatric sickle cell disease patients in terms of health outcomes that you have observed in your practice?

15. What are the consequences of strokes in pediatric sickle cell disease patients in terms of financial and related costs that you have observed in your practice?

TCD Screening

16. What is the impact of TCD screening in your setting currently?

17. What role would expanding TCD screening play in your current patient population?

18. What is your overall impression of the TCD training and supervision program?

19. What areas would you like your site's TCD examiners to improve in their TCD skills, if any?

20. If you could change three things about the TCD training process, what would they be?

21. If you could change three things about the ongoing supervision for certified examiners, what would they be?

22. Who communicates TCD results to your patients and their families? Please describe the interactions in your clinic.

23. What are the ethical considerations and cultural factors that should be considered when implementing a TCD screening program?

24. Who are the key stakeholders and partners that can be involved in the implementation of a TCD screening program? Please describe in as much detail as you would like.

25. What are the potential long-term health-related benefits of implementing an effective screening program for pediatric patients with sickle cell disease at risk for stroke?

26. What are the potential long-term financial and socieconomic benefits of implementing an effective screening program for pediatric patients with sickle cell disease at risk for stroke?

27. Consider both health-related outcomes and economic benefits.

28. What are the potential challenges or barriers to implementing a screening program in your setting, and how can we address them?

29. How should the data and outcomes of the screening program be monitored and evaluated?

30. What are the potential risks associated with not implementing an effective screening program for this population?

31. Is there anything else you would like to share about your experiences with TCD exams and their use? About the local population and your role? About capacity building and technology transfer in general?

Optional Questions

Sickle Knowledge Questions: (T/F)

1. Sickle cell disease only affects Africans	**True/False**
2. Sickle cell disease affects the red blood cells	**True/False**
3. Providers should be notified when the child has a temperature of 101 degrees	**True/False**
4. Children with SCA are not affected by hot or cold temperatures.	**True/False**
5. Ice can be used if the child injures themselves.	**True/False**
6. Sickle cell disease can cause pain anywhere in the body.	**True/False**
7. Children with SCA are at a higher risk of stroke than other people	**True/False**

How are patients screened for SCA in your setting? _____

Does your facility perform screening as part of a new patient examination?

- ☐ Blood screening for sickle cell trait/SCA
- ☐ Asking about medical history/symptoms on a medical history form
- ☐ Asking about family history for sickle cell trait

How much does a screening test cost per patient?

_____

How is the testing funded?

_____

Do you know approximately how many new patients are tested each year for sickle cell disease?
If so, how many?

Of those that are tested, please estimate the number and percentage of new patients diagnosed by age:

0-1 year_____
2-3 years_____
3-5 years_____
6-10 years_____
10+ years _____

Do you feel sufficiently educated about SCD?

Do you feel sufficiently educated about SCD screening and diagnosis?

What other trainings would benefit you and/or your team?

APPENDIX C: STRETCH Code Book

Theme	Definition/Application of Codes	Code ID	Codes
1. SCA burden and clinical features	Apply these codes when the respondent discusses the clinical features of SCA (with the exception of stroke), the ways in which it is diagnosed within their settings, and the treatments that patients need and/or receive.	1.1	Background: Diagnosis, newborn screening
		1.2	The burden of sickle cell anemia on the community
		1.3	The burden of sickle cell anemia on the healthcare system
		1.4	Treatment options in the US vs. sub-Saharan Africa
		1.5	Access to basic treatment/preventative measures
		1.6	Access to therapies
2. Stroke in SCA	These codes will be applied when respondents specifically discuss issues related to stroke, including clinical morbidity and mortality, effect on family and community and stroke prevention, with the exception of TCD methods	2.1	Stroke in SCA: epidemiology, morbidity and mortality
		2.2	Impact of stroke: family, community, healthcare system
3. Transcranial Doppler Screening: methods, use, training	Apply these codes when respondents describe their knowledge of TCD before training, experiences during training, application of training to their practice and barriers/facilitators to all of the above.	3.1	Overview: background, use, interpretation

Theme	Definition/Application of Codes	Code ID	Codes
		3.2	Training program/Training methodology for TCD: US and in resource-limited settings
		3.3	Context for scale-up based on effective vs. ineffective training methods and program structure
		3.4	The need for TCD in sub-Saharan Africa
		3.5	Challenges of TCD
		3.6	Desire to expand TCD use
		3.7	TCD Training frustrations
4. Healthcare infrastructure, workforce knowledge and technology transfer in resource-limited settings	Apply these codes when respondents describe factors which affect the ability to provide quality screening and care to children with SCA due to resource limitations, organizational or infrastructure gaps, and/or limitations in access to knowledge and technology.	4.1	Volume of patients vs. healthcare capacity
		4.2	Hospital resources - Capacity and resource gaps in sub-Saharan Africa
		4.3	Staffing limitations - Capacity and resource gaps in sub-Saharan Africa
		4.4	Healthcare infrastructure, eHealth, need for operationalizing/building capacity within systems using evidence-based research
		4.5	Barriers to TCD expansion

Theme	Definition/Application of Codes	Code ID	Codes
		4.6	Healthcare resource limitations
		4.7	Training/background of healthcare workers
5. Social determinants of health	These codes will be applied when respondents discuss topics such as healthcare access and quality, social and community context, economic stability and/or built environment. Health literacy issues can be included within these codes as well.	5.1	Capacity and resource gaps in sub-Saharan Africa: the cost of SCA care
		5.2	Capacity and resource gaps in sub-Saharan Africa: patients travel for care
		5.3	Health literacy
		5.4	Costs of screening vs. treatment – economic reasons for screening; influence on policy makers
		5.5	Lack of education
		5.6	Cultural considerations
		5.7	Local context
6. Public health leadership change management, leadership change models and implementation	Apply these codes when respondents discuss barriers and facilitators to organizational and infrastructure change, areas where capacity gaps can be addressed through health policy change, and other leadership or organizationally driven factors which could be addressed through the implementation of policy or programming.	6.1	Stakeholder engagement
		6.2	Organizational structure/change management

Theme	Definition/Application of Codes	Code ID	Codes
		6.3	Workforce gaps and development opportunities
		6.4	Policy opportunities
		6.5	North-South partnerships

APPENDIX D TCD Examiner and Stakeholder Representative Quotes

Table D.1 Experiences with Training Methodology and Program Elements

Participant Type	Program Element	Quote
Super-examiner	Monthly calls, supervision	*About the calls, there are common topics. Usually from the trainers, we give them feedback on how they are doing and if we are noting something that is that they need to improve. For example, you could find a site that is not really following the measuring the head diameter well and getting the bifurcations. Then they are getting the vessels at the wrong depth, you can emphasize that, and say they really need to follow this to the dot. Then, in case there's a low-quality exam, you'd ask what's the problem. Did they have difficult windows? And then the examiners are supposed to give an account of why. Because when you're doing TCD, you go through a window sometimes it's hard to get a window and you can't get the vessel waveforms very well. So, as the examiners, they must state why an exam didn't come out very well. Then we, as trainers, give feedback, depending on what we have seen from the TCD exams they have uploaded into the system. Then the examiners will tell us what is happening on their sides. We usually follow up on the hardware/software issues. If anyone is having any problems with their participants or with a TCD machine. They give us what they are going through, and then we share insights and share tips. It's more of like reporting what is going on and sharing information.*
Examiner	Monthly calls, supervision	*We have our monthly calls where the calls special for examiners, where I was also joined in those meetings. There are other examiners from other sites in other countries. We were having monthly calls for all the examiners and through that call we received training from [the US-based trainer]. I think she's from Cincinnati and also later from [Africa-based trainer]. They continue training us, telling us what to do to improve and to make our exams very perfect. Through our monthly course we receive PowerPoint trainings, and other more directions about the and they have helped us to reach to where we are.*
Examiner	Monthly calls, communication	*Usually, the examiners get a chance to see what their problems are. Then either the trainers or fellow examiners give a solution. It's two-way, yes, it's open, the trainer says things, and the examiner also says things. And maybe for an examiner that is not bold enough to say what their problem is, but they are usually given a chance to express their problems. And then on the call, we can brainstorm together.*
Examiner	Ongoing feedback	*After the training we were doing virtual, and we had several challenges. Yes, we have some patients who windows were difficult to come by, and then they were like 2 among 120 patients. And then also that that challenge was, some children not being cooperative. Moving their legs, moving their body up and down. I didn't have so much of a challenge and after every exam we uploaded on REDCap*

Participant Type	Program Element	Quote
		and [the super-examiners] go to it and give their feedback; usually now it is that we are doing a good job optimizing well and we should keep it up.
Examiner	In-person training	*I can say we had on-site training. [The trainer] was on the ground. She came to train us physically. And the other proceedings, virtual ones, through the meetings. But she was on the ground for the first time and then we talk on Zoom.*
Examiner	Effective training methods	*I think this one from African based trainers, I think it worked well. Open forum discussion meetings, zoom. In person practice session with sickle cell disease patients. In person practice sessions with the demo, I think all of those were most effective.*
Super-examiner	Ineffective training methods	*But the only thing that I found challenging of these on this list is if you're training the skill for the first time and someone is on Zoom. That is very, very hard; trying to train and learn practical skills online. It is very hard because if it's physical training, for example you're not positioning the hand in a particular way, the trainer can just come and support your hand into where it's supposed to be and it's done. But online, someone is saying "No, I'm trying to say, please, I'm going downwards, upwards, straight" The time you use to explain something 6 times, the one who is there physically 'could just touch the hand and put it where it's supposed to be. But one week or 2 weeks of the physical training, then the online forums are very effective because you can continue polishing. But without being grounded in the actual skill within the first one or 2 weeks, Zoom is not very effective, if you've not had any prior training. But after training it can be another very good way of reinforcing what you studied earlier on.*
Examiner	Collaborative relationships, troubleshooting	*When I am challenged with the software and I've tried to troubleshoot with my own knowledge, and it still misbehaves. I can call my friend or colleague. And if I have readings which are not according to the ranges, the abnormal ranges, then I consult. At times we had a complication in the Dolphin, where it was giving us odd numbers. There was a certain point of setting where it gave us odd numbers. You're trying to work on the calculations you have done, but you see, the rating was on the machine, the odd numbers. We had to troubleshoot and set it back to normal. Other times the machine beeps and goes back to the home screen. So initially, we didn't know what to do to go back to where were. These are the points where you need to call your friend for assistance. But I think for the time being, or lately, all these complications when they pop, we know exactly what to do. And there are few cases that we must call another one for support or backup because, like everything now, it's hands on, you know what to do if you work together.*

Table D.2 Representative Quotes Pertaining to Stroke Morbidity, Mortality and Impact

Participant Type	Sub-Category	Quote
Super-examiner	Caregiver/community knowledge	*At that point I think they can see if you attend the referral hospital clinic, you'll see [children with SCA] with stroke. But it's hard to imagine your child would get a stroke. You think "that's far away from me or elsewhere." I don't think many would really want to think their child can get stroke even though you see other [children with SCA] get stroke. They see other patients that have had it. But it's not real unless it happens to them, or it doesn't seem like a risk because it's not them yet. When a sickler gets stroke, it's them and not you until it gets to you.*
Stakeholder	Cost/Economic impact	*Once someone has a stroke, they need a quick blood transfusion which they cannot afford at the time, and they needed access to get transfusion, so they may require an admission and must pay a hospital bill. And then the next thing that happens should be sometimes the doctors would require a CT scan, which is quite expensive to confirm the diagnosis. Sometimes they want both a CT and MRI, and these 2 tests are very expensive, and they are performed in private hospitals which they have to pay quite a big amount. So, investigations around this stroke, the treatment with blood transfusion, and of course they will need to start hydroxyurea if they have not started and they have to follow-up, follow that a long time. And in terms of treatment that will be required—physical therapy, which is also expensive and long, many years. So when you add a cost of investigating the stroke, the treatment of stroke, and follow up, this is expensive, and of course, at the end of it all these are growing children who require to be going on well with their education, [which is] interrupted in a way and sometimes they don't have [the ability] to complete school, so they have to look for other means of boosting their education through private means. All this adds up to a big cost.*
Stakeholder	Cost/Economic impact; morbidity and mortality	*Let me start with the health consequences. Most of them, who get a hemorrhagic stroke, it's rare for them to survive. The ones who get an ischemic type of stroke will be left with a permanent disability somehow. For example, some of them get hemiplegia, and maybe they might not be able to use one side of their body. Which again, has an impact on their parents, because the parents must take care of them. And maybe now, the parents will not be able to even go to work, to look for food for [the child and their siblings]. It brings in the health impact plus the psychosocial, economic impact.*
Stakeholder	Morbidity and mortality	*So, we think about 30% of the children that we have in clinic have experienced stroke and the main consequence is that several of them become disabled. There are those ones who will get obvious symptoms of stroke—weakness of one side of the body, but a majority of them will have what you'd call TIA, which is stroke, which is hidden, and the consequence of this is that these children do not perform well in school, and they are also perceived not intelligent. And so apart*

Participant Type	Sub-Category	Quote
		from the medical consequences where they are disabled others may also die of it, but cognitive impairment is the biggest one, and it's the biggest complaint from parents and even relatives of these children. They will be unable to move around freely. They can't write to their hands properly, they tend to be able to repeat strokes here and there, and this will make life difficult on top of having sickle cell disease which is a genetic heritable disease. They also now have a disability attached to it.
Super-examiner	Effects of stroke	*The biggest challenge I have found is when the person has either condition or abnormal. Especially the abnormal ones. You tell this to the mother that after the second reviewer has verified the results and confirm this person is at a very high risk of stroke, and they have abnormal results. Then it's very hard to break the bad news to the parents to say, "Hey, after what we've done, looks like the risk of stroke is very high. And so, you need to do this and this an this an this to help avoid it. If you don't do it, a child could get a stroke or if you see this and this and this sign, make sure you run to hospital because your risk, your child is at high risk of stroke." And usually, we put in the books, their patient files. Usually, patients have books and when I see someone at high risk of stroke, I'll put it in there and I tell them if the child is feeling numb, they're having detached speech, they feel weak on a certain side, just run to hospital with this result and tell whatever health care provider, "I was checked. Some test was done, and they told me my child is at high risk of stroke, and now maybe they are having deteriorating speech or weakness on this side, please help." So, to dispatch is breaking the bad news, but the good news is easy to break to tell them that you're okay, but you still have to protect yourself*
Super-examiner	Impact of TCD	*TCD screening has had an impact on your patient population, yes, because it has helped us know and sort out those who were at high risk of getting stroke, and so that we can deal with them immediately to prevent that. Most of our community has congratulated that, especially those who are in our project. They've really congratulated, that for this service to be there cause, at least, there is an alert of the condition of the child. They have received it in a positive way, and that has impacted on us in a positive way. It makes us take a quick action to the child before anything better happens.*
Stakeholder	Effects of stroke, importance of treatment	*After they have a stroke, there are harder issues. It's really a bit complicated. But in post critical care that we include, they have to perform facial therapy sessions. And apart from that, we just try to know the origin of the stroke. Most of the time it's bad compliance to the treatment daily. So most of the patient who are performing stroke, they don't really take the hydroxyurea very well and we just help them with education to emphasize on the good side of the of taking the hydroxyurea.*

Participant Type	Sub-Category	Quote
Stakeholder	Effects of stroke	*The consequences for those patients, especially the pediatric patients, that happened after they had a stroke occurred especially in pediatric patients. The most important consequence for them is because they are school age, so it means that they really don't attend school. And we noted school failures, and sometimes truancy. I think that's the very important consequence. It's of an educational nature.*
Stakeholder	Effects of stroke	*The consequences of, as you've said to the individual, to the family, to the community, to the healthcare system. The consequences to the individual. So, these are children. First is the fact that well, the child could die from a stroke; it could be fatal. If they don't die, they could end up with significant neurologic deficits which could affect their motor system. It could affect their cognitive system so their learning ability could affect their speech and processing. That immediately limits that child's potential. It also potentially could limit that child's ability to integrate into regular school. The child may not be able to go to school because they can't keep up with the rest of the class if they're having problems with writing or processing. You have a child whose educational journeys truncated. Even if the educational journey is not truncated, maybe subject to bullying and stigma and all other issues in school, just because they're a little bit different, or they are walking a little bit different, or they're talking a little bit different than their peers. Stroke also constitutes a significant financial burden for the families because of all the supportive and rehabilitative care that is required: speech therapy, physiotherapy, occupational therapy, walking aids, all those things, can financially cripple families. It's a source of stress for the parents emotionally and can even be the reason for marital discord and for families to break apart. The money that is spent on managing a child who has had a stroke means that their funds that are being taken away from other children in the family and funds that could have gone into doing other things for other children in the family now have to be poured into dealing with this stroke. Of course, it constitutes a burden on the health care system as well. And the problem with sickle cell stroke is that once a stroke has happened, there's really nothing that you can do to 100% prevent another stroke. So that stroke that occurred becomes the biggest risk factor of another stroke happening. Often when the second or the third or the fourth stroke happens, it's a lot more devastating than the first one. So really the best thing to do is to prevent the first stroke from occurring. Because once a stroke happens it just has a lot of ripple effects beyond just the child and the and the families.*

CURRICULUM VITAE

Teresa Smith Latham, MA, LPCC-S
Curriculum Vitae

Name and Personal Data

Name: Teresa Smith Latham
Work Address: 3333 Burnet Ave ML 7015, Cincinnati, OH 45229
Email: teresa.latham@cchmc.org
Office Phone: (513) 803-7922

Education

1. Undergraduate Education:
   American University
   Washington, DC, 1999 - 2002
   Majors: Psychology, Law & Society
   Degree: Bachelor of Arts

2. Master's Degree:
   Marymount University
   Arlington, VA, 2003 – 2005
   Degree: Master of Arts in Clinical Counseling

3. Doctoral Education
   Indiana University Fairbanks School of Public Health
   Indianapolis, IN, 2021-2024; *in progress – target completion May 2024*
   Degree: Doctor of Public Health (DrPH), Global Health Leadership

   Maastricht University
   Maastricht, Netherlands, 2022 – 2024; *in progress – target completion September 2024*
   Degree: Doctor of Philosophy (PhD), Public Health

Academic Appointments

Director of Clinical Research, Cancer & Blood Diseases Institute, Cincinnati Children's Hospital Medical Center (February 2020 – Present)

Hematology Clinical Research Manager, Cancer & Blood Diseases Institute, Cincinnati Children's Hospital Medical Center (Sept 2011 – Present)

Adjunct Professor, Xavier University College of Social Sciences, Health & Education (2011-2019)

Previous Employment
Clinical Research Manager, University of Cincinnati Department of Psychiatry and Behavioral Neuroscience (2008-2011)

Professional Licensure
Licensed Professional Counselor with Supervision Designation (Ohio E.0601083-SUPV)

Clinical Service
Clinical Expertise and Activities

- Chapter Lead & Clinical Advisor (trauma/parental bereavement), MISS Foundation/MISS International (2009-present)
- Clinical Therapist, Center for Children and Families (2007-2008) Cincinnati, OH
- Social Worker/Armed Forces Emergency Services Counselor (2006-2007) Cincinnati, OH
- Clinical Therapist, Fairfax Alcohol and Drug Youth Services (2004-2006) Fairfax, VA
- Clinical Counselor, Psychiatric Rehabilitative Services, Inc. (2004) Alexandria, VA

Research and Scholarly Activities

Research and Scholarly Activities
My research focuses on sickle cell anemia in resource-limited settings, specifically sub-Saharan Africa and the Caribbean. I serve as a Co-Investigator on nine international therapeutic trials and oversee data management and trial operations at partner trial sites in numerous resource-limited settings. My doctoral research projects describe the methods by which public health leaders can most effectivity improve care for children with sickle cell anemia in resource-limited settings, with a focus on stroke prevention as well as capacity building through knowledge and technology transfer using North-South Partnerships for sustainable, lasting change. With a broad skill set in management of multi-disciplinary teams in the US and around the world, my personal academic interests are focused on building capacity for research and improving healthcare outcomes in areas of the world that are most underserved.

Director of Clinical Research, Cancer & Blood Diseases Institute, Cincinnati Children's Hospital Medical Center (February 2020 – Present)

- Work in partnership with expert physician-scientists in Hematology, Oncology, Bone Marrow Transplant, and Immunology to support our Institute's mission and vision to be the global leader in cancer and blood disease care, research, and education.
- Lead a team of 95 people who provide comprehensive clinical trials operations services to the faculty researchers within the CBDI, collectively managing approximately 600 studies.
- Oversight of Data Management Center for investigator-initiated trials, managing team that provides database development, validation and maintenance, website and web-based

application development, and data analytics (e.g. DSMB report preparation, trend analysis).

- As a Co-Investigator on international sickle cell trials through the division of Hematology and the Global Health Center, participate in the design, implementation, and ongoing oversight of study teams working in Angola, Democratic Republic of Congo, Kenya, Uganda, Tanzania, Ghana, the Dominican Republic, and Jamaica.
    - Data Management Center Director for international sickle cell trials with focus on capacity building for therapeutic clinical trials in resource-limited settings in sub-Saharan Africa and the Caribbean.
    - Lead database, website, and application design; clinical trial monitoring; and training of personnel in research operations and their management of study participants.
    - Each trial and each team require a different approach, considering the cultural backgrounds, language differences, local challenges, and logistical issues.
    - Maintain regular contact with clinical trial sites in Democratic Republic of Congo, Kenya, Uganda, Ghana, Tanzania, Angola, Dominican Republic, and Jamaica for all operational and participant management needs.
- Build and maintain study databases for all CBDI investigator-initiated trials (OnCore, REDCap, REDCap Cloud, Advarra EDC)
- Lead risk-based management of quality assurance for the division, including preparation and facilitation of FDA inspections.
- Prepare data for biostatistical analysis (R, SAS, Stata, MicroStrategy)
- Negotiation of industry clinical trial budgets and clinical trial agreements

Notable Clinical Trial Involvement:

- Director, Data Coordinating Center: Prospective Identification of Variables as Outcomes for Treatment (PIVOT): A Phase II Clinical trial of hydroxyurea for children and adults with HbSC disease – study conducted in Ghana
- Director, Data Coordinating Center: Alternative Dosing And Prevention of Transfusions (ADAPT), A prospective study to reduce transfusion requirements for children with sickle cell anemia using pharmacokinetics-based hydroxyurea dosing – study conducted in Uganda
- Director, Data Management Center: Realizing Effectiveness Across Continents with Hydroxyurea (REACH): a phase I/II pilot study of hydroxyurea for children with sickle cell anemia – study conducted in Angola, Democratic Republic of Congo, Kenya, and Uganda
- Director, Data Coordinating Center: Novel Use of Hydroxyurea In An African Region with Malaria (NOHARM): A randomized, double-blinded, placebo-controlled trial for children with sickle cell anemia – study conducted in Uganda
- Director, Data Coordinating Center, NOHARM Maximum Tolerated Dose Extension Trial – study conducted in Uganda
- Project Manager, Repeated Employee Testing for Understanding our Recovery to Normal (RETURN) – COVID-19 study conducted at CCHMC

- Project Manager, Serology to COVID for Recording Exposures and Evaluating Needs, (SCREEN) – COVID-19 study conducted at CCHMC
- Project Manager, Antibody Detection of Vaccine-Induced Secretory Effects (ADVISE) – COVID-19 study conducted at CCHMC
- Director, Data Coordinating Center: Expanding Treatment for Existing Neurological Disease (EXTEND) – study conducted in Jamaica
- Director, Data Coordinating Center: Stroke Prevention with Hydroxyurea Enabled through Research and Education (SPHERE): A Prospective Trial to Reduce Primary Stroke in Children with Sickle Cell Anemia – study conducted in Tanzania
- Project Manager and Director, Data Coordinating Center: Stroke Avoidance for Children in Republica Dominicana (SACRED), A Prospective Trial to Reduce Primary Stroke in Children with Sickle Cell Anemia – study conducted in Dominican Republic
- Director, Data Management Center: Establishment of the Collaborative Network for Neuro-Oncology Clinical Trials (CONNECT) – study conducted in the United States
- Director, Data Management Center: Early Intervention with Eculizumab to Treat Thrombotic Microangiopathy/atypical Hemolytic Uremic Syndrome-associated Multiple Organ Dysfunction Syndrome (MODS) in Hematopoietic Stem Cell Recipients – study conducted in the United States
- Monitor: TCD with Transfusions Changing to Hydroxyurea (TWiTCH) – study conducted in the United States

Hematology Clinical Research Manager (Sept 2011 – Present)
Prior title held: Senior Project Management Specialist

- Facilitate trial design & implementation for all aspects of clinical trial management within Hematology division (sickle cell disease, hemophilia/thrombophilia and general hematology).
- Initiation & oversight of clinical trials in Hematology (average of 125 active trials), including directing study management, regulatory, and data safety monitoring for local, multi-site and international trials.

Clinical Research Manager, University of Cincinnati Department of Psychiatry and Behavioral Neuroscience, NIH-NIDA Clinical Trials Network Regional Research & Training Center (2008-2011)

- Provided study oversight, implementation, training, and consultation to clinical sites for pharmaceutical, industry-sponsored, and NIH-funded clinical trials
- Participated in protocol development and implementation for clinical trials at a local and national level
- Implemented training plan requirements for assigned studies locally and remotely
- Coordinated study conduct with sponsor and local agencies
- Managed training and orientation of staff, oversaw annual training renewals for FDA, IRB, VA, and sponsors
- As licensed research mental health clinician, supervised administration of eligibility assessments, administered clinical study-related interventions, provided referral services

to study participants, and assessed study participants for mental health status, risk, and related diagnostics.

Notable Clinical Trial Involvement:

- Assistant Project Manager, CTN-0032 HIV Rapid Testing & Counseling
- Project Manager, CTN-0037: Stimulant Reduction Intervention Using Dosed Exercise (STRIDE)
- Study Clinician, CTN-0046: Smoking Cessation for Stimulant Treatment (S-CAST)
- Assistant Project Manager, CTN-0047: Screening, Motivational Assessment, Referral and Treatment in Emergency Departments
- Project Manager and Study Clinician, CPP 01004: Vigabatrin for Cocaine Dependence: a randomized, placebo-controlled trial
- Project Manager and Study Clinician, TA-CD 09 Human Cocaine Vaccine for Cocaine Dependence

Grants and Contracts

2016156 ICRA 09/15/13 – 10/31/24 1.2 CM
Doris Duke Charitable Foundation $1,188,000 total costs
PI: Russell E. Ware, MD PhD

Role: Co-Investigator and Director, Data Management Center

Novel use Of Hydroxyurea in an African Region with Malaria (NOHARM) with follow-on study for optimizing for maximum tolerated dose

Major Goals: To compare the safety and efficacy of fixed-dose oral hydroxyurea treatment at 20 mg/kg/day versus escalation to maximum tolerated dose, for both laboratory and clinical effects for malaria in children with SCA who live in a malaria endemic area of Uganda.

Theravia, Inc. 09/01/21 – 08/31/26 1.2 CM
$4,425,531 total costs
PI: Russell E. Ware, MD PhD

Role: Co-Investigator and Director, Data Management Center

Prospective Identification of Variables as Outcomes for Treatment (PIVOT): A Phase II Clinical trial of hydroxyurea for children and adults with HbSC disease

Major Goals: To measure the toxicities of hydroxyurea treatment on laboratory parameters; To assess the effects of hydroxyurea treatment on a variety of sickle-related clinical and laboratory parameters in a large cohort of children and adults with HbSC disease; To identify which study

endpoints are suitable for a future Phase III trial of patients with HbSC disease receiving hydroxyurea therapy.

U01 HL133883 08/01/22 – 07/31/27 1.2
CM
NIH-NHLBI $7,117,945 total costs
PI: Russell E. Ware, MD PhD

Role: Co-Investigator and Director, Data Management Center

Realizing Effectiveness Across Continents with Hydroxyurea (REACH): A Phase I/II Study of Hydroxyurea for Children with Sickle Cell Anemia

Major Goals: Phase 1/2 pilot trial of hydroxyurea in sub-Saharan Africa to determine the safety, feasibility, and benefits of hydroxyurea treatment for children with sickle cell anemia. Recently extended from original 5 year study to a total of 10 years.

Publications

1. Anyanwu JN, Williams O, Sautter CL, Kasirye P, Hume H, Opoka RO, Latham T, Ndugwa C, Ware RE, John CC. Novel use Of Hydroxyurea in an African Region With Malaria: Protocol for a Randomized Controlled Clinical Trial. JMIR Res Protoc 2016;5(2): e110. doi:10.2196/resprot.5599 PMID: 27339303

2. Rankine-Mullings AE, Little CR, Reid ME, Soares DP, Taylor-Bryan C, Knight-Madden JM, Stuber SE, Badaloo AV, Aldred K, Wisdom-Phipps ME, Latham T, Ware RE. JMIR Res Protoc 2016;12;5(3):e185. doi:10.2196/resprot.5872. PMID: 27619954

3. McGann PT, Tshilolo L, Santos B, Tomlinson GA, Stuber S, Latham T, Aygun B, Obaro SK, Olupot-Olupot P, Williams TN, Odame I, Ware RE. REACH Investigators. Hydroxyurea therapy for children with sickle cell anemia in sub-Saharan Africa: Rationale and design of the REACH trial. Pediatr Blood Cancer 2016;63(1):98-104. doi:10.1002/pbc.25705. PMID: 26275071

4. Opoka RO, Ndugwa CM, Latham TS, Lane A, Hume HA, Kasirye P, Hodges JS, Ware RE,* John CC.* (co-senior authors) Novel use Of Hydroxyurea in an African Region with Malaria (NOHARM): a randomized controlled trial. Blood 2017. 130(24):2585-2593. PMID: 29051184

5. Jeste ND, Sánchez LM, Urcuyo GS, Bérges ME, Luden JP, Stuber SE, Latham TS, Mena R, Nieves RM, Ware RE. Stroke Avoidance for Children in REpública Dominicana (SACRED):

A prospective study of stroke risk and hydroxyurea treatment in sickle cell anemia. JMIR Research Protocols 2017 Jun 2; 6(6):e107. PMID: 28576754

6. McGann PT, Williams TN, Olupot-Olupot P, Tomlinson GA, Lane A, Stuber S, Howard TA, McElhinney K, Aygun B, Latham T, Santos B, Tshilolo L, Ware RE. Realizing Effectiveness Across Continents with Hydroxyurea: Enrollment and baseline characteristics of the multicenter REACH study in sub-Saharan Africa. Am J Hematol 2018 Aug; 93(4):537-545. doi:10.1002/ajh.25034. PMID: 29318647

7. Sanchez LM, Nieves RM, Latham T, Stuber S, Luden JR, Urcuyo GS, Berges ME, Florencio C, Gonzalez C, Del Villar P, Lane A, Schultz W, Jeste N, Mena R, Ware RE. Building capacity to reduce stroke in children with sickle cell anemia in the Dominican Republic: the SACRED trial. Blood Adv 2018;2(suppl 1):50-53. doi:10.1182/bloodadvances.2018GS110818. PMID: 30504201

8. Tshilolo L, Tomlinson G, Williams TN, Santos B, Olupot-Olupot P, Lane A, Aygun B, Stuber S, Latham T, McGann PT, Ware RE. Hydroxyurea for Children with Sickle Cell Anemia in Sub-Saharan Africa. N Engl J Med 2019; 380:121-131. doi:10.1056/NEJMoa1813598. PMID: 30501550

9. John, CJ, Opoka, RO, Latham TS, Hume, H, Nabaggala, C, Kasirye, P, Ndugwa, C, Lane A, Ware RE. Hydroxyurea Dose Escalation for Sickle Cell Anemia in Sub-Saharan Africa. N Engl J Med 2020; 382:2524:2533. doi:10.1056/NEJMoa2000146. PMID: 32579813

10. Ambrose EE, Smart LR, Charles M, Hernandez AG, Latham T, Hokororo A, Beyanga M, Howard TA, Kamugisha E, McElhinney KE, Tebuka E, Ware RE. Surveillance for sickle cell disease, United Republic of Tanzania. Bull World Health Organ 2020; 98:859-568. doi: 10.2471/BLT.20.253583. PMID: 33293746

11. Opoka RO, Hume HA, Latham TS, Lane A, Williams O, Tymon J, Nakafeero M, Kasirye P, Ndugwa CM, John CC, Ware RE. Hydroxyurea to lower transcranial Doppler velocities and prevent primary stroke: the Uganda NOHARM sickle cell anemia cohort. Haematologica 2020;105:e272-e275. doi:10.3324/haematol.2019.231407. PMID:31649130

12. Rankine-Mullings A, Reid M, Soares D, Taylor-Bryan C, Wisdom-Phipps M, Aldred K, Latham T, Schultz WH, Knight-Madden J, Badaloo A, Lane A, Adams RJ, Ware RE. Hydroxycarbamide treatment reduces transcranial Doppler velocity in the absence of transfusion support in children with sickle cell anaemia, elevated transcranial Doppler velocity, and cerebral vasculopathy: the EXTEND trial. Br J Haematol 2021;195(4):612-620. PMID:34291449

13. Ambrose EE, Latham TS, Songoro P, Charles M, Lane AC, Stuber SE, Makubi AN, Ware RE, Smart LR. Hydroxyurea with dose escalation for primary stroke risk reduction in

children with sickle cell anaemia in Tanzania (SPHERE): an open-label, phase 2 trial. Lancet Haematol 2023;10(4):e261-e271. doi: 10.1016/S2352=3026(22)00405-7. PMID: 36870358

14. Smart LR, Ambrose EE, Balyorugulu G, Songoro P, Shabani I, Komba P, Charles M, Howard TA, McElhinney KE, O'Hara SM, Odame J, Nakafeero M, Adams J, Stuber SE, Lane A, Latham TS, Makubi AN, Ware RE. Stroke Prevention with Hydroxyurea Enabled through Research and Education: A Phase 2 primary stroke prevention trial in sub-Saharan Africa. Acta Haematol 2023;146(2):95-105. doi: 10.1159/000526322. PMID: 35977532

15. Olupot-Olupot P, Tomlinson G, Williams TN, Tshilolo L, Santos B, Smart LR, McElhinney K, Howard TA, Aygun B, Stuber SE, Lane A, Latham TS, Ware RE. Hydroxyurea treatment is associated with lower malaria incidence in children with sickle cell anemia in sub-Saharan Africa. Blood 2023;141(12):1402-1410. doi: 10.1182/blood.2022017051. PMID: 36375125

16. Ware J, McElhinney K, Latham T, Lane A, Dienger-Stambaugh K, Hildeman D, Spearman P, Ware RE. Sustained and boosted antibody responses in breast milk after maternal SARS-CoV-2 vaccination. Breastfeed Med 2023;18(8):612-620. doi: 10.1089/bfm.2023.0106. PMID: 37615566

17. Smart LR, Segbefia CI, Latham TS, Stuber SE, Amissah-Arthur KN, Dzefi-Tettey K, Lance AC, Dei-Adomakoh YA, Ware RE. Prospective identification of variables as outcomes for treatment (PIVOT): study protocol for a randomized, placebo-controlled trial of hydroxyurea for Ghanaian children and adults with haemoglobin SC disease. Trials 2023; 24(1):603. doi: 10.1186/s13063-023-07649-7. PMID: 37737189

18. Sadaf A, Dong M, Pfeiffer A, Latham T, Kalfa T, Vinks AA, Ware RE, Quinn CT. A population pharmacokinetic analysis of L-Glutamine exposure in patients with sickle cell disease: Evaluation of dose and food effects. Clin Pharmacokinet 2024;63(3):357-365. doi: 10.1007/s40262-024-01349-4. PMID: 38401036

19. Power-Hays A, Tomlinson GA, Tshilolo L, Santos B, Williams TN, Olupot-Olupot P, Smart LR, Aygun B, Lane A, Stuber SE, Latham T, Ware RE. Reducing transfusion utilization for children with sickle cell anemia in sub-Saharan Africa with hydroxyurea: analysis from the phase I/II REACH trial. Am J Hematol 2024;99(4):625-632. doi:10.1002/ajh.27244. PMID: 38332651

20. Aygun B, Lane A, Smart LR, Santos B, Tshilolo L, Williams TN, Olupot-Olupot P, Stuber SE, Tomlinson G, Latham T, Ware RE, REACH Investigators. Hydroxyurea dose optimization for children with sickle cell anaemia in sub-Saharan Africa (RECH): extended follow-up of a multicentre, open-label, phase 1/2 trial. Lancet Haematol, in press.

21. Latham T. Sickle cell anemia treatment with hydroxyurea in low-resource settings: challenges and opportunities for global North-South partnerships. Int. J Public Health, in press.

Quality review of publications (5 selected)

1. Opoka RO, Ndugwa CM, Latham TS, Lane A, Hume HA, Kasirye P, Hodges JS, Ware RE,* John CC.* (co-senior authors) Novel use Of Hydroxyurea in an African Region with Malaria (NOHARM): a randomized controlled trial. Blood, Dec 14, 2017. 130(24):2585-2593. PMID: 29051184

   Significance: The NOHARM study showed that when compared with placebo, hydroxyurea did not increase the incidence or severity of malaria events in Ugandan children with sickle cell anemia, and provided significant clinical and laboratory benefits, suggesting that hydroxyurea will be a safe and effective therapy across sub-Saharan Africa.

   Contribution: I provided operational oversight to the study performance site, lead the Data Coordinating Center, monitored the study, participated in the data analysis, and was part of the manuscript writing process.

Total Citations	**2024**	**2023**	**2022**	**2021**	**2020**
85	8	25	13	16	23

2. Tshilolo L, Tomlinson G, Williams TN, Santos B, Olupot-Olupot P, Lane A, Aygun B, Stuber S, Latham T, McGann PT, Ware RE. Hydroxyurea for Children with Sickle Cell Anemia in Sub-Saharan Africa. N Engl J Med 2019; 380:121-131.

   Significance: The REACH primary results manuscript demonstrated that hydroxyurea treatment was feasible and safe in children with sickle cell anemia living in sub-Saharan Africa. Hydroxyurea use reduced the incidence of vaso-occlusive events, infections, malaria, transfusions, and death, supporting the need for wider access to treatment.

   Contribution: I provided operational oversight to the study performance sites, lead the Data Management Center, monitored the study remotely and onsite, and participated in the data analysis, and was part of the manuscript writing process.

Total Citations	**2024**	**2023**	**2022**	**2021**	**2020**
221	14	63	46	47	51

3. John CC, Opoka RO, Latham TS, Hume, H, Nabaggala C, Kasirye P, Ndugwa C, Lane A, Ware RE. Hydroxyurea Dose Escalation for Sickle Cell Anemia in Sub-Saharan Africa. N Engl J Med 2020; 382:2524:2533.

   Significance: The NOHARM MTD study primary results from the blinded treatment phase showed that hydroxyurea with dose escalation had superior clinical efficacy to that of fixed-dose hydroxyurea, with equivalent safety. The blinded phase of this trial was stopped early by the Data Safety Monitoring Board due to the differences in outcomes between the treatment arms, and children were offered open-label hydroxyurea with dose escalation.

Contribution: I provided operational oversight to the study performance site, lead the Data Coordinating Center, monitored the study, participated in the data analysis, and was part of the manuscript writing process.

Total Citations	2024	2023	2022	2021	2020
90	13	30	18	24	5

4. Ambrose EE, Latham TS, Songoro P, Charles M, Lane AC, Stuber SE, Makubi AN, Ware RE, Smart LR. Hydroxyurea with dose escalation for primary stroke risk reduction in children with sickle cell anaemia in Tanzania (SPHERE): an open-label, phase 2 trial. Lancet Haematol 2023;10(4):e261-e271. doi: 10.1016/S2352=3026(22)00405-7. Epub 2023 Mar 1. PMID: 36870358

   Significance: The SPHERE primary results manuscript demonstrated key findings that children with sickle cell anemia in Tanzania have a high baseline stroke risk, and that hydroxyurea at maximum tolerated dose significantly lowers transcranial Doppler velocities and reduces primary stroke risk.

   Contribution: I provided operational oversight to the study performance site, lead the Data Coordinating Center, monitored the study, participated in the data analysis, and was part of the manuscript writing process.

Total Citations	2024	2023	2022	2021	2020
7	3	4	NA	NA	NA

5. Olupot-Olupot P, Tomlinson G, Williams TN, Tshilolo L, Santos B, Smart LR, McElhinney K, Howard TA, Aygun B, Stuber SE, Lane A, Latham TS, Ware RE. Hydroxyurea treatment is associated with lower malaria incidence in children with sickle cell anemia in sub-Saharan Africa. Blood 2023;141(12):1402-1410. doi: 10.1182/blood.2022017051. PMID: 36375125

   Significance: Key findings of this secondary analysis of REACH trial data suggest that hydroxyurea at maximum tolerated dose is associated with lower malaria incidence in children with sickle cell anemia through incompletely defined mechanisms, however treatment with a target of absolute neutrophil count $<3.0x10^9$/L is particularly beneficial.
   Contribution: I provided operational oversight to the study performance site, lead the Data Coordinating Center, monitored the study, participated in the data analysis planning and execution, and was part of the manuscript writing process.

Total Citations	2024	2023	2022	2021	2020
15	4	10	1	NA	NA

Patents - None

Abstracts - None

Teaching and Mentoring

Teaching
Adjunct Professor of Clinical Counseling, Xavier University (2011 – 2019)
Instructor, Cincinnati Children's Informed Consent Curriculum (2011 – 2019)
Instructor, Cincinnati Children's Hospital Medical Center Core Clinical Research Training Program (2012 - present)
Chair, Cincinnati Children's Hospital Medical Center Clinical Research Professionals Education Subcommittee, 2012-2013
Program Co-Lead, Cincinnati Children's Hospital Medical Center Clinical Research Advancement Mentorship Program

Mentoring
Since 2013, I have had the pleasure of mentoring several talented clinicians and research team members in Africa and the Caribbean as well as many clinical researchers at Cincinnati Children's on topics including clinical research Good Clinical Practice, research operations, trial implementation, data management and analytics, leadership and quality assurance/compliance methods.

Mentor List

Mentee	Organization/Institution	City/Country	Dates
Amy Shova	Cincinnati Children's Hospital Medical Center	Cincinnati, OH	2011 – Present
Isaac Birungi	Mulago Hospital Sickle Cell Clinic; Global Health Uganda	Kampala, Uganda	2014 – Present
Lori Backus	Cincinnati Children's Hospital Medical Center	Cincinnati, OH	2020 – Present
Maria Nakafeero	Cincinnati Children's Hospital Medical Center	Kampala, Uganda	2019 – Present
George Mochamah	KEMRI Wellcome Trust, Kilfi District Hospital	Kilifi, Kenya	2022 – Present
Phiona Milly	Jinja Regional Referral Hospital, Global Health Uganda	Jinja, Uganda	2021 – 2023
Amanda Pfeiffer	Cincinnati Children's Hospital Medical Center	Cincinnati, OH	2014 – Present

Service and Leadership

With more than 15 years of experience managing research operations at all levels, including high-risk FDA-regulated therapeutic trials within the US and internationally, I strive to be a leader in executing the highest quality clinical research trials across disciplines. I currently serve as Data Management Center Director for nine international trials, overseeing multi-disciplinary

research operations with a focus on capacity-building among research teams in limited-resource settings. As Director of Clinical Research in the Cancer and Blood Diseases Institute at Cincinnati Children's Hospital Medical Center, I am responsible I lead a highly skilled and experienced management team that works together to oversee research operations among more than 90 team members supporting over 600 clinical trials within the Cancer and Blood Diseases Institute. I also serve as an institutional leader and subject matter expert on clinical trials management and research ethics at CCHMC, and currently lead the Clinical Research Professional Advancement Committee as well as the institutional task force supporting research processes and Clinical Trials Management System (CTMS) assessment and implementation.

Distribution of Effort:
Clinical Service 0%
Research and Scholarly Activities 70%
Teaching and Mentoring 10%
Service and Leadership 20%