Statistical Analysis Plan

1 Purpose

This document details the proposed final analysis plan for the research study Bridging the Childhood Epilepsy Treatment Gap in Africa (BRIDGE). The final version of this statistical analysis plan will amend the protocol document submitted paper presenting the study objectives and design.

TRIAL FULL TITLE	Bridging the Childhood Epilepsy Treatment Gap in Africa (BRIDGE)
SAP VERSION	1.6
SAP VERSION DATE	02-28-2023
TRIAL STATISTICIANS	Bryan Shepherd, Gregory D. Ayers, Liping Du
Protocol Version (SAP associated with)	Version 1.7
TRIAL PRINCIPAL INVESTIGATOR	Edwin Trevathan
SAP AUTHOR(s)	Gregory D. Ayers, Bryan Shepherd, Liping Du, Ed Trevathan

2 Abbreviations and Definitions

AE	Adverse Event
BRIDGE	Bridging the Childhood Epilepsy Treatment Gap in Africa
cRCT	Cluster Randomized Trial
CHW's	Community Health Workers
EUC	Enhanced Usual Care
FAS	Full Analysis Set
GEE	Generalized Estimating Equations
GLMM	General Linear Mixed Model
ICC	Intraclass (within cluster) correlation
LGA	Local Government Areas (Wards)
PHC	Primary Healthcare Centers
PP	Per Protocol
SAP	Statistical Analysis Plan
TSC	Task Shifted Care
WHO	World Health Organization

3 Introduction

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. This protocol is intended to test the hypothesis that task shifted epilepsy care (TSC) to CHWs is not inferior to physician epilepsy care, enhanced with epilepsy trained CHWs helping families navigate the healthcare system (EUC).

4 Study Objectives and Endpoints

4.1 Study Objectives

To estimate treatment success by study arm (TSC and EUC) with the ***primary outcome*** being 6-months or greater period with no seizures as determined at the blinded physician follow-up visit 24 months after enrollment. ***Secondary outcomes*** are (a) **accuracy of epilepsy diagnosis**, or the diagnostic accuracy of epilepsy after a positive epilepsy screen in the TSC arm and in the EUC arm, with the diagnosis of the blinded physician (who has epilepsy expertise) as the gold standard, (b) ***75% or greater reduction in seizure frequency compared to baseline***, as measured at the blinded physician visit 24 months after enrollment, (c) ***status epilepticus***, (d) ***mortality***, (e) ***hospitalizations***, (f) ***ASM side effects***, (g) ***electroencephalograms (EEGs) performed***.

4.2 Hypotheses and Endpoints

Primary Efficacy Endpoints. 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 (TSC) compared to control (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 care; TSC) and control (enhanced usual care; EUC) arms of the BRIDGE cRCT: (a) accuracy of epilepsy diagnosis; (b) 75% or greater reduction in seizure frequency compared to baseline at 24 months as measured at the 24-month blinded physician visit; (c) status epilepticus; (d) mortality; (e) hospitalizations; (f) ASM side effects; ; and, (g) EEGs performed.

5 Study Methods

5.1 General Study Design and Plan

This study is a noninferiority cluster randomized clinical trial of TSC compared to EUC, with outcomes determined by physicians with expertise in epilepsy who were blinded as to study arm. Study subjects receive the treatment modality depending on the primary healthcare center (e.g. cluster), where the child was consented and met preliminary eligibility for the study. Measurements and treatment follow informed consent and preliminary eligibility at baseline, week 1, and at 3, 6, 12, 18 and 24 months. Blinded physician assessment of final eligibility and disease outcomes provide the basis for the primary outcome.

5.2 Inclusion-Exclusion 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 a physician or 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.*

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 Randomization and Blinding

The treatment approach an individual child receives depends on the PHC to which they are referred. Sixty primary health care centers (PHC's) were randomly selected from 378 PHCs that deliver

maternal and child services - 30 from Kano, 15 each from Kaduna and Zaria. The 378 PHCs were numbered within each metropolitan area, and then 30 PHCs were randomly selected from Kano, 15 PHCs were randomly selected from Kaduna, and 15 PHCs were randomly selected from Zaria using a random number generator. Then the sixty PHCs were randomly assigned to either the TSC arm or the EUC arm of the cRCT with 30 clusters randomized to the TSC arm and 30 clusters randomized to the EUC arm of the study. The 30 PHC's in Kano were randomly assigned in equal proportion to TSC and EUC. In Kaduna, 8 of 15 PHC's were randomly assigned to TSC, and 7 PHCs to EUC care. In Zaria, 7 of 15 PHC's were randomly assigned to EUC and 8 to TSC.

Outcomes, or endpoints, noted above are determined by blinded physicians, physicians with expertise in epilepsy whose only role in the study was to examine children in the cRCT and determine their seizure diagnosis, seizure frequency and other study endpoints. Blinded physicians also determine whether children suffer from any adverse events, such as drug side effects, and establish the diagnosis of co-morbid conditions such as cerebral palsy (CP). These blined physicians evaluate study subjects at 6, 12, 18, and 24 months after enrollment, every child enrolled in the cRCT (both arms). To ensure blinding, blinded physicians do not participate in group study meetings, and are not granted access to to the BRIDGE study offices. Blinded physicians meet separately with study principal investigators at meetings without the data team or study data available. As with other study data collection, blinded physicians enter data into case report forms (CRFs) in REDCap using dedicated study android tablet computers – one for each blinded physician. Data from the blinded physician evaluations are uploaded weekly to the Nigeria BRIDGE data office and to the data coordinating center (DCC) at Vanderbilt.

Sample Size

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% assuming a one-sided type I error of 5% an intraclass correlation (ICC) among children of 0.05, and equal 6-month seizure free proportions at 24 months in each arm of 60%. 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). Actual accrual was adjusted to 1530 (from 1378) children to correct for a 10% dropout rate. An analysis (10-27-2020) of imbalances in PHC (cluster) size suggested further increases in sample size by a factor of 1.118 to 1731 total children (1,2). A maximum accrual to 1800 children was approved by the DSMB (protocol version 1.7 approved 12-09-2020).

6 General Analysis Considerations

6.1 Timing of Final Analyses

The final analysis will be performed on data transferred to the folder "//VUMCvolumes/BRIDGE/Biostat/Archive/FinalAnalysis/Data", having been documented as meeting the approval requirements of the DSMB, sponsor and after the finalization and approval of this SAP document.

6.2 Analysis Populations

8.2.1 Seizure Frequency Assessment

All consented and eligible (based on blinded physician assessment) children treated on this protocol.

8.2.2 Diagnostic Assessment

All consented and pre-screened eligible (based on community health worker assessment) children treated on this protocol.

8.2.3 Per Protocol Population (PP)

All consented, eligible (based on blinded physician assessment) children receiving assigned study treatment and completing the 24-month outcome assessment.

8.2.4 Safety Population

All consented children who received any study intervention, including diagnostic evaluations after a positive screen for epilepsy (for epilepsy diagnosis evaluations) and management for epilepsy, but excluding subjects who drop out prior to receiving any diagnostic evaluation or epilepsy management.

8.3 Summary of Study Data

All continuous variables will be summarized by providing n (non-missing sample size), median, interquartile range, maximum and minimum, mean and standard deviation. The frequency and percentages (based on the non-missing sample size) of groups will be reported for all categorical measures. Generally, data organized by treatment arm, PHC and subject, and visit number (as appropriate) within subject. All summary tables will be structured with a column for each treatment (EUC and TSC) and overall, including missing observations.

8.4 Primary Analysis

The following analysis plan applies to the SFA and PP study populations. 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 the generalized estimating equation for logistic regression with an exchangeable covariance matrix and adjusting for key baseline variables including seizure frequency, type of epilepsy, cerebral palsy, age, and sex. Continuous variables will be modeled with restricted cubic splines (4 knots). The GEE estimates a marginal effect, i.e., a "population average" effect that is consistent with the objectives of this trial. Based on our simulations, standard GEE works well (i.e., type I error close to the nominal level) with 60 clusters of our size, so we do not consider small sample corrections. Non-inferiority of TSC management will be declared if the lower limit of the covariate adjusted one-sided 95% confidence interval for the ratio

of the odds of being seizure-free in the intervention (TSC) vs. standard-of-care (EUC) 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 EUC arm, then non-inferiority would be declared if the lower-limit of the one-sided 95% CI was greater than 2/3 (= [(0.6- δ)/(1-0.6+δ)]/[0.6/(1-0.6)], with δ=0.1, the non-inferiority margin described in 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. We will also report two-sided 95% confidence intervals for the intervention odds ratio. In addition, estimates (and 95% confidence intervals) for the marginal average treatment effect on the absolute difference scale will be derived from the primary model and reported. Secondary outcomes will also be compared using GEE models, with appropriate link functions and outcome transformations based on the specific endpoint.

8.5 Supporting Models

Complementary models will be constructed including the GEE model unadjusted for covariates, the generalized mixed model (GLMM) with a logit link and random intercepts for each PHC with and without covariates, and the cluster (PHC) level model comparing the success proportion for the primary outcome at the PHC level by study arm. There is no general agreement on whether the population average model (GEE) or the cluster specific GLMM is better. Although we prefer the marginal interpretation, GEE estimation does not have as much flexibility with respect to missing outcomes (e.g. likelihood-based estimation is unbiased under the less restrictive missing at random assumptions). In addition, GEE seems to have a harder time with smaller numbers of clusters, though our simulations show that GEE approximately conserves the type I error rate in settings similar to our trial (60 PHC's with an average of 29 children per cluster and ICC varying between 0.05 to 0.11)(3,4).

8.6 Subgroups

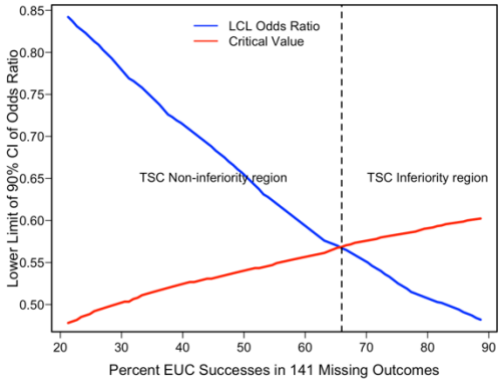
The analyses regarding the primary endpoint (percentage of children seizure-free) will be conducted among children with non-convulsive epilepsy and convulsive epilepsy, among specific common seizure types (e.g., generalized tonic-clonic seizures and focal seizures), and cerebral palsy. The differential treatment effects of subgroups will be estimated via treatment by covariate interactions. However, given the paucity of data regarding the epidemiology of specific childhood seizure types in northern Nigeria's children with untreated epilepsy, and even in Africa, it is not possible now to determine whether we will have adequate sample sizes for such analyses.

8.7 Missing Data

8.7.2 Imputation for Missing Covariates

Under the assumption that data are missing at random, we will employ multiple imputation to address missing data in covariates.

8.7.3 Sensitivity Analysis for Missing Primary Outcomes



The goal of these analyses is to assess the robustness of a non-inferiority result based on children with completed 24 month assessments. In our first sensitivity analysis, we will impute all the missing outcomes from the EUC arm as successes and all of the missing outcomes from the TSC arm as non-successes and construct the appropriate one-sided confidence for non-inferiority based on the primary GEE model. If non-inferiority is maintained, then original non-inferiority result will be considered robust. If the TSC arm is no longer statistically non-inferior, we will conduct a "tipping point" sensitivity analysis as follows. Missing outcomes will be imputed at random among TSC children at the rate of success already observed children in the TSC arm with completed outcomes. In the EUC arm, a success will be added randomly one subject at a time sequentially from no successes to all successes for the missing outcomes and statistical non-inferiority recorded. The lower limit of the one-sided 90% confidence interval will be based on the covariate adjusted GEE model. The critical value is $[(p_{EUC} - \delta)/(1- p_{EUC} +\delta)]/[p_{EUC} /(1- p_{EUC})]$, where δ=0.1 is the non-inferiority margin and p_{EUC} is the iterated overall success probability in the EUC arm. In the graphic above, the intersection of the iterated critical and covariate adjusted lower CI for the odds ratio separates the region vertically into TSC non-inferiority and inferiority. The tipping point occurs when the critical value line versus EUC success rate of the comparison crosses the line of the lower confidence versus EUC success rate as shown in the figure above. This approach will be repeated (10,000 replicates) and summary estimates of the tipping point generated. The decision of whether the tipping point of EUC success rate in the body of missing outcomes is a likely event is left to critical review.

8.8 Multiple Testing

The final model and main subgroup analyses have been fully specified. No adjustment for multiplicity will be employed. All other analyses will be considered exploratory, hypothesis generating or descriptive in nature.

9 Quality Assurance of Data and Statistical Programming

9.1 Back up

VUMC IT backs up all network storage including applications, servers, and databases on a regular basis to assure availability in the event of a data loss or data corruption. Backing up network data requires copying and archiving computer data so that it is accessible when needed. The VUMC IT Data Retention policy provides for rolling backups as follows:

Daily Production system/application backup - every 21 days
Daily Database Backup - every 16 days

Database Point-in-Time (Transaction Logs) - every 72 hours

9.2 Programming and Reporting

All statistical reports in HTML format and the R code that generated them will be dated and archived with the author(s) name imbedded in the document. Cleaned, final data will be generated from REDCap and archived under the pathname //VUMCvolumes/IGH/Bridge/Biostat/Archive/FinalAnalysis/Data/. Code sets will be archived under the pathname //VUMCvolumes/IGH/Bridge/Biostat/Archive/FinalAnalysis/Code/ with dates imbedded in the file name and code. Reports will be in HTML format will be archived under the pathname //VUMCvolumes/IGH/Bridge/Biostat/Archive/FinalAnalysis/Reports/ with dates imbedded in the file name and report name.

9.3 Data and Data Monitoring

Procedures for data monitoring and quality checks are available in separate documentation upon request.

10 Literature Cited

1. Guittet L, Ravaud P, Giraudeau B. Planning a cluster randomized trial with unequal cluster sizes: practical issues with continuous outcomes. *BMC Medical Research Methodology* 2006, 6:17 doi:10.1186/1471-2288-6-17
2. Eldrige SM, Ashby D, Kerry S. Sample size for cluster randomised trials: effect of coefficient of variation of cluster size and analysis method. *International Journal of Epidemiology*, 2006, 9p. doi:10.1093/ije/dyl129.
3. McNeish D, Stapleton LM. Modeling cluster data with very few clusters. *Multivariate Behavioral Research* 2016; 51: 495-518. doi:10.1080/00273171.2016.1167008.
4. Thompson JA, Leyrat C, Fielding KL, Hayes RJ. Cluster randomized trials with a binary outcome and a small number of clusters: comparison of individual and cluster level analysis method. *BMC Medical Research Methodology 2022*. 15 p. doi:10.1186/s12874-022-01699-2.