Bridging the Childhood Epilepsy Treatment Gap in Africa (BRIDGE)

National Clinical Trial (NCT) Identified Number: NCT04290975

Pan African Clinical Trial Registry Identification Number: PACTR202003864779691

Principal Investigator/Program Director: Edwin Trevathan

Sponsor: Vanderbilt University Medical Center

Grant Title: Bridging the Childhood Epilepsy Treatment Gap in Africa (BRIDGE)

Grant Number: R01NS113171

Funded by: National Institute of Neurological Diseases and Stroke (NINDS)/NIH

Version Number: v.1.9 3 September 2021

Table of Contents

Amendment History and Justification

Version 1.4

1. More detailed clarification of the descriptions within the protocol in order to provide a clear and concise presentation. For example, Figure 3 has been added to demonstrate the consent and assent timeline within the context of screening, diagnostic evaluations and enrollment. These clarifications have been requested by biostatisticians and the DSMB assigned to the project since the prior protocol submission.
2. An increase in the sample size for Aim #2 of the study - specifically for the qualitative interviews of a sample of parents and guardians of children in the study. This increase in sample size is well within the scope of work for the study and within the budget. The percentages of parents/guardians sampled for the qualitative interviews is still less than about 10% of the children enrolled in the cluster randomized clinical trial (cRCT).
3. Change in the format of the protocol document to adhere to NINDS/NIH recommended formats - also requested by the DSMB and by NIH.
4. Upon additional review by our Nigerian colleagues, there was concern that some of the blanks to be filled in by community health workers in the consent forms were confusing and a source for potential error. There was also concern that the term “study subjects” would not translate well in Hausa and that there would be confusion on the part of parents/guardians and children. Very minor changes in the consent form to eliminate prior possible confusion related to the identification of parents/guardians and children enrolled in the study by using terms such as “study subjects”. We have eliminated these potential confusions in the revised consent forms.

Sections affected:

- 1.1, 2.3, 4.1, 4.4, 5.5, 6.1, 6.3, 7.2, 8.1, 8.2, 8.3, 9.1, 9.4 (see highlighted areas)

Amendment #2

Version 1.5

- Questions regarding Child Care, the Child Care Questionnaire, were added to Visit 1 Week, visit 12 months, and Visit 24 months to enhance the cost-effectiveness analysis for Aim #3. These questions fall into the Child Healthcare category and hence no additional changes on the consent forms were needed.
- Age for ADHD questionnaire to be given to children was modified to 5-10 years of age. Questionnaire was not modified in content.
- Detailed description of planned interim analysis was added to section 9.4.6, which explains the analysis more completely.

Sections affected:

- 1.3, 8.1, 9.4.6,

Amendment #3
Version 1.6

- Figure 1. BRIDGE Cluster Randomized Controlled Trial Design was edited. Seizure free definition was corrected from > 6 months to ≥ 6 months.
- Lost to Follow-Up section was expanded to clarify some changes intended to apply during the follow up period. In the event that a child can't assist in person to a follow up appointment, the follow up visit will be done via phone by the Community Health Worker. These visits will require the approval of the PI and will be evaluated on a case by case basis. In addition, CHWs will be able to make the house call and complete follow up visits in the homes of the child if needed. This expansion on the Follow up care does not require any additional consent or modification to the data collecting tools.

Sections affected:
1.2 and 7.3

Amendment #4
Version 1.7

- Section 1.1, Minor change in phrase to clarify that the arm of the cluster randomized clinical trial (cRCT) in which epilepsy care is provided by physicians is "Enhanced Usual Care".
- The maximum children enrolled and followed in the cRCT is now increased from 1700 to 1800. The target enrollment is changed from 1530 to 1730. (Sections 1.2, 4.1, 5.5, 8.1, 9.3)
- Section 10.4 eliminated, as it is redundant with the Amendment History and Justification at the beginning of the protocol.

Sections affected:
1.1, 1.2, 4.1, 5.5, 8.1, 9.3, 10.4

Amendment #5
Version 1.8

- Add the Pan African Clinical Trial Registry Identification Number on the Title Page
- Interim Analysis. The interim analysis was previously planned after half of the enrolled study subjects completed 24 months of follow-up. At the request of the Data Safety Monitoring Board (DSMB), and in response to the rapid enrollment in which BRIDGE enrollment is expected to be completed within approximately 12 months compared to the previously anticipated 24 months, the interim analysis will be performed after about half of the enrolled study subjects have completed 12 months of follow-up after enrollment.
- Co-morbid Neurodevelopmental Disorders. Up to half of the children enrolled in BRIDGE have screened positive for one or more neurodevelopmental disorders – a higher proportion than anticipated. The study investigators, and the DSMB, believe that it is important that the common neurodevelopmental co-morbidities among study enrollees be well-characterized. Therefore, all enrolled children will be examined by blinded physicians at their 1-, 6-, or 12-month blinded physician visit for possible cerebral palsy (CP), and for whether children have an absence of language function. A system has been developed for performing diagnostic evaluations for children who screen positive for a neurodevelopmental disorder, and who can complete the evaluation. Parents/guardians will be given the opportunity to opt out of these specialist diagnostic evaluations, that will be fully paid by the study, without withdrawing from the BRIDGE cluster randomized clinical trial; therefore, separate consent forms will be provided for these additional diagnostic evaluations for neurodevelopmental disorders.
- Second-Level Blinded Physician Evaluations. When blinded physicians are uncertain as to whether an enrolled child has epilepsy, or makes a diagnosis of an enrolled child as not having epilepsy, then a second-level blinded physician evaluation will be obtained by another physician with expertise in epilepsy. If the epilepsy expert performing the second-level blinded physician evaluation is uncertain regarding the diagnosis, and if he/she believes that an electroencephalogram (EEG) is indicated to assist with diagnosis, then an EEG will be performed, with the cost paid by the BRIDGE study.
- Clearer and more detailed explanation of sample size calculations, correction of cluster enrollment imbalance, and statistical analysis. Upon further review of the statistical section, the BRIDGE statistics team believes that the amended description of the sample size calculation and the correction of the imbalance in cluster enrollment is helpful to readers. These clarifications and more detailed explanations to not involve any change in the prior approved protocol practice, but a more detailed explanation.
- More detail regarding the study in the assent form for children $\geq$ 13 years and < 17 years.

Sections affected: Title page, Section 1.1 (p. 8), Section 6.3 (pp 34-35), Section 8.1 (pp. 44-46), Section 9.2 (pp. 55-57), Section 9.4.2 (p. 61) Section 9.4.3 (p. 62), Section 9.4.6 (p. 63-65).

Amendment #6
Version 1.9

- Clarification was made on the adverse event reporting protocol to outline process of informing the DSMB of a serious adverse event within 14 days from first time both PIs become aware of the event
- Clarified that the official final report is due to the DSMB at earliest possible event
  Sections affected: 8.3.6

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the NINDS Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), if applicable, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent forms, recruitment materials, and all participant materials will be submitted to IRBs for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using previously approved consent forms.

INVESTIGATOR'S SIGNATURE

Principal Investigators (Multi-PIs) or Clinical Site Investigator:

Signed:  Date: 3 September 2021

Name: Edwin Trevathan, M.D., M.P.H.

Title: Amos Christie Chair in Global Health, Professor of Pediatrics and Neurology, Vanderbilt Institute for Global Health, Vanderbilt University Medical Center

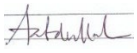
Investigators (Multi-PIs) Contact Information:

Affiliation: Vanderbilt Institute for Global Health

Address: 2525 West End Avenue, Suite 725

Telephone: 615-343-4174

Email: edwin.trevathan@vumc.org

Signed:  Date: 3 September 2021

Name: Aminu Taura Abdullahi, M.B.B.S., M.Sc.

Title: Senior Lecturer and Consultant

Affiliation: Aminu Kano Teaching Hospital, Kano, Nigeria

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

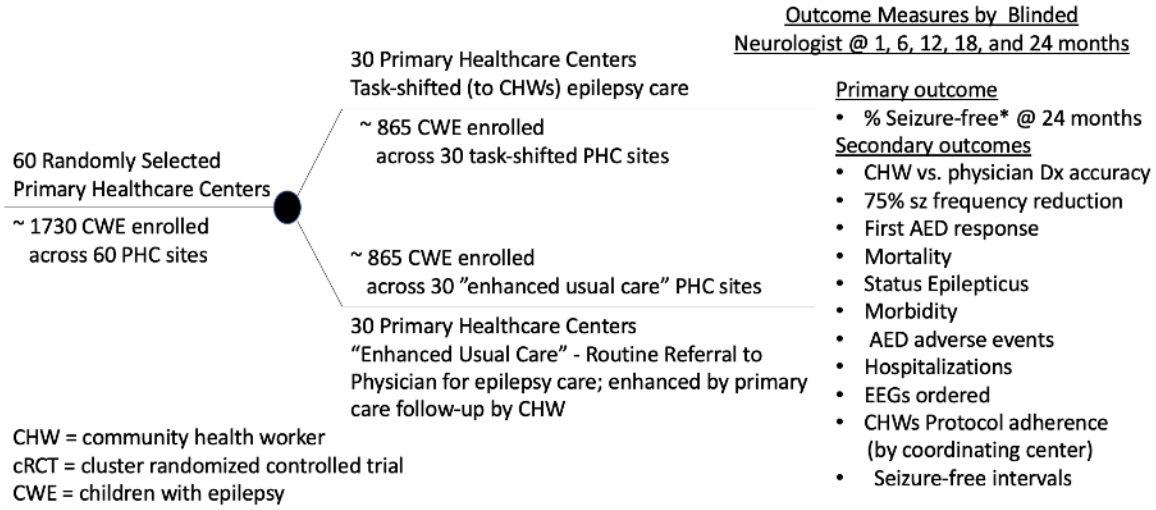
Title:	Bridging the Childhood Epilepsy Treatment Gap in Africa (BRIDGE)
Grant Number:	R01 NS113171
Study Description:	***BRIDGE*** is composed of **three specific aims**: (1) a non-inferiority cluster randomized clinical trial (cRCT) of task-shifted childhood epilepsy care provided by epilepsy-trained community health workers (CHWs) compared to epilepsy care provided by physicians [or enhanced usual care (EUC)], performed at sixty primary healthcare centers (PHCs) in three cities in northern Nigeria (Kano, Zaria, Kaduna); (2) studies of the socio-behavioral and implementation outcomes of task-shifted childhood epilepsy care; and, (3) an economic evaluation of task-shifted childhood epilepsy care in northern Nigeria.
Objectives:	Primary Objective: Efficacy of task-shifted epilepsy care to epilepsy-trained CHWs Secondary Objectives: Socio-behavioral and implementation outcomes, and cost-effectiveness of task-shifted childhood epilepsy care
Endpoints:	Primary Endpoint: Percentage of children who are seizure-free for $\geq$ 6 months at 24 months after enrollment Secondary Endpoints: 75% reduction in seizure frequency; response to first AED; diagnostic accuracy; mortality; neurodevelopmental morbidity; status epilepticus; hospitalizations; diagnostic tests ordered; task-shifted protocol adherence; percentage of patients with a $\geq$ 6-month seizure free interval(s) anytime during the 24-month follow-up visit.
Study Population:	Children, ≥ 6 months and < 17 years, with active epilepsy (2 or more unprovoked seizures, ≥ 1 in the past year) not currently treated with anti-epileptic drugs (AEDs).
Phase or Stage:	N/A
Description of Sites Enrolling Participants:	Children with untreated epilepsy will be identified by screening children in primary healthcare centers (PHCs), community door-to-door surveys, hospital-based clinics, schools and other community locations. The PHCs are randomly selected among the series of government run PHCs that serve as the primary facilities for primary healthcare in the communities. The hospital-based clinics will be

	those at both major comprehensive tertiary care centers as well as those at smaller community-based healthcare facilities.
Description of Study Intervention:	Sixty randomly selected PHCs (30 in Kano; 15 in Zaria; 15 in Kaduna) will be randomly assigned to deliver either task-shifted epilepsy care [to community health workers (CHWs)] or enhanced usual care (referral to a physician plus follow-up at a participating PHC by a CHW). Children with untreated epilepsy will be assigned to the participating PHC closest to their home.
Study Duration:	Five years (six months for start-up, 24 months of enrollment, with each enrolled child followed for 24 months, and then six final months for wrap-up).
Participant Duration:	Twenty-four months after enrollment
Registration:	The BRIDGE cRCT is registered with ClinicalTrials.gov (NCT04290975) and with the Pan African Clinical Trial Registry (PACTR; PACTR202003864779691).

1.2 SCHEMA

Figure 1. BRIDGE Cluster Randomized Controlled Trial Design

A non-inferiority cRCT of a task-shifted epilepsy care system



Funded by NINDS/NIH 1R01 NS113171

*Seizure-free = no seizures for > 6 months

1.3 SCHEDULE OF ACTIVITIES

Table 1. BRIDGE **SCHEDULE OF ACTIVITIES**	S*	0@	1 wk	1 mo	2 mo	4 mo	6 mo	9 mo	12 mo	15 mo	18 mo	24 mo
Consent for screening & diagnostic exam	X											
Epilepsy screen & seizure classification tool for screening	X											
Diagnostic exam for possible epilepsy	X											
Children with untreated epilepsy identified - inclusion & exclusion criteria	X											
Matching home address with closest participating PHC - TS& vs. EUC+		X										
Consent for TS or EUC arms of cRCT		X										
Demographic, social status		X										
Weight, height, vital signs		X	X	X	X	X	X	X	X	X	X	X
Physical exam, neurological exam		X	X	X	X	X	X	X	X	X	X	X
Seizure classification; epilepsy syndrome classification.	X	X										
Select 1st AED#-TS		X										
AED log & adjustment per protocol		X	X	X	X	X	X	X	X	X	X	X
Seizure history & classification			X	X	X	X	X	X	X	X	X	X
Adverse event log			X	X	X	X	X	X	X	X	X	X
QOLIE-AD-48 questionnaire@@		X			X							X
ADHD rating scale		X			X							X
23-question questionnaire			X									X
Aim #3 Child Care Questionnaire			X						X			X
Aim #2 quantitative surveys**			X						X			X
Aim #2 qualitative data collection&&									X			X
Quantify use of diagnostic tests!			X	X	X	X	X	X	X	X	X	X

***S = Visit S** = Epilepsy screening with epilepsy screening and seizure classification tool; and, diagnostic exams for those who screen positive.
@0 = Visit 0 = First visit after consent for cRCT. Children assigned to TS will start medication. Children assigned to EUC referred to physician.
&TS = Task-shifted arm of the cRCT. **+EUC** = Enhanced usual care of the cRCT. **#AED** = anti-epileptic drug.
@@QOLIE-AD-48 - Quality of Life in Epilepsy questionnaire at Visit 0 and 24 mo for children ages 11-17 yrs; QOLIE-31 if 18 years old at visit 24 mo.
****Aim #2 Quantitative Surveys** = trust in healthcare system, epilepsy knowledge & attitudes, stigma at Visit 1 week.
&&Aim #2 Qualitative Data Collection = baseline qualitative data from CHEWs and study physicians prior to Visit S.
!Diagnostic tests (e.g., blood tests, EEGs, MRI), performed per TS protocol and/or provider judgement, since prior visit will be measured.

2 INTRODUCTION

2.1 STUDY RATIONALE

Epilepsy is the most common severe neurological disorder among children. The majority of children with epilepsy, if treated, can live normal lives. Yet among the world's children living with epilepsy, about 80% of whom reside in low- and middle-income countries (LMICs), about half do not receive treatment and many of these are not diagnosed with epilepsy - "the childhood epilepsy treatment gap." Among the LMICs of Africa, the childhood epilepsy treatment gap is about 67%-90% – unchanged for over twenty years.[1-16] Prolonged seizures (or status epilepticus) among children are associated with high morbidity and mortality in northern Nigeria - 21% mortality or higher according to our initial studies.[17] Although the World Health Organization (WHO) and other health agencies recommend that the epilepsy treatment gap be bridged by task-shifting epilepsy care to *community health workers (CHWs)* in primary care settings close to the homes of people with epilepsy,[18-23] this recommendation has not been implemented or evaluated on a large scale. This failure to scale up task shifting in epilepsy care is due to (a) inadequate evidence of efficacy of task-shifted epilepsy care, (b) a lack of methods and tools for implementing epilepsy task shifting, (c) inadequate understanding of task-shifted epilepsy care barriers, and (d) a lack of cost-effectiveness data for health policymakers.[18-21,24,25] CHWs providing task-shifted epilepsy care must identify children with epilepsy, disadvantaged by stigma[26] and unknown to the healthcare system, who are without access to neurologists or diagnostic technology such as electroencephalograms (EEGs).[27,28] An epilepsy screening tool in the local language (e.g., Hausa) is essential for epilepsy diagnosis, seizure type classification, and medical management.[27,29,30]

Hausa, the most commonly spoken language in west Africa, with an estimated 120 million Hausa speakers,[31] is used in daily life, commerce, and education; BRIDGE will be conducted in three major cities in Hausa-speaking Africa - Kano, Zaria, and Kaduna. The materials for this project will be in both English and Hausa, translated by a team of healthcare professionals with expertise in epilepsy and fluency in both English and Hausa, and with consultation by linguists at the Centre for Nigerian Languages and Folklore at Bayero University Kano.

Funded by an R21 grant (R21 TW010899) in preparation for this cluster-randomized clinical trial (cRCT), the BRIDGE team developed and piloted in Kano, Nigeria (a) a scalable epilepsy training program for CHWs,[32] (b) an epilepsy community education program in Hausa to facilitate screening, diagnosis and treatment; and (c) an epilepsy data management system.[27] We also (d) validated an epilepsy screening, diagnosis, and seizure classification tool in Hausa, (e) demonstrated feasibility of screening and enrolling children in a cRCT of task-shifted epilepsy care, and (f) piloted a task-shifted epilepsy diagnosis and management protocol.[27,29] The BRIDGE team is ready to implement the current study, "*Bridging the Childhood Epilepsy Treatment Gap in Africa (BRIDGE)*," with its three specific aims: (1) Conduct a non-inferiority cRCT of task-shifted childhood epilepsy care compared to enhanced usual care; (2) Assess socio-behavioral and implementation outcomes among providers, guardians, and patients in the cRCT; and, (3) Determine the cost-effectiveness of the task-shifted epilepsy intervention.

2.2 BACKGROUND

2.2.1. *High burden of untreated childhood epilepsy in sub-Saharan Africa (henceforth, Africa)*

Epilepsy is the most common serious neurological disorder among children worldwide, about 80% of whom live in low- and middle-income countries (LMICs). About half of the world's children with epilepsy remain untreated. In the LMICs of Africa such as Nigeria, where half or more of the population is under 18 years of age, children with epilepsy suffer poor health outcomes and high risk of serious co-morbid conditions and injuries; uncontrolled epilepsy is a major cause of overall accidental death among African children.[1-3,5,6,9,10,12,33-37] Childhood epilepsy also has hidden burdens associated with stigma,[2,26,38-40] discrimination, and human rights violations. The childhood epilepsy treatment gap – those children with untreated, and often undiagnosed, epilepsy – is very high in Africa (67%-90%) and is a major contributor to the ~50% worldwide childhood epilepsy treatment gap.[4,10,13-16,27,41-44]

2.2.2. *Bridging the childhood epilepsy treatment gap will require new innovative care systems*

Efforts to close the childhood epilepsy treatment gap by scaling up the number of physician specialists with epilepsy and electroencephalogram (EEG) expertise have failed, due in part to 'brain drain" of physician specialists to higher paying countries, dramatic shortages of diagnostic technology, and difficulty maintaining diagnostic equipment in LMICs.[10,15,16] Based upon our preliminary data from Kano State (pop. ~ 4.7 million children estimated childhood epilepsy prevalence = 9 to 15 per 1000 and an epilepsy treatment gap ~70%), there are 29,600 to 49,350 children with untreated epilepsy in a region with three fully-functioning EEG machines and only 5-6 physicians with epilepsy expertise. Prior experience demonstrates that simply providing anti-epileptic drugs (AEDs) to LMICs without developing systems for educating healthcare providers and delivering epilepsy diagnosis and management services is not effective. *It is <u>not</u> possible to close the epilepsy treatment gap in Africa by scaling up systems of epilepsy diagnosis and care used in high-income countries.*[5,13,15,16,45]

2.2.3. *Task shifting proposed to bridge the epilepsy treatment gap - evidence lacking, not implemented*

<u>The World Health Organization (WHO) and the Nigerian Federal Ministry of Health</u>, recognizing the success of task shifting to community health workers (CHWs) to improve HIV and TB care access, and improved access in some non-communicable diseases,[22,24,25,27,46-54] realized that a new epilepsy care paradigm was essential and offered a pragmatic solution to the epilepsy treatment gap - integrating task-shifted epilepsy care into primary healthcare centers (PHCs) using CHWs.[19,21] The Ministries of Health in Nigeria and other African LMICs have also suggested that task-shifting to CHWs might bridge the treatment gap for epilepsy.[23] Investigators have suggested that task-shifting for brain disorders in primary care settings is feasible in LMICs if more personnel are available to employ the task-shifted methods, medications have reasonable availability, supervision of task-shifted care at the primary care level is maintained, and task-shifted workers are adequately trained and compensated[12] - all conditions that are present or potentially present in northern Nigeria. Furthermore, <u>finding methods to bridge the epilepsy treatment gap is a priority for the Nigerian Federal Ministry of Health.</u>[23] Task-shifting is innovative and has been piloted for depression.[55-58] Yet few studies and no clinical trials have evaluated task-shifting to improve access to epilepsy care in Africa or elsewhere in the world.[53,59,60] Task-shifting to

CHWs to reduce the childhood epilepsy treatment gap has not been implemented on a large scale anywhere in the world, due in part to a lack of established methods for training and supervising CHWs who provide epilepsy care, inadequate tools for epilepsy diagnosis for use by CHWs, a lack of evidence of efficacy of task-shifting for epilepsy diagnosis and care, and a lack of cost-effectiveness economic data for policy makers.[12]

2.2.4. *Efficacious task-shifting for childhood epilepsy care would be a major public health advance*

A cluster-randomized clinical trial (cRCT) demonstrating efficacy of task-shifted childhood epilepsy care in Africa would be a major public health advance - offering possible solutions to an intractable challenge of extending basic epilepsy care to half of the world's children with epilepsy who are untreated. Other than our feasibility studies we are not aware of a rigorous, large-scale effort that has been undertaken to develop and evaluate methods for task-shifted epilepsy care in Africa. Demonstrating the efficacy for task-shifted childhood epilepsy care in Nigeria could provide insights into methods for improving epilepsy care access in resource-limited areas of the U.S. Likewise, lack of efficacy of task-shifted epilepsy care would force policy makers to reconsider prior recommendations by WHO and by other agencies.

2.2.5. Implementation strategies and cost-effectiveness data for task-shifted epilepsy care are needed

There is evidence for cost savings and efficiency improvements from task-shifting related to tuberculosis and HIV/AIDS,[49,51] and possible cost savings from task-shifting for non-communicable diseases such diabetes, hypertension, and childhood malnutrition.[24,25,51,61] A pilot study in southern Nigeria of task-shifting for psychiatric and neurological disorders used the WHO *mhGAP implementation guide* that only addresses convulsive seizures (ignores non-convulsive seizures) and suggested that task-shifting for brain disorders (including epilepsy) was feasible but did not report cost-effectiveness analyses.[62] However, the task-shifted pilot study in southern Nigeria identified only a small number of people with epilepsy,[62] probably because they did not use any active case finding methods. Our preliminary studies, consistent with others,[63] have documented that community education plus active case finding methods are essential in cultures where treatment for epilepsy is not known to be available and where the general population does not realize that epilepsy is a treatable medical condition.[15,39,64] Based upon our discussions with Ministry of Health officials and local health leaders, demonstration of task-shifted epilepsy care efficacy and data on implementation strategies and cost-effectiveness of task-shifted epilepsy care are essential for African health authorities to consider large-scale task-shifted epilepsy care implementation.

2.2.6. Strategically located, designed, staffed, and organized to optimize generalizability of results

This first NIH-funded cRCT of task-shifted epilepsy care, ***'Bridging the Childhood Epilepsy Treatment Gap in Africa (BRIDGE)***', will be performed in a Hausa-speaking region of west Africa. Effectively diagnosing and managing epilepsy requires effective communications with patients and families in their local language, respect for local culture, and a goal of building trust and long-term relationships. The need to adapt epilepsy diagnosis- and management-related communications to local language and culture is of great importance in low-resource environments without access to physician specialists and EEG. Hausa is the third most commonly spoken language in Africa, behind only Arabic and Swahili, and is

the most commonly spoken language in west Africa;[31,65] therefore, Hausa-translated educational materials and instruments demonstrated as effective in this study can be used across other Hausa-speaking populations. This project is located in the largest population of children in a Hausa-speaking area and allows BRIDGE to generalize to other populations of children with untreated epilepsy. BRIDGE investigators were selected for expertise in epilepsy, clinical trials, and managing large teams. Our investigative team includes academic physicians who have previously managed other clinical trials in Nigeria, as well as large, multi-site, international clinical trials. Our team's administrative expertise and experience will enhance training and supervision of the large number of study personnel and facilitates political relationships in northern Nigeria - essential for the integration of the BRIDGE project into the large system of PHCs and key relationships with local health leaders. The methods of staffing CHWs with physicians who have also received additional epilepsy training, and these physicians receiving ongoing continuing education from epileptologists, is a model that also has the potential for scalability.

2.2.7. Random selection of PHCs (clusters) in three major Hausa-speaking cities

In our R21 project (R21 TW010899), we randomly selected 8 PHCs - one from each of 8 local governmental areas (LGAs) in Kano. Likewise, for the BRIDGE cRCT, we will randomly select 60 PHCs from three major Hausa-speaking cities [Kano (30 PHCs), Zaria (14 PHCs), and Kaduna (16 PHCs)], randomly allocating 30 of these PHCs to the task-shifted epilepsy care intervention and 30 PHCs to enhanced usual care (EUC). EUC will involve referral to a physician for epilepsy care plus primary care by an epilepsy trained CHW. Random selection of PHCs and random assignment of management protocols will allow us to perform this cRCT in a study population representative of the patients, and of the primary care system, of northern Nigeria.

2.2.8. Epilepsy diagnosis and management by CHWs

Epilepsy diagnosis traditionally involves neurologically trained physicians determining whether descriptions of paroxysmal events are consistent with epilepsy - long-perceived as too difficult for CHWs. Therefore, many epilepsy studies in African LMICs, and WHO recommendations, have essentially ignored the presence of more difficult to diagnose non-convulsive epilepsy,[43,66-69] which constitutes a large percentage, or even the majority,[70] of childhood epilepsy. We have (a) developed and piloted a successful and scalable childhood epilepsy training program for CHWs,[32] (b) modified an epilepsy diagnosis and seizure classification tool to ascertain convulsive and non-convulsive seizures,[27] (c) validated the tool used by CHWs in Hausa,[29] (d) piloted the screening and diagnosis of children with epilepsy by CHWs according to a standard protocol, and (e) piloted the enrollment of children with untreated epilepsy, including non-convulsive epilepsy, into a task-shifted childhood epilepsy management protocol. We will utilize the validated tool and this successful CHW training protocol in the current study.[27]

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The drug regimens and general epilepsy care services provided in this study are standard of care in northern Nigeria, with indications and doses long approved for use in Nigeria. Phenobarbital, carbamazepine, valproate and phenytoin are listed on the World Health Organization (WHO) Essential Drug list. We anticipate that phenobarbital, carbamazepine, and valproate will be first-line drugs used in this cRCT. (Levetiracetam has become a first-line drug for epilepsy in the US because it is broad-spectrum (effective against all seizure types), easy to dose, does not interact with other drugs, does not bind to plasma proteins, and has a good safety profile. CHWs have been trained in the prescribing and management of phenobarbital, carbamazepine, valproate, and levetiracetam. Levetiracetam may become more available and become a first-line drug for epilepsy in Nigeria during the course of this cRCT.

A minority of children with epilepsy fail to respond to commonly used anti-epileptic drugs (AEDs). In Nigeria some of these children may be referred to specialists, who will recommend treatment with AEDs that are approved as standard of care but are less commonly used. A minority of children in the EUC and in the task-shifted arms of this study might fail the commonly used AEDs noted above and may be prescribed other AEDs by specialists. Although CHWs in the task-shifted arm of the cRCT will be trained to prescribe and manage only commonly used drugs without physician consultation, they will not be trained to manage AEDs other than phenobarbital, carbamazepine, valproate, phenytoin, and levetiracetam. CHWs in the task-shifted arm of the cRCT are required to consult supervising physicians if routine AEDs are not effective, and these supervising physician specialists may provide detailed direction and oversight regarding dosage and management of less commonly used AEDs via CHWs in the task-shifted arm. Similarly, physicians who manage children in the EUC arm of the cRCT are free to consult with any specialist they routinely refer to in their practice.

<u>Potential Risks to Subjects</u>

- In spite of all appropriate safeguards, an unintentional violation of confidentiality is possible.
- Error in diagnosis or in medical treatment decision-making may occur in either arm of the cRCT. Based upon our preliminary data from our R21 pilot data, we do not expect higher rates of misdiagnosis among epilepsy trained CHWs, but this cRCT will have a substantially larger sample size. It is possible that there is a higher risk of error in diagnosis or medical treatment decision making by physicians or by CHWs with additional training in childhood epilepsy.
- No investigational treatments will be given to any study subjects. All medications prescribed by CHWs in the task-shifted intervention arm are routinely prescribed and routinely available in northern Nigeria. However, all medication has risk, and participants will be educated regarding potential side effects and other adverse events that may occur.

Epilepsy in many communities is associated with *stigma*,[2,26,38-40,44,71] and yet epilepsy-associated stigma in Kano has not been considered as major a problem as the very large number of children with epilepsy who do not receive care because of lack of epilepsy care access. Psychiatrists at Aminu Kano Teaching Hospital (AKTH) with expertise in stigma associated with epilepsy provide epilepsy education as part of their routine epilepsy care practice, and this education has been incorporated into the case studies incorporated into the education provided to CHWs in both arms of this cRCT.[32] The CHWs working with this project will receive additional training in epilepsy education by the physician epilepsy specialists, including discussions of stigma and misinformation about causes, treatment, and living with epilepsy. CHWs will likewise use this knowledge to educate their patients as part of their routine care. We do not expect additional psychological or social harms to occur, and we hope that by participating in the study, some study subjects, if not all, will have access to expert epilepsy care not typically available in northern Nigeria.

2.3.2 KNOWN POTENTIAL BENEFITS

Participants in both the intervention arm and the EUC (control) arm will benefit from epilepsy trained CHWs providing medical care to children with epilepsy. We do not know whether clinical outcomes vary by whether childhood epilepsy management (diagnosis and treatment) is performed by a community physician (as in the EUC arm), or by an epilepsy-trained CHW (as in the task-shifted arm) - a key question driving this clinical trial.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Epilepsy-associated mortality is common in Africa, and this risk is higher among children with epilepsy who are not receiving treatment. Patients' risks from participating in research will be kept to a minimum with measures to protect confidentiality and planned interim analysis for safety and the primary outcome. Trained health care professionals will perform all standard care and research procedures. Additionally, all sites will have designated and trained study staff working with participants. Blinded physicians will monitor study subjects, objectively monitoring their seizure outcomes and safety measures.

Steps to protect privacy will include assignment of study codes to all records, without patient names, with the key for connecting patient names and study codes kept in a secure site separate from the study records at the local site only. All study records will be kept in a secure locked location to prevent unauthorized access. In the opinion of the BRIDGE investigators, the potential benefits of the BRIDGE project, including knowledge that can impact the treatment of very large numbers of children with epilepsy throughout Africa's LMICs, and improved access to epilepsy care by specially trained health professionals, far outweigh the risks.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Percentage of children in each arm of the cRCT who are seizure free.	Seizure-free for six or more months at the 24-month follow-up visit.	Seizure-freedom for six or more months when followed for 24 months likely identifies the response to established treatment performed by the healthcare provider. Seizure-freedom for six or more months, in the opinion of the Kano-based investigators, is also associated with a resumption of usual pre-epilepsy activities of daily living.
(a) diagnostic accuracy; (b) 75% reduction in seizure frequency; (c) First AED response; (d) Mortality; (e) Status epilepticus; (f) Morbidity; (g) AED adverse events; (h) time to next seizure after 3 months of seizure freedom; (i) Diagnostic tests ordered.	(a) Diagnostic accuracy among study subjects in the task-shifted arm (TS) compared to the Enhanced Usual Care (EUC) arm, as determined by blinded physicians; (b) 75% reduction in seizure frequency at 24 months follow-up over the prior six months compared to the estimated seizure frequency at enrollment; (c) Seizure-freedom with first AED selected by the treating healthcare professional; (d) Mortality during the cRCT; (e) Status epilepticus during the cRCT; (f) Morbidity, including neurodevelopmental morbidity, associated with epilepsy that emerged during the cRCT; (g) AED adverse events, cumulative over the entire cRCT; (h) Time to next seizure after a study subject is seizure-free for three months,	(a) Blinded physicians with expertise in epilepsy will evaluate children in the cRCT at 1 month, 6 months, 12 months, 18 months and 24 months after enrollment. Diagnostic accuracy of epilepsy-trained CHWs, compared to physicians is important for eventual policy decisions regarding taking task-shifted epilepsy care to scale. (b) 75% reduction in seizure frequency compared to enrollment baseline is typical for RCTs in epilepsy. (c) Measuring seizure-freedom with the first AED selected may be a surrogate measure of the healthcare provider's ability to choose medications and manage medications. (d) Differences in mortality between the arms of the cRCT that cannot be explained by potential differences in severity of epilepsy syndromes, may be an important distinction between the two cRCT arms. (e) Differences in frequency of status epilepticus among children enrolled in the two arms of the cRCT may be a measure of effective epilepsy management. (f) Differences in new epilepsy-associated morbidity, including neurodevelopmental morbidity associated with epilepsy, is an important measure. (g) Differences in the frequency of AED adverse events may be a surrogate measure of the skill of the healthcare professional. (h) Time to next seizure after a period of seizure freedom for three months is a measure of ongoing epilepsy management. (i) Differences in diagnostic tests ordered may have an impact on costs of task-shifted care compared to enhanced usual care.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	(i) Diagnostic tests (EEGs, MRIs) ordered.	
CHWs adherence to the task-shifted protocol	CHWs adherence to the task-shifted protocol in the task-shifted arm.	Adherence to protocol will be a key factor in potential implementation of the task-shifted protocol on a larger scale.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The basic framework of these studies is a cRCT in which 60 PHCs (clusters) will be randomly selected from about 399 eligible PHCs in three major cities in the Hausa-speaking areas of northern Nigeria - 30 of about 167 PHCs in Kano, 15 of about 124 PHCs in Kaduna, and 15 of about 108 PHCs in Zaria. Half of the overall PHCs will be randomly assigned to the task-shifted care arm of the cRCT - 15 of 30 PHCs in Kano, 8 of 15 PHCs in Kaduna, and 7 of 15 PHCs in Zaria (Figure 1 or Schema in section 1.2).

1. Approximately 1530-1800 (target of 1730) children with epilepsy (CWE) will be enrolled across 60 sites, approximately 765-875 CWE at intervention/task-shifted sites and approximately 765-875 CWE at EUC/control sites. **This cRCT is not a clinical trial of a drug(s), but rather a cRCT of a system of epilepsy care (task-shifted epilepsy care) designed to use routinely available anti-epileptic drugs (AEDs) in northern Nigeria. There are no study drugs; AEDs used by health care providers in each arm of the cRCT will be standardly available AEDs used as part of standard epilepsy care in northern Nigeria. CHWs are routinely able to prescribe and manage phenobarbital and carbamazepine in current clinical practice. This cRCT, like our pilot in task-shifted care, will be approved by the Ethics Committee of the state Ministry of Health (MOH) for the CHWs to prescribe and manage phenobarbital, carbamazepine, valproate, and levetiracetam according to our standardized protocol with physician supervision (Figure 2 and Appendix F).** CHWs will also be trained to prescribe and manage phenytoin. The primary outcome in this non-inferiority cRCT will be the percentage of children seizure free in each arm of the study, defined as seizure-free for ≥ 6 months at the 24-month follow-up visit. The secondary outcomes determined by neurologists blinded as to whether the CWE are in the task-shifted/intervention arm or EUC/control arm of the cRCT trial will include the diagnostic accuracy of the CHWs versus the physicians, 75% reduction in seizure frequency, response to the first AED selected (a surrogate measure of the selection and management of the first drug), seizure-associated mortality, AED adverse events, hospital admissions, EEGs, and other diagnostic tests ordered. In addition, CHW adherence to the task-shifted protocol will be measured for the task-shifted care sites (Figure 1), by comparing the protocol to CHW management by the data coordinating center (DCC) investigators and the PIs. The socio-behavioral and implementation outcomes among providers, parents/guardians and patients in the cRCT (Aim 2) and the cost-effectiveness of the task-shifted intervention (Aim 3) will conducted in the context of the cRCT five-year timeline (see Appendix A.).

Location and role of institutions and Principal Investigators (PIs)

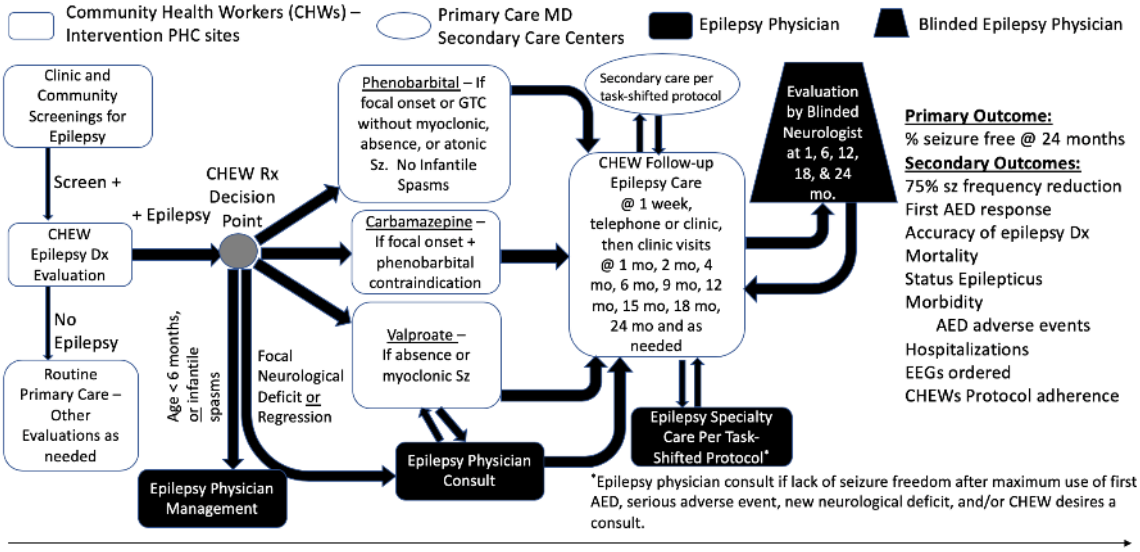
All study subjects will be recruited among children in the northern Nigerian cities of Kano, Zaria, and Kaduna. **Aminu Kano Teaching Hospital (AKTH) in Kano**, Nigeria will serve as the study's institution in Kano, where one-half of the study clusters (PHCs) are located. Dr. Aminu Taura Abdullahi, the study Multi-PI based at AKTH in Kano, will have overall responsibility for the day-to-day operations and staff of the BRIDGE study in Kano. Dr. Abdullahi and the AKTH-based staff will also have responsibility for

managing subcontracts to sites in Kaduna and Zaria, as well as data management, software support, and hardware support for the study staff at all of the study sites.

Dr. Hafsat Ahmad is the co-investigator and Zaria site lead with day-to-day responsibility for Zaria BRIDGE operations; Dr. Ahmad is based at **Amadu Bello University in Zaria**. Dr. Ahmad will be directly responsible for the study staff and operations in Zaria and report to Drs. Abdullahi and Trevathan regarding the BRIDGE operations. Dr. Folorunsho Nuhu is the co-investigator and Kaduna site lead with day-to-day responsibility for Kaduna BRIDGE operations and is based at the **Federal Neuropsychiatric Hospital in Kaduna**. Dr. Nuhu will be directly responsible for the study staff and operations in Kaduna and report to Drs. Abdullahi and Trevathan regarding the BRIDGE operations.

Dr. Edwin Trevathan, the BRIDGE PD/Multi-PI, has responsibility for the overall operations of the BRIDGE studies and is based at Vanderbilt University Medical Center in Nashville, Tennessee, USA. Dr. Trevathan has responsibility for the **BRIDGE Data Coordinating Center faculty and staff located at the Vanderbilt Institute for Global Health (VIGH)**. Dr. Trevathan with Dr. Abdullahi, who is responsible for the day-to-day operations of the Nigeria-based faculty and staff, are responsible for the overall BRIDGE project. All study subject data maintained at VIGH will be de-identified. ***The BRIDGE studies are focused on faculty and staff in northern Nigeria identifying potential solutions to major epilepsy care problems in northern Nigeria. The knowledge gained from the BRIDGE studies are intended to benefit the children and the healthcare system of northern Nigeria and will not necessarily be generalizable to the children with epilepsy in the USA. There will be no study subjects enrolled in BRIDGE studies in the USA.***

Figure 2. BRIDGE Task-Shifted Childhood Epilepsy Protocol



4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The purpose of this NIH R01 project is to test the efficacy of the World Health Organization's (WHO's) currently proposed, but unproven, recommendation to enhance access to epilepsy care among people with epilepsy who do not receive treatment (and often do not receive a diagnosis) – thereby bridging

the epilepsy treatment gap. The investigators' primary interest and expertise is in the pediatric epilepsy treatment gap, which is especially problematic in low-resource northern Nigeria, where half of the very large population is under 17 years of age.

This cRCT, with each cluster being a PHC, has been chosen as the study design as it best approximates the real-world application of the WHO's recommendation to task-shift epilepsy care to epilepsy-trained CHWs located in PHCs close to the homes of people with epilepsy.

4.3 JUSTIFICATION FOR INTERVENTION

The intervention for the BRIDGE cRCT is a task-shifted epilepsy care (to epilepsy-trained CHWs) who work in PHCs in northern Nigeria. This intervention is the specific intervention recommended by the WHO to bridge the epilepsy treatment gap. The control for this cRCT is referred to as 'enhanced usual care' (EUC) because it includes referral to any physician to whom a CHW would normally refer to for medical care (such as epilepsy), with the exception of one of the BRIDGE investigators. The usual care by a community physician is 'enhanced' for children in the EUC arm by follow-up by CHWs who are also trained in epilepsy. The follow-up visits with CHWs in both the task-shifted and the EUC arms of the cRCT ensure that standardized data regarding seizure frequency and adverse events are recorded in both arms of the study. The blinded physician evaluations serve to provide the gold standard for outcome assessments in this cRCT.

4.4 END-OF-STUDY DEFINITION

For this non-inferiority cluster randomized clinical trial (cRCT), study subjects will be enrolled for 24 months, with each study subject followed for 24 months. The follow-up period of 24 months was selected because the period of 24 months allows for a few months of initial dose escalation, as well as the potential need to change medications in order to achieve seizure control, while still having a sustained period from which to judge the management and outcomes of children with epilepsy.

The multi-PIs and the DSMB will review all serious adverse events including deaths, and the DSMB may recommend to the NINDS/NIH and the Multi-PIs that the study be ended prior to the planned date. Serious adverse events may occur which are causally unrelated to the intervention (task-shifted care to CHWs), such as serious drug reactions, status epilepticus, or sudden unexplained death in epilepsy (SUDEP). Serious adverse events determined to be causally associated with the intervention (task-shifted care), as determined by a careful review by the multi-PIs of the study, and agreed to be causally-due to the intervention, may be considered by the Multi-PIs and the DSMB as grounds for ending the cRCT prior to the planned date, in discussion with NINDS/NIH. However, these decisions will need to be made with great care and will not be possible based solely on statistical considerations for the following reasons: (a) the mortality associated with epilepsy in Africa is high, even with local standard-of-care provided by physicians; (b) epilepsy is very heterogeneous with many different seizure types and different epilepsy syndromes, each with different prognoses; and, (c) the distribution of specific epilepsy syndromes within the general population in northern Nigeria and other areas of sub-Saharan Africa is not well-described. The DSMB and the Multi-PIs will carefully evaluate serious adverse events in each

arm of the cRCT with consideration of the occurrence of serious adverse events in specific epilepsy syndromes and seizure types.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Inclusion criteria for enrollment into this cRCT are:

- Resident of Kano or Kaduna states and living in the Kano, Zaria, or Kaduna metropolitan areas of northern Nigeria
- Children ages ≥ 6 months, < 17 years
- Parent or guardian provide informed consent for the screening questionnaire given to the parent/guardian, and parent or guardian consent and assent for children ≥ 7 years able to provide assent, for epilepsy diagnostic evaluation if the screening for possible epilepsy is positive.
- Diagnosed with possible epilepsy through initial screening, and then
- diagnosed with epilepsy upon further evaluation by an epilepsy trained CHW working with the BRIDGE project, who may consult a BRIDGE physician for diagnostic questions.
- Parent or guardian provide consent, and assent for children ≥ 7 years able to provide assent, for enrollment in the cRCT of task-shifted epilepsy care versus enhanced physician epilepsy care.

Both male and female children will be included in this cRCT. Because this cRCT is being conducted in northern Nigeria, we anticipate that almost all participants will be black Africans who speak the Hausa language, and therefore representative of the local population. *No potential study participant will be excluded because of race, ethnicity, religion, gender, or sexual orientation.*

5.2 EXCLUSION CRITERIA

Exclusion criteria are:

- Children who have previously been diagnosed with epilepsy and are currently enrolled in other care and treatment, or who have been treated for epilepsy within three months prior to screening.
- Children who are currently receiving care by a neurologist or neurosurgeon for a serious brain disorder (e.g., brain tumor, stroke)
- Lack of informed consent, and/or lack of assent from children ≥ 7 years who are able to provide assent.
- Inability of the parent or guardian to communicate with healthcare providers in Hausa or English

- Any child who screens positive for epilepsy, has epilepsy upon clinical evaluation, but does not live in Kano, Zaria, and Kaduna, and who is in the judgement of the parents and/or BRIDGE staff to not able to comply with the study visits because of travel distance from home.

5.3 LIFESTYLE CONSIDERATIONS

The study procedures, documents, and educational materials are, and will be, developed with respect for the local language, culture and lifestyle.

5.4 SCREEN FAILURES

Children who screen negative for seizures or epilepsy, and children who screen positive but after clinical assessment do not have epilepsy, will not be enrolled in the study. Children who have epilepsy but who are already receiving medical care and treatment for their seizures will not be enrolled in the study.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Community Engagement Strategy

A key to our recruitment and retention for this cRCT is our community engagement strategy, which begins with the local health authorities, and then extends to community leaders and communities. Our community engagement started as a component of our R21 projects in late 2017 and continued thru August 31, 2019. We started with developing collaborative relationships with the officials in the Kano State Ministry of Health (for Kano City) and the Kaduna State Ministry of Health (for Kaduna city and Zaria). As part of our R21 work in preparation for this large cRCT, we obtained Ethics Committee Approval from the Kano State Ministry of Health and have maintained contact with the Kano State Ministry of Health officials regarding our work in Kano. Likewise, we have initiated work with the Kano state epidemiologist and have benefited from his insights regarding the area demographics and strategies for screening. We will also engage the Kaduna State Ministry of Health officials prior to launching this R01 project. The state ministries of health and the state epidemiologists have important insights regarding how to launch community relations programs, and their collaborations are invaluable.

PHCs and Wards. The cities of Kano, Kaduna, and Zaria are organized into LGAs, each of which contain approximately 8-25 wards (similar to US census tracks); each ward has approximately one PHC that is eligible for random selection for participation in the BRIDGE cRCT of task-shifted epilepsy care. Each ward has a ward leader and a community council that address local community issues.

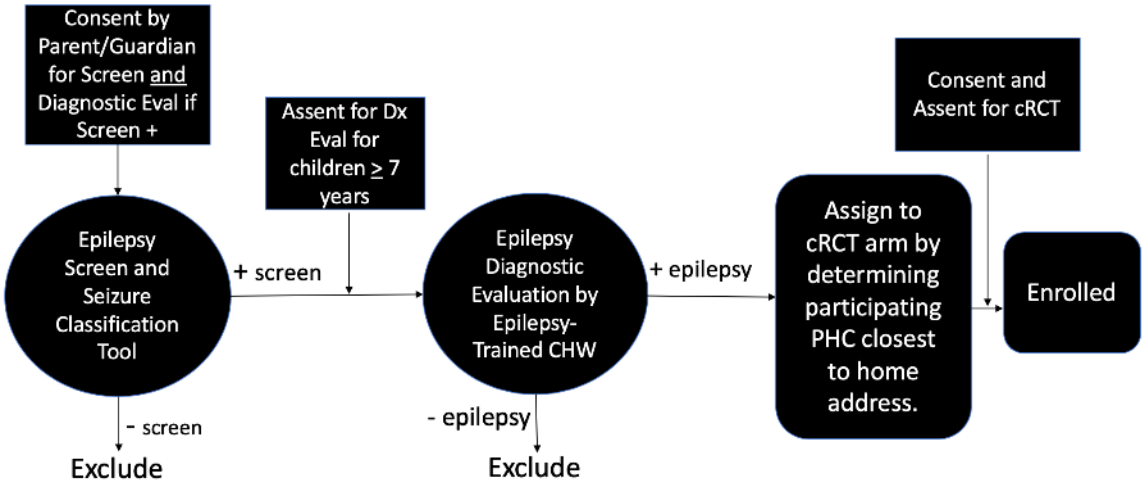
Relationships with Ward Leaders. In our R21 BRIDGE project, we reached out to ward leaders to educate them about the treatable nature of childhood epilepsy and the epilepsy treatment gap and obtained the ward leaders' support in advance of community education programs and epilepsy screening in clinics, schools, and door-to-door surveys. With the ward leaders' support, we found that the interest and trust in the community increased and there was increased receptiveness to our educational programs. Drs. Abdullahi, Sabo, Salihu, Trevathan, and Iliyasu have all met with individual ward leaders and groups of ward leaders to help launch the BRIDGE project in Kano, and we will do the same in Kaduna (with Dr. Nuhu) and in Zaria (with Dr. Ahmad).

Epilepsy Education Radio Broadcasts: Many children with untreated epilepsy in northern Nigeria, as in most areas of sub-Saharan Africa, are not known to the healthcare system. Whether through misinformation, a belief that treatment is not available, or stigma associated with informing people that a family member has epilepsy, most people with epilepsy, including life-threatening epilepsy, are not seeking treatment in northern Nigeria. After meeting with ward leaders, and before launching community education and screening events, a series of previously piloted Hausa radio broadcasts will be aired. These radio broadcasts, led by Dr. Auwal Sani Salihu (who has extensive experience with radio educational programs) will be recorded in Hausa and have a format in which Dr. Salihu introduces the topic, introduces the BRIDGE team of Nigerian physicians and CHWs, and then explains the treatable nature of epilepsy and the magnitude of the childhood epilepsy treatment gap.

Questions from the audience of parents allow for exploration of important topics related to epilepsy. The program will then air weekly for four weeks at the beginning of a series of community education events and will launch the door-to-door and pediatric clinics epilepsy screening program. During the R21 BRIDGE study, analysis of interview data from community members found that the radio broadcast helped prepare for the broader educational programs and enhanced screening efforts.

Screening and Recruitment of Study Subjects. In northern Nigeria, the CHWs are traditionally women, as women caring for children at home generally feel most comfortable only speaking with other women during the day. Following informed consent of the parent/guardian for epilepsy screening and a diagnostic evaluation for the child if the child screens positive, the previously-validated Hausa epilepsy screening and seizure classification tool[29] will be administered to the parent/guardian, who will answer screening questions regarding all of her children ages ≥ 6 months and < 17 years (Figure 3; see Appendix B). When a parent/guardian's child screens positive for epilepsy, assent will be obtained from children > 7 years who are able to provide assent, and then the child will undergo an evaluation by the epilepsy-trained CHW to determine if the child has epilepsy and whether the child's epilepsy is currently untreated. Parents/guardians of children with untreated epilepsy will receive additional verbal and written educational material on epilepsy and be offered consent for their child's enrollment in the BRIDGE study. Educational materials are available in English or in Hausa.

Figure 3. Screening and Enrollment of Study Subjects



The home addresses for children with untreated epilepsy will be determined with the aid of laminated satellite maps of the area where the parent/guardian can indicate. The participating PHC closest to each child with untreated epilepsy will be determined. If the closest participating PHC was previously randomly assigned to EUC, then the consent offered to the parent/guardian will be for the EUC arm of the cRCT with follow-up at the closet participating PHC. If the closest participating PHC was previously randomly assigned to task-shifting, then the consent offered to the parent/guardian will be for the task-shifted arm of the cRCT with follow-up at the closet participating PHC (figure 3).

Parents/guardians of children who are enrolled in the task-shifted care intervention of the cRCT will be given a schedule for study visits with a CHW and visits with the study (blinded) neurologist for their city. Parents/guardians of children who enroll EUC/control arm of the cRCT will be referred to a physician for epilepsy care (the usual practice of that PHC), and given a schedule of study visits for primary care with an epilepsy-trained CHW at a study PHC, plus blinded neurologist evaluations (see figure 2).

In addition to screening and recruiting study subjects in door-to-door surveys, children will also be screened in pediatric clinics. Door-to-door surveys will ensure that the immediate neighborhoods around the participating PHCs are included. In communities where epilepsy screening at local schools is supported by ward leaders and school leaders, we will initiate screening and study enrollment at local schools close to the participating PHCs - an efficient way to screen and enroll.

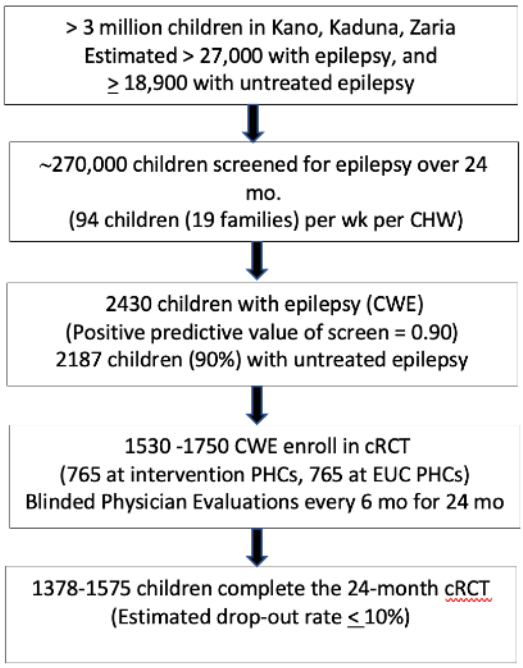
Often, the mother will consent to enrolling in task-shifted care for her child's epilepsy during the initial discussion regarding the study. The enrollment decision may also include the mother consulting with her husband and/or family members, plus another CHW visit to the family home for discussions regarding epilepsy and epilepsy treatment with the father and/or other family members. Developing trust in a healthcare professional is essential in the Hausa culture, and may take time.

Determined by a combination of the power/sample size calculations, the capacity of the available clinical investigators, the budget for this NIH-funded project, our preliminary data in screening, and diagnosing and enrolling patients into a feasibility study, we have determined that approximately 120-130 epilepsy-trained CHWs (50% effort, or more, each) will screen up to about 270,000 children for possible epilepsy over 24 months; based on preliminary data we anticipate that 1% (2700) will have a positive screen for epilepsy, of which 2430 will be diagnosed with epilepsy after clinical evaluations, of which 1700 will have untreated epilepsy. We have also determined, based upon our pilot project funded by the R-21 grant, that recruiting and training 120-130 CHWs across three cities (Kano, Zaria, and Kaduna) is feasible. Based on our preliminary experience with enrolling patients in a task-shifted care pilot, we anticipate the following (Figure 4):

- ~ 1530 to 1800 (target enrollment 1730) children with untreated epilepsy will enroll in the study over 24 months (this may be an underestimate, given that our rates of consent in our pilot study and other studies in northern Nigeria have all exceeded 90%).

- ~ 1378 to 1575 of 1730 (maximum 1800) enrolled children will complete the cRCT (a conservative estimate of 10% drop-out rate, higher than in prior studies in northern Nigeria)
    - If 1378 children (23 children per PHC, 30 PHCs per arm) complete the 24-month follow-up period, we will have 83% power to rule out a non-inferiority margin of ≥ 10% in the seizure-free proportions in each arm (assuming ~ 60% of children in each arm will be seizure-free).
    - If 1140 children (19 children per PHC, 30 PHCs per arm) complete the 24-month follow-up period, we will have 80% power to rule out a non-inferiority margin of ≥ 10%.
- Therefore, conservative estimates based upon current rates of screening recruitment targets are calculated as shown below (assuming 1% positive screen rate; predictive value positive of screen = 0.9; treatment gap of 60%; rate of enrollment is 90% of eligible).

Figure 4. Patient Recruitment into Cluster RCT



We know, based upon our preliminary studies, that we can achieve a higher positive screening rate by screening more in primary care and specialty care clinics, where unfortunately there are children with untreated epilepsy, than in neighborhood door-to-door surveys. Therefore, screening in pediatric clinics may be emphasized if the rate of enrollment drops below what is deemed appropriate to meet study timelines. The pediatric clinics where epilepsy screening will be performed receive patients from all of a city, making over-representation of patients from neighborhoods around a single PHC highly unlikely.

We also plan work with local schools to invite parents to bring their children to the local school to be screened on weekends, or after-school hours - a method that has been productive in other studies in Kano and Zaria.

- Year 1 of enrollment
    - Each CHW enrolls 9 children with epilepsy in the first year

- First year total enrollment is therefore 18 per PHC at 60 PHCs = 1080 children
    - 5 children enrolled per PHC per month (<1 child enrolled per CHW per month)
    - At any time in the first year, the Multi-PIs may decide to shift the emphasis of screening to pediatric clinics in the participating hospitals, where we have found the prevalence of children with epilepsy (and of untreated epilepsy) to be higher than in door-to-door surveys.

- Year 2 of enrollment:
    - The number of children identified in door-to-door surveys with untreated epilepsy may decrease due to coverage of much of the areas closest to the PHCs with prior screening. Therefore, in Year 2, if behind in enrollment, or if drop-out rates exceed the expected 10% over 2 years, we will begin to screen for children with untreated epilepsy in the pediatric clinics at major hospitals in the participating cities where the prevalence of untreated epilepsy is higher).
    - CHWs will spend slightly less time screening in the community as they will need to follow the patients who have been enrolled.
    - Second year total enrollment is estimated at 10 children per PHC at 60 PHCs = 600 children
    - **Total estimated enrollment over 2 years is at least 28 per PHC (or 0.6 enrolled study subjects per 0.5 FTE CHW per month) ~ 1680-1800 (target 1730)**

      Children completing 24-month study ~ 1378-1575
        - **Minimum children completing the 24-month study ~ 1140**

Enrollment Targets

- Enrollment target for Year 1 is at least 1.5 children per PHC (0.75 children per 0.5 FTE CHW) enrolled per month
- Enrollment target for Year 2 may be modified based upon the progress in the first year, but will probably be 0.8 children per PHC enrolled per month.
- For the qualitative data collection for Aim 2 (socio-behavioral and implementation outcomes) we will recruit 30 (of 120) CHWs and all physicians involved with the study, as well as a sample of 60 parents of children enrolled in the task-shifted intervention arm of the cRCT for qualitative interviews. The same principles of recruitment and retention for the cRCT apply to the recruitment and retention for these components of the study.

Barriers to enrollment: About 90% of children with untreated epilepsy who were offered enrollment in the task-shifted feasibility study enrolled in the task-shifted feasibility study. About a third of those who

refused to enroll did so because they believed that epilepsy is a spiritual disorder that medicine could not help. Others state problems with local travel, stigma, or other reasons. Financial issues may also cause families to not seek care for their children. Medications available for treatment of epilepsy (e.g., phenobarbital, carbamazepine, valproate) tend to be relatively inexpensive, especially phenobarbital and carbamazepine which are the most commonly used. However, for some families, the cost of medication in this low- to middle-income country is a barrier.

During the pre-clinical trial studies, a donor in Nigeria was identified who helped pay for medication for children whose families were unable to pay for medication. Outside of the study budget, if donor funds become available to pay for medication for children, or if free medication becomes available for children whose families are not able to afford medication, such funding (or free medication) will be equally available for children in each arm of the cRCT.

Breaking down barriers to enrollment: In our preliminary studies, including qualitative analysis of focus groups, we found that an important factor that encourages enrollment is the mother's trust in the CHW, as well as the information the CHW provides (reinforced by the radio broadcasts) indicating that epilepsy is a treatable medical problem.

Long-term, we will encourage the ministries of health to consider our cost-effectiveness analyses in this study to make decisions regarding payment for routine AEDs, consistent with our Aim 3 goals.

Retention Strategies

In our experience, once families in northern Nigeria understand that their child's epilepsy is a medically treatable condition, they tend to be compliant with medical care. The drop-out rates in our feasibility study of task-shifted epilepsy care are consistent with the sickle cell-stroke prevention clinical trials in Kano that have experienced drop-out rates of much less than 10%. Helpful strategies for retention that we have used in prior studies will continue to be used in the BRIDGE cRCT and include the following:

(a) Our long-term interest and commitment to the patient is emphasized in the context of the enrollment into the cRCT, as well as the information that epilepsy is a treatable condition. We will explain that some epilepsy cases are difficult to treat, but that most children with epilepsy can be effectively treated with significant reduction in seizure frequency, or even seizure freedom.

(b) Clearly explain, and reinforce with written materials and videos in Hausa, the schedule and expectations of the study. We are planning educational videos for mothers, recorded by a Hausa female health professional, whom we believe that the mothers will identify with and trust.

(c) We will obtain the names and the cell phone numbers, if available, of several family members, neighbors, and other community contacts. If a child in either arm of the study does not show up for a follow-up visit with a CHW, then the CHW will follow up via phone call and/or home visits to arrange for a clinic appointment.

(d) Small inexpensive tokens of appreciation for participating in the study (e.g., birthday cards for enrolled children).

(e) Study newsletters will be produced quarterly in Hausa to inform the participants and the community regarding the progress in the study.

(f) For families who have difficulty with local travel to appointments, we will aid with local travel equally for children enrolled in both the intervention arm (task-shifted care) and Enhanced Usual Care arm.

(g) For prolonged visits (e.g., visits at 6, 12, 18, and 24 months when there are blinded physician exams and Aim 2 questionnaires) we will provide lunch for the child and parent/guardian.

(h) Effort will be made to provide families with information regarding where routinely used and approved anti-epileptic medication can be obtained; this service will be provided for families of children in each arm of the study in order to provide equal medication access to study subjects in each arm of the cRCT.

Recruitment and retention strategies will be reviewed every three months and may be enhanced or modified as needed, with approval by the IRBs/ethics committees.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

The study intervention is the task-shifted childhood epilepsy care to epilepsy-trained community health workers (CHWs), and the protocol that they follow in an effort to increase access to epilepsy diagnosis and epilepsy care and to bridge the childhood epilepsy diagnosis and treatment gap in Africa (figure 2). The access to epilepsy diagnosis should not be unequally distributed to one group of PHCs compared to another and should not be unequally distributed between the two arms of the cRCT.

6.1.2 ADMINISTRATION AND/OR DOSING

There is no investigational drug or investigational treatment for this cluster randomized clinical trial (cRCT). All treatments are routine standard of care in northern Nigeria.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Epilepsy Education for Community Health Workers
Preliminary Experience from BRIDGE R21 funded period. A four-month epilepsy training program for CHWs was developed and piloted in Kano among 20 CHWs using a 'flipped classroom' pedagogy with 30 brief (10-15 minute) video lectures, plus 30 small group activities (up to 60 minutes each) that reinforced each lecture topic. All CHWs received tablet computers loaded with the video lectures and other educational materials to facilitate frequent review and reinforcement of concepts during the supervised clinic experiences. The following key topics were included in the program.

- functional cortical neuroanatomy
- vascular neuroanatomy/stroke
- neurological exam
- seizure types, epilepsy syndromes, febrile seizures
- causes of seizures and epilepsy
- anti-epileptic drugs (AEDs)
- non-epileptic events and non-epileptic seizures

- co-morbid conditions associated with epilepsy
- status epilepticus seizure/epilepsy prognosis
- women's reproductive health and epilepsy
- cerebral malaria, bacterial meningitis, viral encephalitis, TB meningitis
- stigma associated with epilepsy
- depression

After the 1-2 weeks of video lectures and group activities, CHWs evaluated and treated patients with possible epilepsy in clinics while supervised by physicians with epilepsy expertise. CHWs were trained in administering the validated childhood epilepsy screening questionnaire in Hausa. Assessments included pre- and post-education focus groups of CHWs and post-course tests of essential epilepsy knowledge. Eighteen of 20 CHWs in Kano who enrolled successfully completed the course.

During the pre-clinical trial studies, the 18 CHWs who completed the training program, using the epilepsy screening and seizure classification tool and their clinical epilepsy knowledge, scored ≥ 80% on exams that required them to (a) correctly diagnose and classify seizure types and epilepsy syndromes based upon historical and clinical data, with an emphasis on recognition of seizures versus non-epileptic events (e.g., breath holding spells); (b) classify focal onset seizures versus primarily generalized seizures and identify epilepsy syndromes that might be associated with seizure exacerbation with carbamazepine or phenytoin (e.g., juvenile myoclonic epilepsy); (c) demonstrate an understanding of and ability to follow basic epilepsy diagnosis and management protocols.(14) Post-course focus groups of CHWs documented understanding of the childhood epilepsy burden, use of epilepsy educational materials, and social needs of people with epilepsy.

Implementation of Epilepsy Education for CHWs for the cRCT

Drs. Trevathan, Abdullahi, Salihu, Sabo, and Adamu will train the BRIDGE epilepsy physician specialists (except for the blinded physicians) to administer the epilepsy course for CHWs, using the series of previously piloted video lectures and group activities. Approximately 140 CHWs will begin the Childhood Epilepsy Training Program in Kano, Kaduna, and Zaria. After the initial two weeks of classroom activities, the CHWs will have 12 weeks of supervised epilepsy clinic experience under physicians with epilepsy expertise, plus weekly additional educational sessions and group activities on epilepsy diagnosis and management. Epilepsy-trained CHWs who are not among the 120 CHWs initially hired for this project will have potential opportunities to cover for CHWs during illnesses and other time away from work and will be offered opportunities for continuing education.

Training of CHWs, supervising physicians, blinded physicians, and study staff in the BRIDGE protocol

Training in the details of the BRIDGE protocol will be performed throughout the first six months of the BRIDGE funded period, and then for the following groups of study personnel; (a) epilepsy-trained CHWs, (b) physicians supervising CHWs in the task-shifted arm of the cRCT, (c) blinded physicians (physicians

performing assessments of study subjects who are blinded as to whether children are receiving the intervention (task-shifted epilepsy care) or control (local physician care enhance by follow-up by CHWs who do not alter medication; EUC); and other study staff based in Kano, Kaduna, Zaria and Nashville. Periodic training of the study CHWs, physicians, and staff will be conducted monthly.

Some of the training in the BRIDGE protocol will include all study employees in northern Nigeria together (or all employees in a specific city) in order to help study staff understand the roles of the other members of the BRIDGE team. However, the blinded physicians will only be trained in their group of blinded physicians, under the direct supervision of Dr. Auwal Sani Salihu and Dr. Aminu Taura Abdullahi. The blinded physicians will *not* interact with the other study staff, other than the PIs and Dr. Salihu. CHWs from both arms of the study may assist with appointments of their study subjects (from both arms of the cRCT) with the blinded physicians, but blinded physicians and study CHWs will not discuss patient care. All study staff, and the parents of children enrolled in the study, will be instructed to carefully avoid discussing the arms of the study with the blinded physicians.

Tracking of adherence to the study protocol will be the responsibility of the data coordinating center staff at Vanderbilt, interacting daily to weekly with the PIs in Kano, Zaria, and Kaduna and with the BRIDGE study staff based in Kano working under Dr. Aminu Taura Abdullahi.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomized Selection of Clusters (Primary Health Care Centers, PHCs)

From about 399 eligible PHCs, 60 will be randomly selected [Kano (30 of 167 PHCs), Kaduna (16 of 124 PHCs) and Zaria (14 of 108 PHCs)] to participate in the cRCT. Criteria for a PHC being included in the random selection are (1) location in one of the wards of the urban local government areas (LGAs) in Zaria, Kano, or Kaduna cities, and (2) offering of basic maternal and child health services, with at least one full-time CHW currently employed. PHCs will be randomly selected within each LGA, assuring a relatively equal distribution of participating PHCs across the study area. Steps for the random selection will be as follows.

- Random selection of PHCs will be performed within wards which are within local government areas (LGA) to assure distribution of PHCs across the cities.
- The wards within each LGA will be listed in a numerical order and assigned a number (e.g., 1 through 15 or the total number of wards in the LGA), and then using random number generation wards from that LGA will be randomly selected for a total of 30 wards in Kano, 15 in Zaria, and 15 in Kaduna.
- Then if there is more than one PHC in the selected wards, PHCs be assigned numbers and then one PHC within each randomly selected ward will be randomly selected by random number generation.
- The selected PHCs (30 PHCs in Kano; 15 PHCs in Kaduna; and, 15 PHCs in Zaria) will be designated as “study PHCs”.

Preliminary data: Eight PHCs were randomly selected from 167 PHCs in Kano - one from each of Kano city's eight LGAs. This selection method ensured that randomly selected PHCs were distributed across the entire city and not clustered together. The leadership of all eight participating PHCs agreed to CHW epilepsy training and to allow their respective PHCs to participate in a pilot study of the task-shifted childhood epilepsy protocol.

Random assignment of clusters (study PHCs) to task-shifting vs. EUC

Fifteen of 30 study PHCs in Kano will be randomly assigned (using random number generation) to task-shifted care (intervention) and the other fifteen study PHCs in Kano will be assigned to EUC (control). Eight of the fifteen study PHCs in Kaduna will be randomly assigned (using random number generation) to task-shifted care (intervention) and the other seven study PHCs in Kaduna will be assigned to EUC. Seven of the fifteen study PHCs in Zaria will be randomly assigned (using random number generation) to task-shifted care (intervention) and the other eight study PHCs in Zaria will be assigned to EUC. Therefore, within the BRIDGE cRCT there will be thirty task-shifted clusters (study PHCs) - 15 in Kano, 8 in Kaduna, and 7 in Zaria. There will be thirty EUC clusters (PHCs) in the BRIDGE cRCT - 15 in Kano, 7 in Kaduna, and 8 in Zaria.

Objective Assessment of Outcomes by Blinded Physicians with Expertise in Epilepsy

At month 1 and then at 6, 12, 18, and 24 months after enrollment, every child enrolled in the cRCT (both arms) will be evaluated by an epilepsy-trained physician who has no other role in the cRCT; this blinded physician will evaluate each child's seizure frequency, AED selection and dosing, potential AED-related adverse events, and monitoring of the child's neurological deficits and developmental problems (if any). The blinded physician's evaluations will be recorded on standardized case report forms (CRFs) in REDCap and uploaded to the data coordinating center at Vanderbilt (Figure 2). Parents/guardians of enrolled patients in both arms of the cRCT will maintain written seizure diaries, recording frequency and duration of seizures and documenting medication administration; the seizure diaries will be evaluated by providers at all visits, data will be entered into the CRFs, and photographs of the seizure diaries will be retained as part of the study records. The blinded physician evaluations will not be interventions but are rather a method of objective recording of clinical data.

Blinded physicians will be directly supervised by a senior epileptologist BRIDGE co-investigator, Dr. Auwal Sani Salihu, whose primary responsibility for the cRCT will be to supervise the four blinded physicians (two in Kano, one in Zaria, and one in Kaduna). The blinded physicians will be directly trained in the protocol by Drs. Trevathan, Salihu and Abdullahi. Blinded physicians will meet on a regular basis as a group with Dr. Salihu and will not meet with the other study staff in order to help facilitate the blinding of the study outcomes.

The only study personnel who are blinded as to allocation of either task-shifted care or enhanced usual care (EUC) are the blinded physicians; the blinded physicians are the only study personnel who have the potential to alter the primary outcome data. Blinding other study personnel is not possible, extremely difficult, and/or counterproductive. Allocation to task-shifted care versus EUC is determined by the study subjects' home address and the closest primary healthcare center (PHC), which are objective fixed

values that cannot be altered or influenced. The case report forms (CRFs) for the CHWs at task-shifted care sites are different from CRFs for CHWs from EUC sites - details that all analyzing the data and managing data will need to observe. For example, the task shifted CRFs for CHWs include details about drug prescribing by the CHWs, while the CRFs for CHWs at EUC sites do not contain details of how CHWs prescribe drugs. Therefore, only the blinded physicians will be blinded as to intervention allocation.

If a blinded physician notices serious concerns regarding a child's medical condition or treatment that she/he believe poses a risk to the child, then the blinded physician will so note in the her/his CRF for that child, and also discuss with the blinded physician supervisor, Dr. Salihu. Dr. Salihu will then review the concern with Dr. Abdullahi, the Multi-PI in Nigeria. The same concerns may have been raised by the DCC for a child in either arm of the study upon review of CRFs, and/or by the supervising physicians in the task-shifted arm of the study. If the child's welfare and safety cannot be addressed within the study, the child will be withdrawn from the study and Dr. Trevathan (with Dr. Abdullahi) will report such as an AE or SAE to the DSMB.

Second-Level or Second Opinion Blinded Physician Evaluations Regarding Epilepsy Diagnosis and Classification of Seizure Type and Epilepsy Syndrome. Even among physician with expertise in epilepsy, the diagnosis of epilepsy is difficult, is based upon skillful history taking, and may require re-evaluations and sometime second opinions from colleagues. Therefore, the BRIDGE cluster randomized clinical trial has made provision for second-level (or second opinion) blinded physician evaluations of children. Two situations may trigger a second-level blinded physician evaluation on a particular child: (1) a blinded physician requests a second opinion because of he/she is uncertain regarding the diagnosis, seizure classification, or another epilepsy-related issue considered of importance in order to maintain safety for the enrolled study subject; and/or, (2) the blinded physician makes a diagnosis of "no epilepsy" or is uncertain as to whether the enrolled child has a diagnosis of epilepsy. The second-level blinded physician evaluation will be conducted by an expert in pediatric epilepsy, with the cost covered by the BRIDGE study. If the second-level blinded physician determines that an electroencephalogram (EEG) would help make a diagnosis on an enrolled study subject, then an EEG will be performed and the results of the EEG will be used by the blinded physicians to arrive at a final diagnosis. If there is a disagreement between the two blinded physician diagnoses, then the blinded physicians will meet to discuss and develop consensus regarding the diagnosis. If the blinded physicians who have evaluated the child are unable to come to an agreement regarding the diagnosis, then all of the BRIDGE site leads (Drs. Aminu Taura Abdullahi, Hafsat Ahmad, and Folorunsho Nuhu) plus Dr. Umar Sabo (pediatric neurologist) will meet to review the data and will develop a consensus regarding the diagnosis.

Children who are determined by the second-level blinded physicians to not have epilepsy will be withdrawn from the BRIDGE clinical trial in terms of final seizure-related outcomes. However, outcomes related to diagnosis will be compared in the two arms of the study. Parents of children enrolled in the task-shifted arm of the study will be notified by the community health workers (CHW) and/or CHW supervising physicians if the final diagnosis of an enrolled child is that the child does not have epilepsy. The community physicians caring for children in the enhanced usual care (EUC) arm of the study will

likewise be notified if a final blinded physician evaluation finds that the child does not have epilepsy by the site/city lead or principal investigator.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Study subjects will each be assigned a unique BRIDGE study number, which will identify them to BRIDGE study staff. Study subjects will not be able to cross over from the task-shifted intervention PHC sites to the EUC sites and vice versa.

6.5 CONCOMITANT THERAPY

6.5.1 RESCUE THERAPY

The BRIDGE cluster randomized clinical trial (cRCT) is not a drug trial, and so there is no concomitant therapy in the traditional sense. However, the protocol allows for medical problems other than epilepsy (e.g., asthma, anemia, malaria) identified by CHWs or study physicians to be referred for all appropriate medical care. This additional medical care will be recorded in the REDCap-based study records.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

At the end of the 24-month follow-up period for each enrolled study subject in the EUC arm of the cRCT, the study subject will be returned to their local physician for ongoing care for their epilepsy.

At the end of the 24-month follow-up period for each enrolled study subject in the task-shifted arm of the cRCT, the study subject's parent/guardian (or the study subject if they are ≥ 18 years of age) will be given the option of continuing to receive task-shifted epilepsy care in a continuation maintenance protocol, funding permitting from a funding agency or from the Ministry of Health, or being referred to a physician for epilepsy care. If final analysis of the cRCT data fails to demonstrate non-inferiority for the task-shifted care arm, then the study subjects in the task-shifted care arm will be referred to physicians in the area for medical care for their epilepsy.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Study subjects in either arm of the cRCT are able to withdraw consent and withdraw from the cRCT at any time. For each study subject who withdraws from the cRCT reasons for the decision to withdraw will be requested with respect and recorded into the case report forms (CRFs).

Defaulting or withdrawing from the intervention arm (task-shifted care) arm of the cRCT will be treated as a participant discontinuation or withdrawal from the study.

7.3 LOST TO FOLLOW-UP

The BRIDGE study personnel will take steps to *minimize lost to follow-up in each arm of the cRCT in order to minimize drop-out rates, and to significantly reduce the risk of differential drop-out rates*. The names and the cell phone number, if available, of several family members, neighbors, and other community contacts will be obtained with permission of the parent or guardian at the time of enrollment. If a child in either arm of the study does not show up for a follow-up visit with a CHW, then via phone call and/or home visits the CHW will follow-up with the parent/guardian to arrange for a clinic appointment. For families who have difficulty with local travel to appointments, the BRIDGE study will aid with local travel. In the event that a child is unable to be seen in the clinic because of travel restrictions, or other reasons, then follow-up visits may be done *via* phone by the CHW. Two or more follow-up visits via phone will require agreement by the city PI. In addition, CHWs may make house calls and complete follow-up visits in the homes of children enrolled.

In calculating the lost to follow-up percentages within each cluster and in each arm of the cRCT, the denominator will be the number of children who were consented (and assented for children able to provide assent) to participate in the cRCT at Visit 0, not the number of children who actually started

treatment or who showed up for a specific number of follow-up visits. Reporting loss to follow-up will be done according to CONSORT guidelines.[72]

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Aim 1. Conduct a non-inferiority cRCT of a task-shifted childhood epilepsy care protocol compared to EUC in three Hausa-speaking cities in northern Nigeria. We will enroll about 1730 (maximum 1800) children (age 6 mo, <17 yrs) with epilepsy across 60 randomly selected PHCs in Kano (30 PHCs), Kaduna (15 PHCs) and Zaria (15 PHCs). PHCs will be randomly assigned to intervention (task-shifted to CHWS childhood epilepsy care; 30 PHCs) or EUC (referral to a physician for epilepsy management; 30 PHCs).

Approach to Aim 1.
In three major cities in Hausa-speaking west Africa (Kano, Kaduna, and Zaria), we will perform a non-inferiority cRCT of a task-shifted (to CHWs) childhood epilepsy care protocol versus EUC (in which children are referred to a local physician for epilepsy diagnosis and management plus primary care by an epilepsy trained CHW, who will monitor study subjects in the EUC arm of the cRCT and carefully monitor and record outcome data. See figure 1).

Screening of Children for Epilepsy
Children will be screened for epilepsy in primary care clinics, neighborhoods and schools using a previously validated epilepsy screening and seizure classification tool in Hausa (Appendix B). Children who screen positive for epilepsy will be evaluated for possible epilepsy by a CHW who has successfully completed a previously piloted childhood epilepsy training program. Then, those children with a diagnosis of epilepsy who are untreated will be assigned to a participating PHC based on their home address. Children enrolled at EUC sites will be referred to a local physician for EUC, including an epilepsy treatment and management. Children with epilepsy enrolled at task-shifted intervention sites will receive task-shifted (to CHWs) childhood epilepsy care as per the protocol taught during the epilepsy education program for CHWs (see figure 2).

Consent and Assent for Epilepsy Screening and for Aims #1 and #2
Consent from a parent (or guardian) will be obtained prior to the screening of their children for possible epilepsy using the Hausa epilepsy screening and classification tool; this consent form will include a consent for screening the child for possible epilepsy using the screening tool (Appendix B) and the exam by a CHW (with physician supervision per the protocol, see figure 2) for children who screen positive.

Children ($\geq$ 6 months, < 17 years) who screen positive for epilepsy and who also are found to have active epilepsy (a seizure(s) within the past year) after a clinical evaluation (history and physical exam), and who also are not being treated for epilepsy will be offered enrollment into the BRIDGE cRCT.

Consent
Parents/guardians of children whose address is closest to a PHC that has been randomized to EUC will be given a consent for this arm of the cRCT (see Appendix C). Parents/guardians of children whose address is closest to a PHC that was randomized to task-shifted care will be given a consent for the task-

shifted arm of the cRCT. Consent forms are found in Appendix C, and will be available in English and in Hausa. *Children who are < 17 years of age, but who have their 18th birthday during the cRCT, will be given a consent form or the cRCT during the scheduled CHW visit immediately following their 18th birthday (Appendix C).* There are separate consent forms for the Zaria, Kaduna, and Kano sites in order to clearly identify city-specific principal investigators and ethics committee contacts

Assent and Dissent

Assent forms will be provided to children ages 7 years to < 17 years, who are able to understand concepts of assent. The consent and assent forms will be available in Hausa and in English, and the parent/guardian will be able to choose which language they prefer for the consent/assent forms. Assent forms are found in Appendix C. There are separate assent forms for the Zaria, Kaduna, and Kano sites in order to clearly identify city-specific principal investigators and ethics committee contacts.

Dissent from children will be clinically assessed in a compassionate and culturally sensitive manner, with parent/guardian involvement; appropriate action will be taken to resolve the dissent. Resolution of the dissent by a potential study subject may include not enrolling the child in the cRCT.

Children who are candidates for the study, but who are not enrolled in the BRIDGE cRCT, will be referred to a local physician for epilepsy treatment.

Overview of EUC and task-shifted intervention arms of the cRCT

Children in both cRCT arms (figures 1 and 2) will be evaluated after enrollment by an epilepsy-trained CHW at week 1, and at months 1, 2, 4, 6, 9, 12, 15, 18, and 24. Children in the EUC arm will be followed by the epilepsy-trained CHW for (a) primary care and (b) to record seizure frequency from seizure diaries (see Appendix D), medication taken, and any apparent adverse events. Children in the EUC arm will be referred to community physicians for epilepsy diagnostic evaluations and epilepsy treatment. Children in the task-shifted epilepsy care arm will receive epilepsy diagnostic services plus epilepsy treatment/management by an epilepsy-trained CHW.

At month 1 and then at 6, 12, 18, and 24 months after enrollment, every child enrolled in the cRCT (both arms) will be evaluated by an epilepsy-trained physician whose only role in the cRCT is to be a blinded physician who will evaluate each child's seizure frequency, AED selection and dosing, potential AED-related adverse events, and monitoring of the child's neurological deficits and developmental problems (if any). The blinded physician's evaluations will be recorded on standardized case report forms (CRFs) in REDCap and uploaded to the data coordinating center at Vanderbilt (Figures 1 and 2). The primary purpose of the blinded physicians' evaluations is the objective, blinded collection of outcome data for the cRCT.

The standardized content of the CRFs was developed from the common data elements recommended by NINDS (https://www.commondataelements.ninds.nih.gov/epilepsy), and then adapted by the investigators for use in a cluster RCT of a task-shifted intervention in northern Nigeria, as outlined in

Appendix E. The CRFs were then developed from the common data elements in Appendix E, as shown in Appendix G.

Parents/guardians of enrolled patients in both arms of the cRCT will maintain written seizure diaries, recording frequency and duration of seizures and documenting medication administration; the seizure diaries will be evaluated by providers at all visits, data will be entered into the CRFs, and photographs of seizure diaries will be retained as part of the study records.

All females of child-bearing age enrolled in the cRCT will be offered by CHWs family planning services at the PHC, also attended by CHWs as part of their routine practice, where oral contraceptives are available, and all will be prescribed multivitamins with folic acid. Any females who become pregnant while on an AED will be referred to a physician for consultation. Marriage and pregnancy are very common among women less than 18 years of age in northern Nigeria, and the investigators anticipate pregnancies will occur as part of the expected cultural norms during the study, in spite of offering family planning services.

Parents of children in both the task-shifted arm and the EUC arm of the cRCT will be provided with paper booklets for recording the day and time, type, and approximate duration of seizures - a ***seizure diary*** (see Appendix D). The seizure diary for each enrolled child will be reviewed by the CHWs at each routinely scheduled visit, and the information regarding the seizure frequency, seizure type, and duration will be recorded at each scheduled visit. For parents unable to read and write, they will be instructed how to make their mark on the seizure diary and to estimate how long the seizure lasts based upon a comparison to the local traditional Islamic "call to prayer" heard daily throughout the region, and lasting approximately 3 minutes. (Most seizures last less than 3 minutes, and those that last longer than 5 minutes often do not stop on their own without intervention - the operational definition of status epilepticus. These more prolonged seizures are associated with increased morbidity and mortality risks.)

Electronic case report forms (CRFs)

All study subject data for the cRCT will be entered into REDCap ®on android tablets or laptop computers. Specific electronic case report forms (CRFs) will capture the demographic data, clinical history data, exam data, EEG data (if any), seizure frequency data and other data for the cRCT. The cRCT clinical personnel (CHWs, study epilepsy physicians, and blinded neurologists) will all receive training on the completion of the CRFs (for content of CRFs see Appendix E).

Task-shifted epilepsy care arm of the cRCT

Children who screen positive for epilepsy and whose home is closest to a PHC randomly assigned as an intervention site will be referred to an epilepsy trained CHW for evaluation and treatment. Children less than 6 months of age (if identified with untreated epilepsy during screening) and children with infantile spasms will be referred to a BRIDGE pediatric neurologist and will be excluded from the task-shifted protocol (Figure 2). Children with a focal neurological deficit and/or developmental regression will be

referred to a study neurologist for evaluation and treatment; children with static neurological deficits may continue in the task-shifted protocol if deemed appropriate by the neurologist.

Epilepsy-trained CHWs will follow the epilepsy management protocol (figure 2). CHWs will prescribe one of three drugs for children with previously untreated epilepsy enrolled in the task-shifted arm of the cRCT - phenobarbital, carbamazepine, or valproate – all of which readily available and which the CHWs have been trained to use in the epilepsy education program for CHWs.

- **Phenobarbital**, the least expensive and most readily available of AEDs in northern Nigeria, may be prescribed for children with focal onset seizures or generalized tonic-clonic seizures without co-existing absence seizures.

- **Carbamazepine** may be prescribed for children with focal-onset seizures or "generalized" tonic-clonic seizures without clinical evidence of myoclonic or absence seizures and, according to local standard of care, will be used for children with focal onset seizures who have experienced prior adverse effects (including increased hyperactivity) with a barbiturate.

- **Valproate** will be prescribed as a first AED for children with a clinical diagnosis of absence seizures or myoclonic seizures. If valproate is prescribed by the epilepsy trained CHW, the epilepsy physician working with the intervention site will be required to see the patient within one week to verify the CHW diagnosis and medication choice.

The CHWs in the task-shifted arm of the cRCT have the option of seeking a consultation from a study epilepsy physician if they have questions regarding the diagnosis or selection of the initial AED (see figure 2). The study epilepsy physician may order an EEG if needed for diagnosis and management according to usual clinical practice in northern Nigeria. The number of times that a CHW seeks consultation from a supervising physician will be counted and included as a descriptive outcome measure, and as data that will inform implementation of task-shifted epilepsy care.

Dosing of AEDs by CHWs will be based on standard dosing guidelines by age and weight of child (Appendix F). The weight-based dosing accuracy of phenobarbital (or phenobarbitone as the same drug is known in Nigeria), carbamazepine, and valproate will be facilitated by the CHWs weighing the children at each visit. Dosing for each of these drugs will be determined within the REDCap eCRFs based upon the following:

(a) "Step 1", the first weight-based dose for each drug;
(b) "Step 2", the second weight-based dose range if seizures were not controlled at Step 1, and if there were no dose-related side effects at Step 1; and,
(c) "Step 3", the third weight-based dose range if seizures were not controlled at Step 2, and if there were no dose-related side effects at Step 2.

The presence of clear persistent dose-related side effects plus seizures at any of the weight-based dose ranges will prompt a consultation with the supervising physician, as supervising physician may consider the child to have failed the drug.

If seizures continue to occur without dose-related AED side effects on Step 2 dosing, then the CHW will receive a message on the REDCap electronic CRF that will advise the CHW that the child may be on close to the maximum dose of the AED, and that a supervising physician should be contacted to determine if Step 3 dosing in the child should be pursued, or another step should be taken in the care of the child. In this situation the supervising physician may recommend an increase in the dose of the AED (Step 3 dosing), a change to a different AED after determining that the child has failed the current AED, or other steps be taken, including an in-person consultation with the supervising physician. The CRF will record the physician's instructions to the CHW and the next step taken by the CHW.

If seizures persist on Step 3 weight-based dosing, or if dose-related side effects plus seizures occur at lower doses of the drug, then the CHW will follow a specific protocol for dosing of the anti-epileptic drug at Step 4. For phenobarbital, carbamazepine, and valproate, the maximum dose used even in the absence of dose-related side effects will not exceed the maximum recommended dose in internationally accepted guidelines.[73-75] Supervising physicians for the task-shifted arm of the study may elect to use doses of levetiracetam higher than 60 mg per kg per day in children with refractory epilepsy, up to 80 mg per kg per day as is common in the U.S., if other treatment options are not believed to be available or a better option for thepatient.[76-78]

Phenobarbital Step 4. If the dose of phenobarbital is $\geq$ 8 mg/kg/day, or if there are any dose-related side effects, then the patient will be considered to have failed phenobarbital, and the supervising physician will be consulted regarding the next step for the child, according to the BRIDGE Task-shifted protocol (figure 2, Appendix F). If the child continues to have seizures, without dose-related side effects, on phenobarbital, then the dose will be increased in increments of no more than 2 mg/kg/day every two to four weeks, to a maximum of 8 mg/kg/day. If seizures continue at a dose of 8 mg/kg/day, even in the absence of side effects, then the child will be considered to have failed phenobarbital, and a consultation will be made with the supervising physician.

Carbamazepine Step 4. If the dose of carbamazepine is $\geq$ 35 mg/kg/day, or if there are any dose-related side effects, then the patient will be considered to have failed carbamazepine, and the supervising physician will be consulted regarding the next step for the child, according to the BRIDGE Task-shifted protocol (figure 2, Appendix F). If the child continues to have seizures, without dose-related side effects, on carbamazepine, then the dose will be increased in increments of no more than 10 mg/kg/day every two to three weeks, to a maximum of 35 mg/kg/day. If seizures continue at a dose of 35 mg/kg/day, then the child will be considered to have failed carbamazepine, and a consultation will be made with the supervising physician.

Valproate Step 4. If the dose of valproate is $\geq$ 60 mg/kg/day, or if there are any dose-related side effects, then the patient will be considered to have failed valproate, and the supervising physician will

be consulted regarding the next step for the child, according to the BRIDGE Task-shifted protocol (figure 2, Appendix F). If the child continues to have seizures, without dose-related side effects, on valproate, then the dose will be increased in increments of no more than 10 mg/kg/day every two to three weeks, to a maximum of 60 mg/kg/day. If seizures continue at a dose of 60 mg/kg/day, then the child will be considered to have failed valproate, and a consultation will be made with the supervising physician.

Levetiracetam (LVT), at present is not a first line anti-epileptic drug (AED) in northern Nigeria but is becoming more available. We anticipate that it may become a first line AED in northern Nigeria within the next 2-4 years, if trends of availability and pricing continues. Therefore, the epilepsy trained CHWs have been trained in the use of levetiracetam. If levetiracetam is used, then the following dosing guidelines will be utilized (Appendix F), using a strict weight-based dosing.

- LVT Step 1. 7-10 mg/kg in the AM and 7-10 mg/kg in the PM (14-20 mg/kg/day). If no side effects and ongoing seizures, then after a minimum of two weeks go to Step 2.
- LVT Step 2. 15-20 mg/kg in the AM and 15-20 mg/kg in the PM (30-40 mg/kg/day). If no side effects and if ongoing seizures, then after a minimum of two weeks go to Step 3.
- LVT Step 3. 25-30 mg/kg in the AM and 25-30 mg/kg in the PM (50-60 mg/kg/day). If no side effects and if ongoing seizures, then after a minimum of two weeks and permission of the supervising physician, go to Step 4.
- LVT Step 4. (with approval by the supervising physician). 35-40 mg/kg in the AM and 35-40 mg/kg in the PM. If no side effects and ongoing seizures, consult the supervising physician as LVT has apparently failed.

If at any time there are apparent side effects of LVT, including potential depression, the dose will not be increased, and the supervising physician will be consulted immediately.

Upon recommendation of the study epilepsy physician, the CHW may then increase the dose of the first AED to a dosage higher than the protocol outlined in Appendix C or begin the child on a second AED. Likewise, if a child enrolled in the task-shifted arm of the cRCT fails to achieve seizure control (typically seizure freedom for most seizure types) with a second AED prescribed at the maximum tolerated dose, then the CHW will refer the child to a study epilepsy physician for consultation.

If a child enrolled in the task-shifted intervention arm of the cRCT fails to achieve seizure control with all three routinely used AEDs (phenobarbital, carbamazepine, valproate) with or without the use of LVT, then as part of the task-shifted protocol, the CHW with the family may decide to refer the child for additional care by an epilepsy specialist with continued follow-up by the CHW.

Enhanced usual care (EUC) arm of the cRCT

Children who screen positive for epilepsy and whose home is closest to a PHC randomly assigned as an EUC site will be referred to a physician who receives referrals for epilepsy for epilepsy diagnosis and care. The standard care will be enhanced by primary care follow-up by an epilepsy-trained CHW who will

not manage the patient's epilepsy but will (a) monitor the child's progress and record the clinical findings (e.g., seizure frequency) during routine clinic visits on standardized CRFs and (b) provide epilepsy educational materials to parents and healthcare providers. As with the task-shifted intervention sites, blinded neurologists will evaluate the patients at the EUC sites and will be blinded as to whether the children are receiving care in intervention or in EUC sites. CRFs completed in REDCap by CHWs and the blinded physicians will be uploaded to the Vanderbilt Coordinating Center.

Assessment of epilepsy-associated neurodevelopmental morbidity

Two separate instruments will be administered to children enrolled in both arms of the cRCT to assess for attention deficit hyperactivity disorder (ADHD), the ***ADHD Rating Scale***,[79] and the ***23-Question Questionnaire (23Q).***[80] The ADHD Rating Scale, which has been used in routine practice in northern Nigeria, will be administered to children ages –5 years to 10 years old at Visit 0 (prior to starting anti-epileptic drug treatment), Visit 2 months, and Visit 24 months by CHWs trained in the administration of the ADHD Rating Scale. The 23-Question Questionnaire (23Q), which was developed for use in low- and middle-income countries in Africa,[80] will be used to screen for intellectual disability, cerebral palsy, hearing impairment, visual impairment, and autism spectrum disorder. There are also two questions within the 23Q designed to screen for convulsive epilepsy; these questions will be omitted, as the epilepsy screening and seizure classification tool developed for use in the BRIDGE project and validated in Hausa will be used for epilepsy screening.[27,29] Administered by epilepsy-trained CHWs who will also be trained to administer the 23Q, the 23Q will be administered at Visit 1 week and Visit 24 months.

Diagnostic Evaluation for Cerebral Palsy (CP) by Blinded Physicians at 12-month Visit. CP is a relatively common co-morbid condition among children with epilepsy. We do not know how frequently CP occurs as a co-morbid condition among children with epilepsy in northern Nigeria, and how frequently CP occurs among children whose epilepsy was previously untreated prior to the BRIDGE project. All blinded physicians who have expertise in epilepsy have sufficient background in CP to make a diagnosis of CP. All children enrolled will be evaluated once by the blinded physicians for CP as part of the 1-, 6-, or 12-month blinded physician visit, which ever visit occurs first after IRB/Ethics committee approval of protocol version 1.8. The assessment will be performed, as with all blinded physician evaluations, with care to prevent the breaking of the blind.

Diagnostic Evaluation for Absent Language Function (Presumed Profound Intellectual Disability) by Blinded Physicians at 12-month Visit. Children without functioning expressive language by the age of 3 years and without functioning receptive language by the age of 3 years, will not be able to complete evaluation for intellectual disability, autism spectrum disorders, or ADHD. Therefore, for all enrolled children who were 24 months or older at enrollment (36 months or older at the time of the 12-month blinded physician visit) will be evaluated by the blinded physicians for possible absent expressive and receptive language function. This information will be recorded in the CRFs, and children with both absent expressive and receptive language function will be classified as "presumptive profound ID"; these children will be excluded from all further evaluations for ID, ASD, and/or ADHD.

Additional Diagnostic Evaluations for Intellectual Disability (ID), Autism Spectrum Disorder (ASD), Attention Deficit Disorder (ADHD), Visual Impairment (VI), and Hearing Impairment (HI). We do not know how frequently children with epilepsy in northern Nigeria have co-existing ID, ASD, ADHD, VI, and/or HI. Children who screen positive for possible ID, ASD and/or ADHD will will receive additional diagnostic evaluations as part of the BRIDGE protocol, unless they have been determined to have an absence of both expressive and receptive language at the 12-month blinded physician visit. All children, except for children diagnosed with "presumed profound ID" by blinded physicians, who screen positive for HI and/or VI will be referred for appropriate hearing and/or visual evaluations. Record of these diagnostic evaluations for co-morbid neurodevelopmental disorders will be maintained within the BRIDGE study CRFs. *A parent/guardian for each child who screens positive will provide consent for additional diagnostic evaluations other than the previously-consented blinded physician visits. Any parent/guardian who does not provide consent for the additional diagnostic evaluations will not receive these evaluations, but will remain enrolled in the BRIDGE study.*

Diagnostic Evaluation for Visual Impairment (VI). Children enrolled in BRIDGE, except for those diagnosed as having "presumed profound ID" by blinded physicians, who screen positive for VI on the 23Q questionnaire will be referred for a vision evaluation, with the single exception of children who have presumed. Children who have VI will have their VI recorded in the BRIDGE CRFs, and they will be referred for appropriate vision care as deemed clinically appropriate, outside of the BRIDGE study, by the vision healthcare professional. The initial vision diagnostic evaluation will be paid by the BRIDGE study, but subsequent vision exams and treatment will be outside of the BRIDGE protocol and outside the BRIDGE study budget.

Diagnostic Evaluation for Hearing Impairment (HI). Children enrolled in BRIDGE, except those children diagnosed as having "presumed profound ID" by blinded physicians, who screen positive for HI on the 23Q questionnaire will be referred for a hearing evaluation. Children who have HI will have their HI recorded in the BRIDGE CRFs, and they will be referred for appropriate hearing care as deemed clinically appropriate, outside of the BRIDGE study, by the hearing/audiology healthcare professional. The initial hearing diagnostic evaluation will be paid by the BRIDGE study, but subsequent hearing exams and treatment will be outside of the BRIDGE protocol and outside the BRIDGE study budget.

Diagnostic Evaluation for Intellectual Disability (ID). Children who are 24+ months of age upon enrollment (and 36+ months of age at the 12-month blinded physician evaluation), who (a) have functioning expressive and/or receptive language skills according to the blinded physician visit at 12 months, and (b) screen positive for possible ID on the 23Q questionnaire will undergo an additional evaluation for ID, after informed consent and when indicated assent. Evaluations for ID will be performed by a qualified psychologist, psychiatrist, or qualified mental health professional under the supervision of a psychologist or psychiatrist according to standards of care in Nigeria. The Raven's Colour Progressive Matrices will be utilized for the evaluations and scored according to standard criteria by the psychiatrists and psychologists. Parents/guardians will receive information, written and verbal, regarding their child's ID evaluation results; these results may be helpful for future educational and

medical evaluations and interventions outside of the BRIDGE study. The results of the ID diagnostic evaluations will be entered into the BRIDGE REDCap database.

Diagnostic Evaluation for Autism Spectrum Disorder (ASD). Children who are 24+ months of age upon enrollment (and 36+ months of age at the 12-month blinded physician evaluation), who (a) have functioning expressive and/or receptive language skills according to the blinded physician visit at 12 months, (b) screen negative for possible ID on the 23Q questionnaire or who screen positive on the ID screening, but are determined to not have ID, or have mild ID or moderate ID, and (c) screen positive for ASD on the 23Q questionnaire upon enrollment will undergo an additional evaluation for ASD, after informed consent and when indicated assent. Evaluations for ASD will be performed by a qualified psychologist, psychiatrist, or qualified mental health professional under the supervision of a psychologist or psychiatrist according to standards of care in Nigeria. The K-SADS-autism module will be utilized for the evaluations and scored according to standard criteria by the psychiatrists and psychologists. Parents/guardians will receive information, written and verbal, regarding their child's ASD evaluation results; these results may be helpful for future educational and medical evaluations and interventions outside of the BRIDGE study. The results of the ASD diagnostic evaluations will be entered into the BRIDGE REDCap database.

Diagnostic Evaluation for Attention Deficit Disorder (ADHD). Children who are 24+ months of age at enrollment (and 36+ months of age at the 12-month blinded physician evaluation), who (a) have functioning expressive and/or receptive language skills according to the blinded physician visit at 12 months, (b) screen negative for possible ID on the 23Q questionnaire or who screen positive on the ID screening, but are determined to not have ID, or have mild ID, (c) screen negative for ASD on the 23Q questionnaire, or are determined by the psychiatrist/psychologist evaluation to not have ASD, and (d) screen positive on the ADHD screening using the ADHD Rating Scale will undergo an additional evaluation for ADHD, after informed consent and when indicated assent. Evaluations for ADHD will be performed by a qualified psychologist, psychiatrist, or qualified mental health professional under the supervision of a psychologist or psychiatrist according to standards of care in Nigeria. The K-SADS-ADHD module will be utilized for the evaluations and scored according to standard criteria by the psychiatrists and psychologists. Parents/guardians will receive information, written and verbal, regarding their child's ADHD evaluation results; these results may be helpful for future educational and medical evaluations and interventions outside of the BRIDGE study. The results of the ADHD diagnostic evaluations will be entered into the BRIDGE REDCap database.

<u>Aim #2</u>. **Assess socio-behavioral and implementation outcomes among providers, parents/guardians and patients in the cRCT.** Outcome measures include: (1) Difference in baseline (Visit 0 or Visit 1 week), 12- and 24-month intervention acceptability, appropriateness, and feasibility measures among providers in the task-shifted intervention arm of the cRCT; (2) Difference in baseline, 12- and 24-month quality of life, epilepsy knowledge and stigma, and trust in the healthcare system and providers among participants; (3) Comparison of 12- and 24-month quality of life, knowledge and stigma and trust measures among participants in the intervention and control arms.

Approach to Aim 2.

Assessment of socio-behavioral and implementation outcomes provides a multi-perspective evaluation of the intervention throughout the duration of the BRIDGE cRCT and is essential for understanding factors influencing success and challenges of this type of task-shifted intervention. Successful implementation of the task-shifted intervention will be facilitated by integration of knowledge regarding cultural, structural, and personal factors influencing service delivery. This information, collected at baseline, will be transmitted to the study team to correct/tailor care delivery before implementation. Qualitative information collected from patients at the study mid- and endpoints will be used to understand activities and relationships that impact the effect of the strategy.

At enrollment, at the 2 months Visit and at the 24-month visit, children ages 11-17 years will be administered the *QOLIE-AD-48* by CHWs trained in the administration of the QOLIE instrument(s). Children who have their 18th birthday prior to the 24-month visit will receive the *QOLIE-31*. There are no published data, to our knowledge, on the *QOLIE-AD-48* on children who have not yet started anti-epileptic drug treatment (literature review, and Joyce Cramer, personal communication). Questions that relate to the use of anti-epileptic drugs will be omitted at the Visit 0 administration of the QOLIE.

At enrollment, all parents/guardians of all enrolled patients and patients (if ages 15-17 years) will complete short interviewer-administered surveys about their trust in the local healthcare system, epilepsy knowledge and attitudes, stigma, and quality of life. At 12 and 24 months, when participants complete scheduled visits with a blinded physician specialist to assess their epilepsy management, these instruments will be repeated. Measures of trust in healthcare provider, as specifically defined by the provider who prescribes and manages AEDs, will be collected at 12 and 24 months from parents/guardians and patients (if age 15-17 years) in both arms of the cRCT. At baseline, 12, and 24 months after enrollment, all health providers (CHWs and physicians) in the intervention arm will provide information via REDCap questionnaires regarding the acceptability, appropriateness, and feasibility of the task-shifted childhood epilepsy care protocol.

Qualitative data collection for Specific Aim 2: Thirty (of 120) randomly selected CHWs and all unblinded physicians supervising the CHWs in the intervention arm will complete baseline qualitative interviews to identify “inner” and “outer” context factors that may support or hinder uptake of the intervention, as well as questions about CHW characteristics that may influence successful implementation of the task-shifted care guidelines. Guided by the Consolidated Framework for Implementation Research (CFIR), interviews will focus on cultural, structural, and personal factors that could limit or enhance delivery of task-shifted epilepsy care services.

One hundred eighty selected parents/guardians in the intervention arm will complete mid- (12-month follow-up) and end-study (24-month follow-up) qualitative interviews about their experiences with their respective CHWs and the task-shifted healthcare team. Experiences of parents/guardians may differ by whether their children are seizure-free or experienced continued seizures while on treatment. Therefore, these participants will be selected randomly from two groups: (1) 90 parents/guardians whose children have been seizure-free for >6 months and (2) 90 parents/guardians who have

experienced a less than a 75% reduction in seizure frequency over the past 6 months. We will assess participants' perceptions of task-shifted epilepsy care using acceptability, appropriateness, and feasibility measures developed by Weiner et al. These scales have been tested and exhibited substantive and discriminant content validity, high factor loadings (0.79 to 0.94) and acceptable Cronbachs alphas (0.85 to 0.91).

Aim #3. Determine the cost-effectiveness of the task-shifted epilepsy care intervention. Direct costs of the intervention and EUC will include personnel costs (including CHW epilepsy training) and expenses for diagnostic (EEG, brain imaging) and laboratory tests and anti-epileptic drugs. *Indirect costs* will include travel time and time away from work for parents/guardians and change in school attendance for patients. Cost-effectiveness will be expressed as US dollars per disability adjusted life year (DALY) averted.

Approach to Aim 3.
Health leaders and policymakers in LMICs have many competing interests for their modest healthcare budgets. Systems of care must be both effective and efficient to receive support from Ministries of Health for initial funding that drives the implementation of new health system interventions. In LMICs of Africa, Asia, and the Middle East, increasing the efficiency of health spending could increase the health-adjusted life expectancy by up to 2 years. As health policymakers inevitably face tradeoffs between health benefits and costs among different healthcare interventions, cost-effectiveness analysis provides a quantitative framework for maximizing health outcomes per funds spent on care. Demonstrating cost-effectiveness is also important for the inclusion of proposed interventions in WHO guidelines, as well as for inclusion in USAID and other national prioritization plans. We will therefore conduct a cost-effectiveness analysis of task-shifted epilepsy care and utilization of diagnostic and management technology for children with epilepsy in the task-shifted sites compared to the EUC sites. We will express cost-effectiveness in both US dollars and in Nigerian Naira per additional disability-adjusted life year averted (DALY) - a measure that quantifies disease burden and reflects changes in both life expectancy and quality of life. It also allows health policy leaders to compare cost-effectiveness across different diseases and health system interventions. We will also perform scenario analyses that consider the increased capacity of the health system to manage large numbers of patients with epilepsy using a task-shifted epilepsy care system. A Child Care Questionnaire, assessing the home care the child requires from caregivers due to her/his epilepsy, will be administered at Visit 1 Week, Visit 12 months, and Visit 24 months.

The baseline capacity of physicians to diagnose and manage childhood epilepsy patients will be determined for a traditional physician specialist setting in northern Nigeria and compared to the capacity for the task-shifted epilepsy care model. During the first six months of Year 1, immediately prior to cRCT enrollment, we will collect data from a large childhood epilepsy clinic in Kumbotso, Kano State, and at pediatric neurology clinics at AKTH and at Murtala Muhammad (both also in Kano) to determine the number of epilepsy patients typically managed per year by a physician without assistance from a CHW. These data will be compared to the number of patients with epilepsy managed per year by a full-time CHW in a task-shifted environment and the number of patients who can be managed per year with

epilepsy by a physician spending approximately 25% effort supervising twenty CHWs in a task-shifted environment.

There is a paucity of electroencephalograms in northern Nigeria (e.g., approximately two available EEG machines in Kano for a referral population of more than 10 million people). Therefore, physicians with epilepsy expertise do not order EEGs routinely and only use EEG in cases in which they are not able to make a diagnosis or management patients based upon history and examinations. Anti-epileptic drug (AED) levels are rarely utilized in northern Nigeria, even by epilepsy physician specialists. In the task-shifted arm of the cRCT, CHWs will not order AED levels. However, epilepsy physician specialists will order AED levels according to their standard-of-care practice.

8.2 SAFETY ASSESSMENTS

The Kano-, Zaria-, and Kaduna-based epilepsy physicians will review the prescription records, medical charts, and electronic case report forms (CRFs) at least monthly of patients followed by the CHWs (in both the task-shifted intervention and enhanced usual care arms) under their supervision, and use the information as feedback to improve provider knowledge and competence as part of usual practice. Any medical errors will be brought to the attention of the CHW and will also be reported to the BRIDGE PIs; medical errors and task-shifted protocol deviations will also be reported to the BRIDGE Data Safety Monitoring Board (DSMB).

In compliance with the NIH requirements, and following the formation of the Data and Safety Monitoring Board (DSMB) with approval by NINDS, we will comply with guidance on DSMB activities for the cluster-randomized trial component of this project. The data and safety monitoring plan will include reporting of serious adverse events to the IRBs and the DSMB.

Higher than expected rates of SAEs may be seen in either or in both arms of the cRCT (epilepsy-associated mortality has been reported to be higher in Africa). Personnel involved in the monitoring of activities will include the following:

- PI/PD, Multi-PIs
- An internal committee consisting of the PI/PD, Multi-PI and the co-investigators on the BRIDGE project.
- The DSMB

Serious adverse events will be reported to the chair of the DSMB by the PI/PD (Dr. Trevathan). The DSMB has the authority to halt the cRCT if it perceives that harm is occurring due to the intervention. Summaries of all adverse events will also be made to the NIH in the yearly progress report, or more frequently as requested.

Aims 2 and 3 study, the components of this cluster-randomized trial that determines the socio-behavioral and implementation outcomes and the cost-effectiveness of a task-shifted intervention, do

not have the same level of risk or complexity as a clinical trial of a drug or an intervention. Therefore, as Multi-PIs, Drs. Trevathan and Abdullahi will assume primary responsibility for data and safety monitoring, with periodic reports to the DSMB.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, **whether or not considered intervention related.**

8.3.3.1 SEVERITY OF EVENT AND SERIOUS ADVERSE EVENTS

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** - Events that require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** - Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe -** Events interrupt a participant usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

A **serious adverse event (SAE)** as one when the study subject has one of the following outcomes.

- Death
- Life-threatening disorder or complication
- Hospitalization potentially related, probably related, or definitely related to the intervention
- New onset disability - significant, persistent or permanent change, impairment, damage or disruption of the patient’s body structure/function, physical activities or quality of life
- Congenital anomaly
- Requires intervention to prevent permanent impairment or damage

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately trained clinician based on temporal relationship and her/his clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** - There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, if available, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.

- **Probably Related** - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, if available, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.

- **Potentially Related -** There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant, clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely to be related** - A clinical event, including an abnormal laboratory test result, if available, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant, clinical condition, other concomitant treatments).

- **Not Related** - The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

  All SAEs will be reviewed by the BRIDGE clinical team (Drs. Trevathan, Abdullahi, Salihu, Adamu, Sabo, Ahmad, and Nuhu), led by Dr. Trevathan, who will meet as quickly as possible after the report of an SAE and will use detailed knowledge and documentation of the SAE and their expertise to classify the SAE as “definitely related”, “probably related”, “potentially related”, “unlikely to be related”, or “not related” using the definitions above. An SAE believed to be causally related to a violation of the task-shifted protocol will be classified as “potentially related”, “probably related” or “definitely related.”

8.3.3.3 EXPECTEDNESS

A clinician with appropriate expertise in will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinicians' assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. Development of an identified neurodevelopmental disorder at Visit 0 or at Visit Week #1 will not be considered an AE, but rather the identification of a baseline neurodevelopmental disorder. A newly identified neurodevelopmental disorder, not present during Visit 0 or Visit Week #1 (at first 23-question questionnaire), but present at Visit 12 months or Visit 24 months, will be considered an AE, even though co-morbid neurodevelopmental disorders are often a part of the natural history of many severe epilepsy syndromes.

If the study participant condition deteriorates at any time during the study, it will be recorded as an AE. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent. BRIDGE study CHWs or study physicians will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the BRIDGE CHW, study physician or investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such evaluation to the DSMB, NIH and the reviewing Institutional Review Board (IRB) as soon as possible. One of the two multi-PIs must report that an SAE has occurred within two weeks from the first time both multi-PIs come aware of the SAE. Multi-PIs will be responsible for ensuring that the DSMB reviews their best and most accurate summary of events of SAE and report will be available by earliest possible date.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Any adverse event that occurs in a study subject will be discussed with that study subject and/or her/his parent/guardian by the CHW and/or a BRIDGE investigator, with all questions addressed and answered. Study subjects will receive information regarding the outcome of the BRIDGE cluster randomized clinical trial following the completion of the cRCT.

8.3.8 EVENTS OF SPECIAL INTEREST

Status epilepticus will be considered an adverse event and reported as such. Unfortunately, epilepsy-associated death is common in Africa. Any deaths among BRIDGE study subjects will be reported as serious adverse events.

8.3.9 REPORTING OF PREGNANCY

All women of childbearing age enrolled in the study will be offered consultation with family planning services at their local PHC. In northern Nigeria, women under the age of 18 years often marry, have planned pregnancies and have children. Any pregnancy that occurs among BRIDGE study subjects, including planned pregnancies, will be reported to the DSMB by the PI/PD.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The co-investigators and the Multi-PI based in Kano will report any unanticipated problems (UPs) to the Multi-PI/PD, who in turn will report such UPs to the DSMB. A report will also be made to the VUMC Institutional Review Board (IRB) and the AKTH Ethics Committee. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number

- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor/funding agency within ten working days of the investigator becoming aware of the event
- Any other UP will be reported to the IRB and to the DCC/study sponsor/funding agency within one month of the investigator becoming aware of the problem
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within one month of the IRB's receipt of the report of the problem from the investigator

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Any UP that occurs in a study subject will be discussed with that study subject and/or her/his parent/guardian by the BRIDGE investigator, with all questions addressed and answered. Study subjects will receive information regarding the outcome of the BRIDGE cluster randomized clinical trial following the completion of the cRCT.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s): We hypothesize that the proportion of children seizure-free for ≥ 6 months preceding the 24 months follow-up (primary outcome) will not be inferior in the intervention (task-shifted) and control (enhanced usual care; EUC) arms of the BRIDGE cluster randomized clinical trial (cRCT).

- Secondary Efficacy Endpoint(s): We hypothesize that the proportion of children with each of the following outcomes will not be inferior in the intervention (task-shifted) and control (enhanced usual care; EUC) arms of the BRIDGE cRCT: (a) epilepsy misdiagnosis; (b) seventy-five percent reduction in seizure frequency at 24 months compared to enrollment baseline (Visit 0); (c) seizure freedom for ≥ 6 months after treatment with the first prescribed anti-epileptic drug (AED); (d) epilepsy-associated mortality; (e) status epilepticus; (f) new neurodevelopmental morbidity between Visit 1 week and Visit 24 months; (g) epilepsy-associated hospitalizations; and, (h) diagnostic tests (e.g., EEG, MRI) ordered.

9.2 SAMPLE SIZE DETERMINATION

This is a cluster randomized trial to test the non-inferiority of the intervention (childhood epilepsy care task-shifted to community health workers [CHWs]) compared to enhanced usual care (EUC- referral to a physician *plus* primary care by an epilepsy-trained CHW). Policy makers may consider task shifted care as a viable option for the treatment of pediatric epilepsy in Nigeria even if it were slightly less effective than enhanced usual care due to the broader reach of TSC in northern Nigerian communities, in the context of a very large childhood epilepsy treatment gap, that in some areas may exceed 90%.

Let p_{EUC} and p_{TSC} be the proportion of patients in their respective treatment arms that are seizure free in the last 6 months of their 24-month study period. We seek to reject the one-sided null hypothesis, H_0, that the success rate of TSC patients (p_{TSC}) is inferior to that of EUC patients (p_{EUC}) by 10% or more in favor of the alternative hypothesis, H_a, that the success rate of TSC treatment is not inferior by a margin of 10%. More simply,

$$H_0: p_{EUC} - p_{TSC} \geq 0.10$$
$$H_a: p_{EUC} - p_{TSC} < 0.10$$

Hemming et al. provide a recent tutorial for estimating sample size for a cluster randomized trial with a fixed number of clusters.[81] Briefly, the correlation of outcomes within clusters, measured by the intraclass correlation (ICC), is used to inflate the standard variance (VIF) by [1 + (*m*-1)*ICC], where *m* is the number of patients per cluster. Some algebra shows that the sample size per arm (nC), nC= *km* where *k* is the number of clusters (PHC's) required to detect a difference *d*, with power 1-b is

$2\sigma^2\left[\frac{(Z_{\alpha/2}+Z_\beta)^2[1+(m-1)ICC]}{d^2}\right]$. Here σ^2, the variance of the proportions, is ≈ p_{EUC} (1- p_{EUC}) + p_{TSC} (1- p_{TSC})]/2.

Assuming an equal primary outcome at 24 months follow-up (proportion of children seizure-free at least 6 months) for the intervention and EUC arms, we will achieve ≥80% power to rule out a non-inferiority margin of ≥10% by enrolling ≥1267 children, with ≥1140 completing the cRCT (30 PHCs in each arm of the cRCT, and 19 children per PHC).

Figure 5 below demonstrates, given 25, 30, or 35 clusters (or randomly selected PHCs) per arm, how the power increases as the sample size within each cluster (or PHC) increases. Note that the rate at which the power increases through per-cluster sample size slows down. Based upon these data, and our clinical and research capacity, we chose to have 60 randomly selected clusters (or PHCs), 30 PHCs per arm of the cRCT, and a minimum of 19 patients per PHC. Our best estimate is that at least 1378 children (23 children per PHC) will complete the 24-month cRCT (see Figures 1 and 2). These calculations assume an intra-cluster correlation coefficient (ICC) of 0.05, assume that approximately 60% of children in both arms will be seizure-free, and are based on a one-sided 95% confidence interval for the difference not including 10%. Power for n=1140 completing children is 80%; power for n=1378 completing children is 83%. Power calculations are similar for similar ICC values (power=90% and 77% for ICC=0.03 and 0.07, respectively; n=1378) and proportions experiencing the primary outcome (power=82% and 88% for seizure free proportions of 50% and 70% in both arms, respectively; n=1378). Assuming loss to follow-up of 10%, to have 1378 children complete the study we will enroll a minimum of 1530 children, and to correct for the imbalance in cluster enrollment we will enroll a maximum of 1800 children.

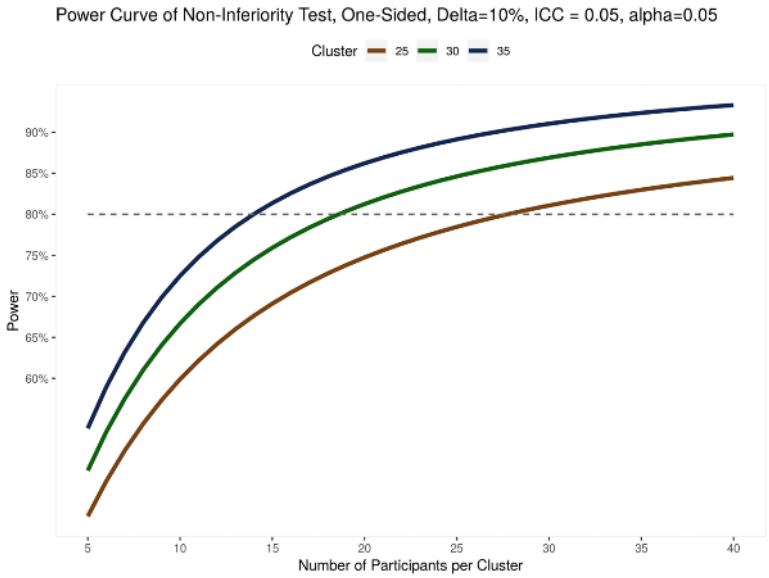


Figure 5. For 25, 30, or 35 clusters per arm, as the sample size within each cluster increases, the power increases accordingly. As the sample size within each cluster increases, the power gained through the sample size increase grows at a slower rate.

Adjustment for Cluster (PHC) size imbalance. We have estimated a total enrollment of 1530 to 1800, after consulting with the DSMB and prior approval by the appropriate Ethics Committees and IRBs in the Fall of 2020. Monitoring of the data in late fall of 2020 revealed a cluster (PHC) enrollment imbalance. While we do not expect pathologic imbalances in cluster sizes where, for example, 80% of observations lie within 20% of the clusters,[82] we explored adjusting enrollment efforts to correct for the observed imbalance. This imbalance, measured by the coefficient of variation (CV), among cluster sizes was variably 0.4 to 0.5. For a CV of cluster sizes <0.23, the effect on sample size is negligible. The maximum possible inflation in sample size (MIS) is $\{1 + [(1 + CV^2)\bar{m} - 1]ICC\}/\{1 + (\bar{m} - 1)\ ICC]$, where ICC is the intraclass correlation coefficient, $\bar{m}$ is the average cluster size.[83] Conservatively assuming CV of 0.5, the MIS for an ICC of 6% is 1.13. The adjusted enrollment estimates to maintain 80% power rises from 1530 to 1730 patients. Given that enrollment is occurring simultaneously at 60 sites in 3 cities in northern Nigeria, where the demand for enrollment is high, plans to start cessation of enrollment will begin when 1730 children are enrolled, with a maximum anticipated enrollment of 1800.

Power for quantitative surveys: Acceptability, appropriateness, and feasibility will be measured at baseline (upon enrollment into the cluster randomized clinical trial [cRCT]), and then at 12 months and 24 months. These measures will be scored on the Likert scale of 1 to 5. The difference of the Likert score between baseline and 12 months (and 24 months) will be calculated. The expected difference has a maximum of 4 and minimum of -4. We conservatively assume that the standard deviation (SD) of the difference is 2 (as ±2 SD covers the range of the data). We estimate that 1140 - 1380 participants (570-690 participants per arm) will complete the 24-month cRCT and be interviewed. If 1140 participants (570 participants per arm) complete the 24-month cRCT, we will have 80% power to detect a difference of 0.46 units on the mean difference of the Likert scale from 1 to 5. If 1380 participants (690 participants per arm) complete the 24 months cRCT, we will have 80% power to detect a difference of 0.44 units on the mean difference of the Likert scale.

Sample size for qualitative interviews: The process for these interviews will be mostly inductive. We are adopting a 'bottom-up' approach, using the participants' perspectives to build broader themes. This aim will explore a topic for which there is little existing research available; therefore, its qualitative nature allows for responses that are meaningful, culturally significant, and stimulate free thinking from participants. The theory of data saturation will inform our final sample size: we will continue to collect data from participants until we generate enough information to understand how this novel implementation strategy impacts participant perceptions and experience. Based on previous experience with participant interviews in the region, we estimate that 30 eligible healthcare providers and 60 patients/parents/guardians will be required to reach saturation.

9.3 POPULATIONS FOR ANALYSES

9.3.1. Aim #1. Non-inferiority cluster randomized clinical trial (cRCT) of task-shifted care (intervention) versus enhanced usual care (EUC). We estimate that approximately 1530 of 1700 children with untreated epilepsy will enroll in the study over 24 months.

- We estimate that about 1378-1575 of about 1730 (maximum 1800) enrolled children will complete the cRCT (a conservative estimate of 10% drop-out rate, higher than in prior studies in northern Nigeria), see figure 3.
    - If 1378 children (23 children per PHC, 30 PHCs per arm) complete the 24-month follow-up period, we will have 83% power to rule out a non-inferiority margin of $\geq$ 10% in the seizure-free proportions in each arm (assuming ~ 60% of children in each arm will be seizure-free).
    - If 1140 children (19 children per PHC, 30 PHCs per arm) complete the 24-month follow-up period, we will have 80% power to rule out a non-inferiority margin of $\geq$ 10%.
    - Evidence to date suggests that the childhood epilepsy treatment gap is equally distributed across the city of Kano, Nigeria. Data regarding the epilepsy treatment gap in Zaria and in Kaduna, both cities close to Kano with similar resources for healthcare, are not available. We assume that the magnitude of the epilepsy treatment gap and the distribution of that treatment gap are similar in Kaduna and in Zaria.
- Therefore, estimates based upon the investigators' experience in Kano with the R21 BRIDGE project rates of screening recruitment targets are calculated as shown below (assuming 1% positive screen rate; predictive value positive of screen = 0.9; treatment gap of 60%; rate of enrollment is 90% of eligible).
    - Year 1 of enrollment
        - Each CHW enrolls about 9 children into the cRCT during the first year
        - First year total enrollment is 18 per PHC = ~1080-1300 children
            - 5 children enrolled per PHC per month (or less than 1 child enrolled per CHW per month)
            - If at any time in the first year the Multi-PIs determine that the study is at risk of not meeting enrollment targets, then the screening will shift to pediatric clinics in the participating hospitals, where we have found the prevalence of children with epilepsy (and of untreated epilepsy) to be higher than in door-to-door surveys.
    - Year 2 of enrollment:

- The number of children identified in door-to-door surveys with untreated epilepsy may decrease due to coverage of much of the areas closest to the PHCs with prior screening. Therefore, in Year 2, if behind in enrollment, or if drop-out rates exceed the expected 10% over 2 years, we will begin to screen for children with untreated epilepsy in the cities' pediatric clinics at major hospitals where the prevalence of untreated epilepsy is higher).
- CHWs will spend slightly less time screening in the community as they will need to follow the patients who have been enrolled.
- Second year total enrollment is estimated at 10 children per PHC

- **Total estimated enrollment over 2 years is at least 28 per PHC (or 0.6 enrolled study subjects per 0.5 FTE CHW per month) ~ 1680-1730** (maximum 1800)

  Children completing 24-month study ~ 1378-1575

  - **Minimum children completing the 24-month study ~ 1140**

<u>9.3.2 Aim #2.</u> Assess socio-behavioral and implementation outcomes among providers, parents/guardians and patients in the cRCT. At the time of enrollment, at Visit 2 months, and at Visit 24 months, all participants ages 11-17 years will complete the QOLIE-AD-48 administered by a trained CHW.[84,85] At 24 months participants who have reached 18 years of age will complete the QOLIE-31 (Table 1). Within approximately one week of enrollment, all parents/guardians of all enrolled patients and patients (if ages 15-17 years) will complete short interviewer-administered surveys about their trust in the local healthcare system, epilepsy knowledge and attitudes, stigma, and quality of life. At 12 and 24 months, when participants complete scheduled visits with a blinded physician specialist to assess their epilepsy management, these instruments will be repeated. Measures of trust in healthcare provider, as specifically defined by the provider who prescribes and manages AEDs, will be collected at 12 and 24 months from parents/guardians and patients (if age 15-17 years) in both arms of the cRCT. At baseline, 12, and 24 months after enrollment, all health providers (CHWs and physicians) in the intervention arm will provide information via REDCap questionnaires regarding the acceptability, appropriateness, and feasibility of the task-shifted childhood epilepsy care protocol.

<u>Qualitative data collection for Specific Aim 2</u>: Thirty (of 120) randomly selected CHWs and all (estimated four) unblinded physicians supervising the CHWs in the intervention arm will complete baseline qualitative interviews to identify "inner" and "outer" context factors that may support or hinder uptake of the intervention, as well as questions about CHW characteristics that may influence successful implementation of the task-shifted care guidelines. Guided by the Consolidated Framework for Implementation Research (CFIR), interviews will focus on cultural, structural, and personal factors that could limit or enhance delivery of task-shifted epilepsy care services.

Sixty selected parents/guardians in the intervention arm will complete mid- (12 month) and end-line (24 month) qualitative interviews about their experiences with their respective CHWs and the task-shifted healthcare team. Experiences of parents/guardians may differ by whether their children are seizure-free or experienced continued seizures while on treatment. Therefore, these participants will be selected randomly from two groups: (1) 30 parents/guardians whose children have been seizure-free for >6 months and (2) 30 parents/guardians who have experienced a less than a 75% reduction in seizure frequency over the past 6 months. We will assess participants' perceptions of task-shifted epilepsy care using acceptability, appropriateness, and feasibility measures developed by Weiner et al. These scales have been tested and exhibited substantive and discriminant content validity, high factor loadings (0.79 to 0.94) and acceptable Cronbachs alphas (0.85 to 0.91).

9.3.3. Aim #3. Determine the cost-effectiveness of the task-shifted epilepsy care intervention.
A cost-effectiveness analysis will be conducted of task-shifted epilepsy care and utilization of diagnostic and management technology for children with epilepsy in the task-shifted sites compared to the EUC sites. Using the study subject population outlined under Aim #1, we will express cost-effectiveness in both US dollars and in Nigerian Naira per additional disability-adjusted life year averted (DALY) - a measure that quantifies disease burden and reflects changes in both life expectancy and quality of life. We will also perform scenario analyses that consider the increased capacity of the health system to manage large numbers of patients with epilepsy using a task-shifted epilepsy care system.

The baseline capacity of physicians to diagnose and manage childhood epilepsy patients will be determined for traditional physician specialist settings in northern Nigeria and compared to the capacity for the task-shifted epilepsy care model. During the first six months of Year 1, immediately prior to cRCT enrollment, we will collect data from a large childhood epilepsy clinic in Kumbotso, Kano State, and at pediatric neurology clinics at AKTH and at Murtala Muhammad (both also in Kano) to determine the number of epilepsy patients typically managed per year by a physician without assistance from a CHW. These data will be compared to the number of patients with epilepsy managed per year by a full-time CHW in a task-shifted environment and the number of patients who can be managed per year with epilepsy by a physician spending approximately 25% effort supervising twenty CHWs in a task-shifted environment.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Statistical Design and Analysis for Aim 1. The primary outcome measure for the cRCT is the proportion of patients who are seizure-free for a minimum of 6 months preceding the 24-month follow-up appointment, as determined by the blinded physician assessment. Secondary outcomes of the cRCT will be (a) percent reduction in seizure frequency; (b) seizure freedom for a minimum of 6 months following administration of the first AED; (c) time to next seizure after achieving seizure freedom for 3 months; (d) accuracy of epilepsy diagnosis and seizure type classification (compared to the gold standard of the blinded physician epilepsy specialist); (e EEGs ordered; (e) brain imaging ordered; (f) CHW protocol

adherence (as determined by review of the CRFs by the Vanderbilt Coordinating Center pediatric neurologist); (g) episodes of status epilepticus; (h) hospitalizations for seizures/epilepsy; and, (i) epilepsy- and AED-related morbidity.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The primary endpoint is seizure-free for ≥ 6 months (i.e., ≥180 days) at the 24-month visit, as determined by blinded physician assessment, will be compared between study arms using generalized linear mixed effects models for logistic regression, adjusting for within PHC correlation and key baseline variables including seizure frequency, type of epilepsy, age (restricted cubic spline with 3 knots), sex, and city. Non-inferiority will be declared if the lower limit of the one-sided 95% confidence interval for the ratio of the odds of being seizure-free in the intervention vs. standard-of-care is below the odds ratio implied by a 10% absolute difference between study arms. For example, if the proportion seizure-free at the end of follow-up is 60% in the SOC arm, then non-inferiority would be declared if the lower-limit of the 95% CI was greater than 2/3 (= $[(0.6 - \delta)/(1 - 0.6 + \delta)]/[0.6/(1-0.6)]$, with δ=0.1, the non-inferiority margin described in Section 9.2 for sample size calculations). This analysis is consistent with sample size calculations, while allowing us to adjust for patient characteristics to improve power and to properly account for correlation between patients seen at the same PHC. The proportion of children with this endpoint in each arm of the cRCT will be compared (details in Section 9.4.5).

Subjects may drop out for reasons related to outcomes of interest, i.e. they may be doing well or poorly. It may not be reasonable to assume that outcomes are missing completely at random (MCAR). In this setting, using likelihood inference, we can obtain unbiased estimates if data are missing at random (MAR), i.e., the outcome is independent of missingness conditional on observed variables in the model. Including a rich set of predictors in the model may make the MAR assumption more plausible.[86,87] The assumptions for MCAR and MAR are untestable. We will also consider multiple imputation or tipping point analyses.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The following secondary endpoints analyses will include the following: (a) percent seizure reduction from enrollment baseline, and specifically the percentage of children in each arm of the cRCT who achieve a >75% reduction in seizure freedom compared to baseline seizure freedom at the time of cRCT enrollment; (b) time to next seizure after three months seizure-free; (c) accuracy of epilepsy diagnosis and seizure classification based on evaluation by physician specialists with epilepsy expertise who are blinded as to whether patients are in the intervention or control arms of the cRCT; (d) percentage of study subjects in each arm of the study who responded to the first chosen anti-epileptic drug (AED); (e) morality among children in both arms of the cRCT; (f) episodes of status epilepticus among children in each arm of the cRCT; (g) new neurodevelopmental morbidity among study subjects in each arm of the cRCT; (h) AED adverse events in both arms of the cRCT; (i) hospitalizations among study subjects in each arm of the cRCT; and, (j) neurodiagnostic tests (e.g., EEG, MRI) ordered in each arm of the cRCT.

Similar to our primary endpoint, we will analyze these secondary endpoints using generalized linear mixed effects models to appropriately account for correlation within PHCs. Specifically, continuous outcomes [i.e., secondary endpoints (a) and (j)] will use the identity link, count data [i.e., secondary endpoints (f) and (i)] will use the log-link, and binary outcomes [i.e., secondary endpoints (a), (c), (d), (e), (g), and (h)] will use the logit link. Time-to-event outcomes [i.e., secondary endpoints (b) and (e)] will be analyzed using Cox proportional hazards regression with random effects (i.e., frailty models).

9.4.4 SAFETY ANALYSES

The Kano-, Zaria-, and Kaduna-based epilepsy physicians will review the prescription records, medical charts, and electronic case report forms (CRFs) monthly of patients followed by the CHWs (in both the task-shifted intervention and enhanced usual care arms) under their supervision and use the information as feedback to improve provider knowledge and competence as part of usual practice. Any medical errors will be brought to the attention of the CHW and will also be reported to the BRIDGE PIs; medical errors will also be reported to the BRIDGE Data Safety Monitoring Board (DSMB) as per the DSMB procedures.

In compliance with the NIH requirements, and following the formation of the Data and Safety Monitoring Board (DSMB) with approval by NINDS, we will comply with guidance on DSMB activities for the cluster-randomized trial component of this project. The data and safety monitoring plan will include reporting of serious adverse events to the IRBs and the DSMB.

Personnel involved in the monitoring of activities will include the following:

- PI/PD, Multi-PIs
- A designated medical monitor with expertise in childhood epilepsy at all three clinical centers (Kano, Kaduna, Zaria) who will provide consultation on medical risks and who will review adverse events.
- An internal committee consisting of the PI/PD, Multi-PI and the co-investigators on the BRIDGE project.
- The DSMB

Serious adverse events will be reported to the chair of the DSMB by the PI/PD (Dr. Trevathan). Summaries of all adverse events will also be made to the NIH in the yearly progress report, or more frequently as requested. The DSMB has the authority to halt the cRCT if it perceives that harm is occurring due to the intervention. Early stopping of the trial could occur based on the recommendation of the DSMB due to high imbalance in SAEs between study arms. Given the possibility that there could be higher than expected rates of SAEs (epilepsy-associated morbidity has been reported to be higher in Africa), we suggest conservative stopping decisions. We will also perform an interim analysis of the primary outcome and adverse events (AEs) and serious adverse events (SAEs) to determine whether the trial should be stopped early for futility or for increases in AEs or SAEs in the task-shifted arm of the

cRCT; details are in Section 9.4.6. We plan an initial DSMB meeting schedule of every six months. The DSMB will be appointed in consultation with NINDS, and we will follow their advice for all safety monitoring and futility analyses.

Aims 2 and 3 study, the components of this cluster-randomized trial that determines the socio-behavioral and implementation outcomes and the cost-effectiveness of a task-shifted intervention, do not have the same level of risk or complexity as a clinical trial of a drug or an intervention. Therefore, as Multi-PIs, Drs. Trevathan and Abdullahi will assume primary responsibility for data and safety monitoring, with periodic reports to the DSMB.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics, including means, standard deviations, and ranges for seizure-free rates will be determined. Adverse medical events and patient dropout will be tabulated. Patient characteristics, both overall and by study arm, will be described using medians and interquartile ranges.

Primary analysis. The primary outcome, seizure-free for $\geq$ 6 months at the 24-month visit (i.e., 180 days prior to the date of the 24-month visit), will be compared between study arms using a mixed effects logistic regression model, with random intercepts included to account for PHC and adjusting for key baseline variables including seizure frequency, type of epilepsy, age, and sex. Non-inferiority will be declared if the lower limit of the one-sided 95% confidence interval for the ratio of the odds of being seizure-free in the intervention vs. standard-of-care is below the odds ratio implied by a 10% absolute difference between study arms. For example, if the proportion seizure-free at the end of follow-up is 60% in the SOC arm, then non-inferiority would be declared if the lower-limit of the 95% CI was greater than 2/3 (= [(0.6-□)/(1-0.6+□)]/[0.6/(1-0.6)], with □=0.1, the non-inferiority margin described in Section 9.2 for sample size calculations). This analysis is consistent with sample size calculations, while allowing us to adjust for patient characteristics to improve power and to properly account for correlation between patients seen at the same PHC. Secondary outcomes will also be compared using mixed effects models, with appropriate link functions and outcome transformations based on the specific endpoint.

9.4.6 PLANNED INTERIM ANALYSES

Interim analysis for primary endpoint and DSMB: We planned a single interim analysis of the primary endpoint when approximately 50% of the enrolled patient endpoints accrued - when 50% of enrolled study subjects completed their 24-month follow-up visits with blinded physicians. Based on the anticipated enrollment, and the 24-month period required to assess the endpoint, we anticipated that this interim analysis would take place about 30-36 months after enrollment began. However, accrual was so rapid that it was determined by the BRIDGE Multi-PIs, statistical team, and DSMB that the initial planned interim analysis on the primary endpoint would not be useful: the interim analysis would take place only a few months before the final analysis, meaning that if the data were such that they favored stopping the trial early due to TSC being inferior to EUC, it would be too late to have much of any benefit on the vast majority of trial participants who would already be only a few months away from finishing the study.

Consequently, based on consultations with the DSMB, we will perform an interim analysis based on the proportion of patients that are seizure-free for ≥ 6 months at the time of their 12-month blinded physician visit. The purpose of this interim analysis is to provide a signal for the principal investigator, DSMB, and sponsor to evaluate continuing the study should the interim data suggest that the task-shifting is inferior to enhanced usual care at 12 months.

A rigorous trial evaluation by the research team, DSMB, and sponsor will be called if the one-sided p-value for testing superiority by a margin of 10% for the enhanced usual care arm at 12 months is <0.05 (type I error =0.05). If at this interim analysis, the task-shifting arm is deemed to be inferior by at least 10% to EUC (i.e., 95% confidence interval concluding that TSC is at least 10% worse than EUC at the 12-month endpoint), then it may be unlikely for the task-shifting intervention to end up being proven non-inferior if the trial were to continue. Assuming a type I error rate of 5% and 40% response rate (seizure-free for 6 months at the 12-month blinded physician visit) among EUC treated patients, we would have approximately 80% power to detect early inferiority of the TSC arm by at least 10% if the response rate at 12 months in the TSC arm is 20% (20% absolute reduction in response rate) and approximately 33% power to for potential inferiority if the response rate is 25% (15% absolute reduction in response rate). More details are given in Table 1 for varying numbers of patients in the 12-month interim analysis and varying TSC response rates. These power calculations for the interim analysis are based on a superiority by a margin difference (10%) null hypothesis.

Like the primary analyses, the interim analysis will fit a generalized linear mixed effects model for logistic regression, including PHC as a random effect to account for correlation between participants within the same PHC, and adjusting for key baseline variables including seizure frequency, type of epilepsy, age (restricted cubic spline with 3 knots), sex, and city.

If the trial continues beyond the interim analysis, our final analysis will not be adjusted for this interim analysis. The rationale for this decision is the following: 1) The endpoint of the final analysis (6-month seizure free at 24-month visit) differs from the endpoint of the interim analysis (6-month seizure free at 12-month visit). Although these different outcomes are likely correlated, the strength of this correlation is not known, particularly since the first 12 months is a period when different treatments are being explored to address epilepsy. 2) The trial will not be stopped early in favor of the TSC arm or for non-inferiority of the TSC arm; therefore, we are not giving ourselves two chances to declare the TSC non-inferior. 3) The interim analysis can be thought of as a safety analysis; a decision to discontinue the trial may be made if there is clear evidence that the TSC is not as safe in the first 12-months as EUC.

Operating Characteristics for Planned Interim analyses: This interim analysis is based on **superiority of the EUC by a margin of 10%** over TSC. Table 1 shows the power to declare that EUC is superior to TSC by at least 10% under various numbers of accrued patients and for varying response rates in the TSC arm.

Table 2. Power for interim analysis to declare EUC superior to TSC by at least 10% in interim endpoint. Calculations assume 40% response rate in EUC arm,[1] type I error rate of 0.05, and intraclass correlation of 0.05.

Cluster size (proportion of total accrual of 1730 patients)[2]	TSC Response Rates		
	20%	25%	30%
14 (49%)	80%	33%	5%
15 (52%)	81%	34%	5%
16 (55%)	82%	34%	5%
17 (59%)	84%	35%	5%

[1] A patient has responded if they have been seizure-free for 6 months at their 12-month blinded physician visit.
[2] Cluster size times 60 clusters divided by DSMB approved total accrual of 1730 patients

Note that when the superiority margin equals the true difference between the TSC and EUC arms (40% in EUC and 30% in TSC, for 10% difference in response rates), the probability of early consideration for termination is the type I error rate (5%). The lower limit of power (probability of early termination) is the type I error rate of the test when the superiority margin equals the true difference. Calculations assume an intracluster correlation of 0.05.

9.4.7 SUB-GROUP ANALYSES

The analyses regarding the primary endpoint (percentage of children seizure-free) may be conducted among children with non-convulsive epilepsy and convulsive epilepsy, or among specific common seizure types (e.g., generalized tonic-clonic seizures). However, given the paucity of data regarding the epidemiology of specific seizure types in northern Nigeria, and even in Africa, it is not possible now to determine whether we will have adequate sample sizes for such analyses.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Participant/study subject level data will be entered into REDCap using portable tablet computers by study CHWs and study physicians and staff. Regular uploads of data to the Vanderbilt Institute for Global Health (VIGH) data coordinating center (DCC) will be conducted daily when the research staff has access to the internet or at least twice weekly; backup copies of the data will be maintained in the Vanderbilt-secured cloud. All children whose parents/guardians give consent will be assigned a unique BRIDGE cRCT study number that includes digits indicating the site of the screening and assignment to intervention or control arm. The patient will be identified by this study number, with all other personal identifying information stripped from the data for the purpose of analysis and reporting of results. Codes for interpreting the study ID numbers will only be available to key study personnel who are not blinded; blinded study physicians will not be able to determine the study arm for a particular patient by looking at the study ID. Key study personnel will have access to select personal identifiers if needed to exclude duplicates and to replace any lost cards with study numbers that will be provided to the enrolled parents or guardians. Ongoing evaluation of the accumulated summary data, including evaluation of adverse events, will be monitored by the VIGH DCC and our Data and Safety Monitoring Board (DSMB). Tabulation of individual participant data will only be utilized in by study investigators and staff for the purpose of ensuring completeness and accuracy of data, and for safety-monitoring purposes.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

As part of the protection of human subjects, we will include informed consent and informed assent procedures in our protocol. The study physicians, study community health workers (CHWs) and research coordinators at the study sites in Kano, Kaduna and Zaria, Nigeria will conduct the consent process. The informed consent documents include information about the study, including the purpose of conducting the cluster randomized clinical trial (cRCT), the cRCT duration, a description of the study procedures, a description of any foreseeable risks, and the extent of confidentiality. Specifically, we will include contact information for the Multi-PIs, study physicians and CHW(s) on the consent form as well as the local IRB/Ethics Committee contact.

We will provide a study document to parents/guardians in the native language (Hausa) and in English, describing the pros and cons of participating in the cRCT. Informed consent will be obtained from parents/guardians of children and assent will be obtained from older children. We will have two consent documentation processes: (1) We will obtain informed consent for the epilepsy screening phase of the study, which includes consent for the parent/guardian to answer screening questions, and if the screen is positive to be evaluated by the CHW (if in the task-shifted intervention arm) or to be referred to a physician (if in the enhanced usual care arm). All children who screen positive for epilepsy, are determined to have epilepsy, and are not currently receiving treatment for epilepsy will undergo the second consent process - (2) consent for enhanced usual care (EUC) if the closest study PHC to the child's home address is an EUC site, or epilepsy care with the task-shifted (to CHWs) protocol if the closest study PHC to the child's home address is a task-shifted site.

Subject Characteristics and Informed Consent

The patient population consists of all children (age 6 months-17 years) with untreated epilepsy whose parent/guardian have provided consent (and older children have provided assent) to enroll in the cRCT of a task-shifted epilepsy care protocol versus enhanced usual care. Informed consent for enrollment and follow-up will be administered at the participating clinical sites where each patient is enrolled. The consent form describes the cRCT for all children eligible to be in the study. Vanderbilt University Medical Center (VUMC) will be the data coordinating center for this trial. The patients are not individually identifiable at the coordinating center. Confidential data, including name, address, and the clinical site to aid in maintaining patient follow-up will be collected. We will also collect information on the parent's employer, and name and address of relatives. Such information will be kept separate from study forms in a secure file.

Adequacy of Protections against Risk

Trained health care professionals, within a medical facility, with appropriate resources available, will perform all standard care and research procedures. Additionally, all sites have designated study staff working with participants. Arrangements have been made with ancillary departments within the study clinical sites to ensure participant safety.

Recruitment of Participants and Informed Consent

The study protocol and informed consents will be submitted and approved by each local site's IRB, including that site's state ministry of health's ethics committee. Informed consent/assent will be obtained for each participant prior to initiating any study procedures.

Protection against Risk

Patients' risks of participating in research will be kept to a minimum with measures to protect confidentiality and planned interim analyses for safety monitoring and early termination. Steps to protect privacy will include assignment of study codes to all records, without patient names, with the key for connecting patient names and study codes kept in a secure site separate from the study records at the local site only. All study records will be kept in a secure locked location to prevent unauthorized access.

Potential benefits of the proposed research to the subjects and others- both the participants in the intervention arm and the participants in the enhanced usual care (EUC, "control") arm will benefit from epilepsy-trained CHWs providing medical care to the child with epilepsy. We do not know whether clinical outcomes vary by whether childhood epilepsy management (diagnosis and treatment) is performed by a community physician, or by an epilepsy-trained CHW - a key question driving this clinical trial.

Importance of the knowledge to be gained

This study tests the efficacy of task-shifted (to CHWs) childhood epilepsy care compared to enhanced usual care for epilepsy. The results of the study may provide an evidence basis upon which task-shifted interventions can implemented to reduce the childhood epilepsy treatment gap in Africa.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials for each of the three cities (Kano, Zaria, and Kaduna) are submitted with this protocol (see Appendix C); (a) screening and diagnostic exams consent forms and assent forms; (b) consent forms and assent forms for enhanced usual care (EUC); and, (c) consent forms and assent forms for task-shifted care. In addition, study subjects who are less than 17 years of age at the time of enrollment into the cRCT who have their 18th

birthday prior to the 24-month follow-up visit will complete a consent form at their next visit after their 18th birthday; these consent forms are also attached.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Consent from a parent (or guardian) will be obtained prior to the screening of their children for possible epilepsy using the Hausa epilepsy screening and classification tool; this consent form will include a consent for screening the child for possible epilepsy using the screening tool (Appendix B) and the exam by a CHW (with physician supervision per the protocol, see figure 3) for children who screen positive.

Children (≥ 6 months, < 17 years) who screen positive for epilepsy and who also are found to have active epilepsy (a seizure(s) within the past year) after a clinical evaluation (history and physical exam), and who also are not being treated for epilepsy will be offered consent for enrollment into the BRIDGE cRCT.

Consent

Parents/guardians of children whose address is closest to a PHC that has been randomized to enhanced usual care (EUC), will be given a consent for the EUC arm of the cRCT (see Appendix C). Parents/guardians of children whose address is closest to a PHC that was randomized to task-shifted care will be given a consent for the task-shifted arm of the cRCT. Consent forms are found in Appendix C and will be available in English and in Hausa. *Children who are < 17 years of age, but who have their 18th birthday during the cRCT, will be given a consent form or the cRCT during the scheduled CHW visit immediately following their 18th birthday (Appendix C).* There are separate consent forms for the Zaria, Kaduna, and Kano sites in order to clearly identify city-specific principal investigators and ethics committee contacts

Assent and Dissent

Assent forms will be provided to children ages 7 years to < 17 years, who are able to understand concepts of assent. The consent and assent forms will be available in Hausa and in English, and the parent/guardian will be able to choose which language they prefer for the consent/assent forms. Assent forms are found in Appendix C. There are separate assent forms for the Zaria, Kaduna, and Kano sites in order to clearly identify city-specific principal investigators and ethics committee contacts.

Dissent from children will be clinically assessed in a compassionate and culturally sensitive manner, with parent/guardian involvement; appropriate action will be taken to resolve the dissent. Resolution of the dissent by a potential study subject may include not enrolling the child in the cRCT.

Children who are candidates for the study, but who are not enrolled in the BRIDGE cRCT, will be referred to a local physician for epilepsy treatment.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be

provided by the suspending or terminating party to study participants, investigator, funding agency, sponsor (NINDS/NIH) and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (Multi-PI/PD) will promptly inform study participants, the IRBs/Ethics Committees, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants in one arm of the cRCT
- Demonstration of efficacy of the intervention (task-shifting) that would warrant stopping prematurely
- Insufficient compliance of study staff to the protocol (i.e., significant protocol violations)
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRBs/Ethics Committees, or other relevant regulatory or oversight bodies (OHRP, DSMB).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally identifiable information from the study will be released to any unauthorized third party.

All research activities will be conducted in as private a setting as possible, given the physical constraints of the healthcare facilities in northern Nigeria. The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB)/Ethics Committees, regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital). The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRBs/Ethics Committees, institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Vanderbilt Institute for Global Health Data Coordinating Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Vanderbilt Institute for Global Health research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Vanderbilt Institute for Global Health.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see https://grants.nih.gov/policy/sharing.htm). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality
To further protect the privacy of study participants, the U.S. Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subject's research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see https://humansubjects.nih.gov/coc/index). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the Vanderbilt Institute for Global Health. After the study is completed, the de-identified, archived data will be transmitted to and stored at the Vanderbilt Institute for Global Health, for use by other researchers including those outside of the study. Permission to transmit data to the Vanderbilt Institute for Global Health will be included in the informed consent.

There will be no biological samples retained as part of this study.

When the study is completed, access to study data will be provided through the Vanderbilt Institute for Global Health. All requests for use of the study data will require the involvement and consent of the study Multi-PIs, consistent with the policies of the Aminu Kano Teaching Hospital (AKTH) in Nigeria. Publications of data from the BRIDGE project will require participation and authorship opportunities by the BRIDGE investigators in Kano, Zaria and Kaduna, Nigeria, and the BRIDGE investigators at the Vanderbilt Institute for Global Health.

Electronic records (computer files, electronic databases, etc.) will be maintained in a secure environment. Duplicate system back-up data will be stored in a secure, off-site facility. Access to the system will be password protected. Paper/hard copy records will be kept in a locked cabinet or office. Data will be de-identified by the local site prior to submission to the clinical coordinating center.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigators, Site Investigators
Edwin Trevathan, MD, MPH, Multi-PI-PD Vanderbilt Institute for Global Health
Aminu Taura Abdullahi, M.B.B.S., M.Sc., Multi-PI Aminu Kano Teaching Hospital
Hafsat Ahmad, M.B.B.S., Zaria site Lead
Folorunsho Nuhu, M.B.B.S., Kaduna site Lead

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including statistics and statistical analysis of clinical trials data, neurology and pediatric neurology, epilepsy, clinical trials in pediatric epilepsy, and epilepsy research in sub-Saharan Africa. Members of the DSMB will be independent from the study conduct and free of conflict of interest, and measures will be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to National Institute for Neurological Disease and Stroke (NINDS)/NIH.

10.1.7 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International

Council on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s). Monitoring activities will be as follows:

- Drs. Trevathan, Abdullahi, Sabo, and/or Adamu will conduct on-site assessments of the clinical sites (PHCs, clinics) in Kano at the prior to study enrollment launch, and at least yearly throughout the period of the cRCT, and training in study protocol and procedures will occur prior to the study launch, with refresher training at least twice yearly for all study staff at each of the Kano sites. 100% data of data collected will undergo checks for completeness and internal consistency at AKTH for the Kano-based sites. Clinical monitoring reports will be submitted to the data coordinating center (DCC) at the Vanderbilt Institute for Global Health (VIGH) and will be made available to the BRIDGE data safety monitoring board (DSMB).

- Drs. Nuhu, Ahmad, Abdullahi, Sabo, and/or Adamu will conduct on-site assessments of the clinical sites (PHCs, clinics) in Kaduna and Zaria at the prior to study enrollment launch, and at least yearly throughout the period of the cRCT, and training in study protocol and procedures will occur prior to the study launch, with refresher training at least twice yearly for all study staff at each of the Zaria-based and Kaduna-based sites. 100% of data collected will undergo checks for completeness and internal consistency at AKTH for the Zaria-based and Kaduna-based sites. Monitoring reports of the data monitoring activities in Zaria and Kaduna will be made available to the VIGH DCC and provided to the DSMB.

- Blinded study physicians, each of whom have expertise in epilepsy (two-to-three in Kano, one-to-two in Zaria, and one-to-two in Kaduna) will evaluate each enrolled patient at 1 month, 6 months, 12 months, 18 months, and 24 months after enrollment. Any concerns regarding patient safety or adverse events will be reported directly to the co-investigator supervising the blinded physicians (Dr. Salihu), the city/site lead investigator (Dr. Abdullahi, Kano; Dr. Ahmad, Zaria; and, Dr. Nuhu, Kaduna) and recorded into the REDCap CRFs. Adverse events reported by blinded physicians will be evaluated as indicated for all adverse events (See section 8.3).

- Independent audits will not be conducted, but electronic records of all changes and edits in the data that are entered into REDCap will be maintained.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. All sites will follow a common quality management plan.

Quality control (QC) procedures will be implemented as follows:
Informed consent - Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with Good Clinical Practice (GCP), accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data - Data will be initially captured in REDCap source documents (see **Section 10.1.9, Data Handling and Record Keeping**) and will ultimately be entered into the study database at VIGH DCC. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.
Intervention Fidelity - Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.
Protocol Deviations - The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.
Should independent monitoring become necessary, the study personnel will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.
All study visit worksheets will be in REDCap and all cRCT materials will be recorded into REDCap on android tablet computers for each participant consented/enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.
Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into [specify name of data capture system], a 21 CFR Part 11-compliant data capture system provided by the Vanderbilt Institute for Global Health (VIGH) DCC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly into REDCap and uploaded to the VIGH DCC.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after completion of all planned data analyses and the end of the study period, whichever is longest. These documents will be retained for a longer period, however, if required by local Nigerian regulations. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.
These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the NINDS/NIH Program Official and VIGH DCC. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:
National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 5 years after the completion of the primary endpoint by contacting Drs. Trevathan and Abdullahi via the VIGH DCC. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore,

persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NINDS/NIH has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CHWs	Community Health Workers
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
EEG	Electroencephalogram
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors

IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LVT	Levetiracetam
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PHC	Primary Healthcare Center
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

11 REFERENCES

1. de Boer HM, Moshe SL, Korey SR, Purpura DP. ILAE/IBE/WHO Global Campaign Against Epilepsy: a partnership that works. Curr Opin Neurol 2013;26:219-25.
2. de Boer HM, Mula M, Sander JW. The global burden and stigma of epilepsy. Epilepsy Behav 2008;12:540-6.
3. Diop AG, de Boer HM, Mandlhate C, Prilipko L, Meinardi H. The global campaign against epilepsy in Africa. Acta Trop 2003;87:149-59.
4. Ndoye NF, Sow AD, Diop AG, et al. Prevalence of epilepsy its treatment gap and knowledge, attitude and practice of its population in sub-urban Senegal an ILAE/IBE/WHO study. Seizure 2005;14:106-11.
5. Mbuba CK, Ngugi AK, Fegan G, et al. Risk factors associated with the epilepsy treatment gap in Kilifi, Kenya: a cross-sectional study. Lancet Neurol 2012;11:688-96.
6. Newton CR, Garcia HH. Epilepsy in poor regions of the world. Lancet 2012;380:1193-201.
7. Wilmshurst JM, Cross JH, Newton C, et al. Children with epilepsy in Africa: recommendations from the International Child Neurology Association/African Child Neurology Association Workshop. J Child Neurol 2013;28:633-44.
8. Wilmshurst JM, Kakooza-Mwesige A, Newton CR. The challenges of managing children with epilepsy in Africa. Semin Pediatr Neurol 2014;21:36-41.
9. Mbuba CK, Newton CR. Packages of care for epilepsy in low- and middle-income countries. PLoS Med 2009;6:e1000162.
10. Mbuba CK, Ngugi AK, Newton CR, Carter JA. The epilepsy treatment gap in developing countries: a systematic review of the magnitude, causes, and intervention strategies. Epilepsia 2008;49:1491-503.
11. Scott RA, Lhatoo SD, Sander JW. The treatment of epilepsy in developing countries: where do we go from here? Bull World Health Organ 2001;79:344-51.
12. Chin JH. Epilepsy treatment in sub-Saharan Africa: closing the gap. Afr Health Sci 2012;12:186-92.
13. Nwani PO, Nwosu MC, Enwereji KO, Asomugha AL, Arinzechi EO, Ogunniyi AO. Epilepsy treatment gap: prevalence and associated factors in Southeast Nigeria. Acta Neurol Scand 2013;128:83-90.
14. Koba Bora B, Lez DM, Luwa DO, et al. Living with epilepsy in Lubumbashi (Democratic Republic of Congo): epidemiology, risk factors and treatment gap. Pan Afr Med J 2015;21:303.
15. Meyer AC, Dua T, Ma J, Saxena S, Birbeck G. Global disparities in the epilepsy treatment gap: a systematic review. Bull World Health Organ 2010;88:260-6.
16. Carter JA, Molyneux CS, Mbuba CK, Jenkins J, Newton CR, Hartley SD. The reasons for the epilepsy treatment gap in Kilifi, Kenya: using formative research to identify interventions to improve adherence to antiepileptic drugs. Epilepsy Behav 2012;25:614-21.
17. Sabo UA, Trevathan E, Abdullahi AT, et al. High short-term status epilepticus-associated childhood mortality in Kano, Nigeria. 33rd International Epilepsy Congress. Bangkok, Thailand: International League Against Epilepsy; 2019.
18. WHO. Mental Health Gap Action Programme: scaling up for mental, neurological and substance use disorders. Geneva, Switzerland: World Health Organization; 2008.
19. WHO. Mental Health Action Plan 2013-2020. Geneva, Switzerland: WHO; 2013:50.
20. WHO. Mental Health Atlas 2014. Geneva, Switzerland: World Health Organization; 2014.
21. WHO. mhGAP Intervention Guide for mental, neurological, and substance abuse disorders in non-specialized health settings. 2.0 ed. Geneva, Switzerland: WHO; 2016.

22. World Health Organization. Task shifting: rational redistribution of tasks among health workforce teams: goals, recommendations, and guidelines. Geneva, Switzerland: World Health Organization; 2008.
23. Federal Ministry of Health. MhGAP Intervention Guide for Nigeria: For Management of Mental, Neurological, and Substance Abuse Disoders in Non-specialized Health Settings. Abuja, Nigeria: Federal Ministry of Health; 2015 2015.
24. Joshi R, Alim M, Kengne AP, et al. Task shifting for non-communicable disease management in low and middle income countries--a systematic review. PLoS One 2014;9:e103754.
25. Labhardt ND, Balo JR, Ndam M, Grimm JJ, Manga E. Task shifting to non-physician clinicians for integrated management of hypertension and diabetes in rural Cameroon: a programme assessment at two years. BMC Health Serv Res 2010;10:339.
26. Kaddumukasa M, Kaddumukasa MN, Buwembo W, et al. Epilepsy misconceptions and stigma reduction interventions in sub-Saharan Africa, a systematic review. Epilepsy Behav 2018;85:21-7.
27. Aliyu MH, Abdullahi AT, Iliyasu Z, et al. Bridging the childhood epilepsy treatment gap in northern Nigeria (BRIDGE): rationale and design of pre-clinical trial studies. Contemporary Clinical Trials Communications 2019;15:100362.
28. Role of EEG in the Management of Convulsive Epilepsy. WHO, 2012. (Accessed December 15, 2016, 2016, at http://www.who.int/mental_health/mhgap/evidence/epilepsy/q5/en/.)
29. Abdullahi AT, Sabo U, Adamu H, et al. Validation of a Hausa epilepsy screening and seizure classification tool. 5th East Mediterranean Epilepsy Congress. Marrakech, Morocco: International League Against Epilepsy 2019.
30. Patel AA, Ciccone O, Njau A, et al. A pediatric epilepsy diagnostic tool for use in resource-limited settings: A pilot study. Epilepsy Behav 2016;59:57-61.
31. Danladi B. Hausa speakers in Nigeria now 120m– Communiqué. Zaria Kaduna State, Nigeria: Department of African Languages and Cultures, Ahmadu Bello University (ABU) 2016.
32. Trevathan E, Abdullahi AT, Aliyu MH, et al. A childhood epilepsy screening, diagnosis, and management education program for community health workers in northern Nigeria. American Epilepsy Society. New Orleans, LA USA: American Epilepsy Society; 2018.
33. Boschini LP, Tyson AF, Samuel JC, et al. The role of seizure disorders in burn injury and outcome in Sub-Saharan Africa. J Burn Care Res 2014;35:e406-12.
34. Carpio A, Bharucha NE, Jallon P, et al. Mortality of epilepsy in developing countries. Epilepsia 2005;46 Suppl 11:28-32.
35. Charlson FJ, Baxter AJ, Dua T, Degenhardt L, Whiteford HA, Vos T. Excess Mortality from Mental, Neurological, and Substance Use Disorders in the Global Burden of Disease Study 2010. In: Patel V, Chisholm D, Dua T, Laxminarayan R, Medina-Mora ME, eds. Mental, Neurological, and Substance Use Disorders: Disease Control Priorities, Third Edition (Volume 4). Washington (DC)2016.
36. Diop AG, Hesdorffer DC, Logroscino G, Hauser WA. Epilepsy and mortality in Africa: a review of the literature. Epilepsia 2005;46 Suppl 11:33-5.
37. Levira F, Thurman DJ, Sander JW, et al. Premature mortality of epilepsy in low- and middle-income countries: A systematic review from the Mortality Task Force of the International League Against Epilepsy. Epilepsia 2016.
38. Achor JU, Ezeala-Adikaibe BA, Obayi ON, Ezeruigbo CFS, Ekenze OS, Onodugo OD. The stigma of epilepsy among outpatients in a tertiary hospital in south-east Nigeria. Open Journal of Psychiatry 2017;7:344-64.
39. Baskind R, Birbeck GL. Epilepsy-associated stigma in sub-Saharan Africa: the social landscape of a disease. Epilepsy Behav 2005;7:68-73.
40. Elafros MA, Sakubita-Simasiku C, Atadzhanov M, Haworth A, Chomba E, Birbeck GL. Stigma and psychiatric morbidity among mothers of children with epilepsy in Zambia. Int Health 2013;5:288-94.

41. Ding X, Zheng Y, Guo Y, et al. Active epilepsy prevalence, the treatment gap, and treatment gap risk profile in eastern China: A population-based study. Epilepsy Behav 2018;78:20-4.
42. Hunter E, Rogathi J, Chigudu S, et al. The epilepsy treatment gap in rural Tanzania: A community-based study in adults. Seizure 2016;36:49-56.
43. Lee B, Asian Status Epilepticus Survey G. Treatment gap for convulsive status epilepticus in resource-poor countries. Epilepsia 2018;59 Suppl 2:135-9.
44. von Gaudecker JR, Taylor AG, Keeling AW, Buelow JM, Benjamin S. Living in the epilepsy treatment gap in rural South India: A focused ethnography of women and problems associated with stigma. Health Care Women Int 2017;38:753-64.
45. Reynolds EH. The ILAE/IBE/WHO Global Campaign against Epilepsy: Bringing Epilepsy "Out of the Shadows". Epilepsy Behav 2000;1:S3-S8.
46. Robbins RN, Remien RH, Mellins CA, Joska JA, Stein DJ. Screening for HIV-associated dementia in South Africa: potentials and pitfalls of task-shifting. AIDS Patient Care STDS 2011;25:587-93.
47. Tsolekile LP, Abrahams-Gessel S, Puoane T. Healthcare Professional Shortage and Task-Shifting to Prevent Cardiovascular Disease: Implications for Low- and Middle-Income Countries. Curr Cardiol Rep 2015;17:115.
48. Asfaw E, Dominis S, Palen JG, et al. Patient satisfaction with task shifting of antiretroviral services in Ethiopia: implications for universal health coverage. Health Policy Plan 2014;29 Suppl 2:ii50-8.
49. Mafigiri DK, McGrath JW, Whalen CC. Task shifting for tuberculosis control: a qualitative study of community-based directly observed therapy in urban Uganda. Glob Public Health 2012;7:270-84.
50. Petersen I, Hanass Hancock J, Bhana A, Govender K. A group-based counselling intervention for depression comorbid with HIV/AIDS using a task shifting approach in South Africa: a randomized controlled pilot study. J Affect Disord 2014;158:78-84.
51. Seidman G, Atun R. Does task shifting yield cost savings and improve efficiency for health systems? A systematic review of evidence from low-income and middle-income countries. Hum Resour Health 2017;15:29.
52. Shumbusho F, van Griensven J, Lowrance D, et al. Task shifting for scale-up of HIV care: evaluation of nurse-centered antiretroviral treatment at rural health centers in Rwanda. PLoS Med 2009;6:e1000163.
53. Some D, Edwards JK, Reid T, et al. Task Shifting the Management of Non-Communicable Diseases to Nurses in Kibera, Kenya: Does It Work? PLoS One 2016;11:e0145634.
54. Long L, Brennan A, Fox MP, et al. Treatment outcomes and cost-effectiveness of shifting management of stable ART patients to nurses in South Africa: an observational cohort. PLoS Med 2011;8:e1001055.
55. Odejide AO, Morakinyo JD, Oshiname FO, Omigbodun O, Ajuwon AJ, Kola L. Integrating mental health into primary health care in Nigeria: management of depression in a local government (district) area as a paradigm. Sishin shinkeigaku Zasshi 2002;104:802-9.
56. Patel V, Weiss HA, Chowdhary N, et al. Effectiveness of an intervention led by lay health counsellors for depressive and anxiety disorders in primary care in Goa, India (MANAS): a cluster randomised controlled trial. Lancet 2010;376:2086-95.
57. Patel V, Weobong B, Nadkarni A, et al. The effectiveness and cost-effectiveness of lay counsellor-delivered psychological treatments for harmful and dependent drinking and moderate to severe depression in primary care in India: PREMIUM study protocol for randomized controlled trials. Trials 2014;15:101.
58. Patel V, Weobong B, Weiss HA, et al. The Healthy Activity Program (HAP), a lay counsellor-delivered brief psychological treatment for severe depression, in primary care in India: a randomised controlled trial. Lancet 2017;389:176-85.

59. Kengne AP, Fezeu LL, Awah PK, Sobngwi E, Dongmo S, Mbanya JC. Nurse-led care for epilepsy at primary level in a rural health district in Cameroon. Epilepsia 2008;49:1639-42.
60. Fleeman N, Bradley PM, Lindsay B. Care delivery and self management strategies for children with epilepsy. Cochrane Database Syst Rev 2015:CD006245.
61. Hendriks ME, Bolarinwa OA, Nelissen HE, et al. Costs of cardiovascular disease prevention care and scenarios for cost saving: a micro-costing study from rural Nigeria. J Hypertens 2015;33:376-684.
62. Gureje O, Abdulmalik J, Kola L, Musa E, Yasamy MT, Adebayo K. Integrating mental health into primary care in Nigeria: report of a demonstration project using the mental health gap action programme intervention guide. BMC Health Serv Res 2015;15:242.
63. Paul A, Adeloye D, George-Carey R, Kolcic I, Grant L, Chan KY. An estimate of the prevalence of epilepsy in Sub-Saharan Africa: A systematic analysis. J Glob Health 2012;2:020405.
64. Birbeck GL. The health care workforce for epilepsy in resource-poor settings: what will work? What is realistic? Epilepsia 2008;49:1642-3.
65. Top 10 Most Widely Spoken Languages in Africa. Eugene Orunga, 2016. (Accessed October 15, 2018, at https://geneeugene.wordpress.com/2016/09/26/top-10-most-widely-spoken-languages-in-african/.)
66. Ezeala-Adikaibe BA, Orjioke C, Ekenze O, et al. Prevalence of active convulsive epilepsy in an urban slum in Enugu South East Nigeria. Seizure 2016;35:100-5.
67. Ngugi AK, Bottomley C, Scott JA, et al. Incidence of convulsive epilepsy in a rural area in Kenya. Epilepsia 2013;54:1352-9.
68. Sadarangani M, Seaton C, Scott JA, et al. Incidence and outcome of convulsive status epilepticus in Kenyan children: a cohort study. Lancet Neurol 2008;7:145-50.
69. Wagner RG, Bottomley C, Ngugi AK, et al. Incidence, Remission and Mortality of Convulsive Epilepsy in Rural Northeast South Africa. PLoS One 2015;10:e0129097.
70. Murphy CC, Trevathan E, Yeargin-Allsopp M. Prevalence of epilepsy and epileptic seizures in 10-year-old children: results from the Metropolitan Atlanta Developmental Disabilities Study. Epilepsia 1995;36:866-72.
71. Ezeala-Adikaibe BA, Achor JU, Aneke E, et al. Pattern and determinants of self-reported enacted stigma among rural dwellers living with epilepsy attending a tertiary health facility in Enugu State Nigeria. Seizure 2018;56:60-6.
72. Campbell MK, Elbourne DR, Altman DG, group C. CONSORT statement: extension to cluster randomised trials. BMJ 2004;328:702-8.
73. Phenobarbital. RxList, 2019. (Accessed 22 Nov 2019, 2019, at https://www.rxlist.com/consumer_phenobarbital/drugs-condition.htm.)
74. Tegretol (carbamazepine). RxList, 2019. (Accessed 22 November 2019, 2019, at https://www.rxlist.com/tegretol-drug.htm.)
75. Depakene. RxList, 2019. (Accessed 22 November 2019, 2019, at https://www.rxlist.com/depakene-drug.htm.)
76. Obeid M, Pong AW. Efficacy and tolerability of high oral doses of levetiracetam in children with epilepsy. Epilepsy Res 2010;91:101-5.
77. Rosati A, Ilvento L, Lucenteforte E, et al. Comparative efficacy of antiepileptic drugs in children and adolescents: A network meta-analysis. Epilepsia 2018;59:297-314.
78. Muramatsu K, Sawaura N, Ogata T, et al. Efficacy and tolerability of levetiracetam for pediatric refractory epilepsy. Brain Dev 2017;39:231-5.
79. DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. ADHD Rating Scale - 5 for Children and Adolescents: Checklists, Norms, and Clinical Interpretation. New York, NY: Guilford Press; 2016.
80. Kakooza-Mwesige A, Ssebyala K, Karamagi C, et al. Adaptation of the "ten questions" to screen for autism and other neurodevelopmental disorders in Uganda. Autism 2014;18:447-57.

81. Hemming K, Kasza J, Hooper R, Forbes A, Taljaard M. A tutorial on sample size calculation for multiple-period cluster randomized parallel, cross-over and stepped-wedge trials using the Shiny CRT Calculator. Int J Epidemiol 2020;49:979-95.
82. Guittet L, Ravaud P, Giraudeau B. Planning a cluster randomized trial with unequal cluster sizes: practical issues involving continuous outcomes. BMC Med Res Methodol 2006;6:17.
83. Eldridge SM, Ashby D, Kerry S. Sample size for cluster randomized trials: effect of coefficient of variation of cluster size and analysis method. Int J Epidemiol 2006;35:1292-300.
84. Cramer JA, Perrine K, Devinsky O, Bryant-Comstock L, Meador K, Herman B. Develpment and cross-cultural translations of a 31-item quality of life in epilepsy inventory. Epilepsia 1998;39:81-9.
85. Cramer JA, Westbrook LE, Devinsky O, Perrine K, Glassman MB, Camfield C. Development of the quality of life in epilepsy inventory for adolescents: The QOLIE-AD-48. Epilepsia 1999;40:114-21.
86. Collins LM, Schafer JL, Kam CM. A comparison of inclusive and restrictive strategies in modern missing data procedures. Psychol Methods 2001;6:330-51.
87. Moons KG, Donders RA, Stijnen T, Harrell FE, Jr. Using the outcome for imputation of missing predictor values was preferred. J Clin Epidemiol 2006;59:1092-101.