Principal Investigator

First Name: Wesley
Last Name: Kerr
Degree: MD, PhD
Primary Affiliation: University of Pittsburgh
E-mail: wesley1610@gmail.com
State or Province: PA
Country: USA

General Information

Key Personnel (other than PI):
First Name: Neo
Last name: Kok
Degree: BA/BS/BSc
Primary Affiliation: University of Pittsburgh
SCOPUS ID:
Requires Data Access? Yes

First Name: Advith
Last name: Reddy
Degree: BA/BS/BSc
Primary Affiliation: University of Pittsburgh
SCOPUS ID:
Requires Data Access? Yes

First Name: Katherine
Last name: McFarlane
Degree: MS
Primary Affiliation: University of Pittsburgh
SCOPUS ID:
Requires Data Access? Yes

First Name: Lavanya
Last name: Biju
Degree: BA/BS/BSc
Primary Affiliation: University of Pittsburgh
SCOPUS ID:
Requires Data Access? Yes

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2023/09/COI-FORM-WK.pdf
https://yoda.yale.edu/wp-content/uploads/2023/10/Kok_YODA_COI2023.pdf
https://yoda.yale.edu/wp-content/uploads/2023/10/COI_McFarlaneYODA.pdf
https://yoda.yale.edu/wp-content/uploads/2023/10/COI_ReddyYODA.pdf
https://yoda.yale.edu/wp-content/uploads/2023/10/COI-FORM-LB.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT00231556 - TOPMAT-EPMN-106 - A Randomized, Double-Blind, Parallel-Group, Monotherapy Study to Compare the Safety and Efficacy of Two Doses of Topiramate in the Treatment of Newly Diagnosed or Recurrent Epilepsy
2. NCT00236418 - YTCE - Topiramate Clinical Trial in Primary Generalized Tonic-Clonic Seizures
3. NCT00236704 - YTC - Topiramate Clinical Trial in Primary Generalized Tonic-Clonic Seizures
4. NCT00236847 - Y2 - Double-Blind, Parallel Comparison of Topiramate 300 mg Twice Daily to Placebo in Patients With Refractory Partial Epilepsy
5. NCT00236756 - YL - A Double-Blind Trial of Topiramate in Subjects With Lennox-Gastaut Syndrome.
6. NCT00236730 - YD - Double-Blind Parallel Comparison of Three Doses of Topiramate and Placebo in Refractory Partial Epilepsy
7. NCT00236873 - Y1 (CC2604-C-101) - Double-Blind Parallel Comparison of Topiramate 200 mg Twice Daily to Placebo in Patients With Refractory Partial Epilepsy
8. NCT00236860 - Y3 (CC2604-C-103) - Double-Blind Parallel Comparison of Topiramate 400 mg Twice Daily to Placebo in Patients With Refractory Partial Epilepsy

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Time to Event Designs for Epilepsy

Narrative Summary:

We propose to evaluate a modern statistical design for clinical trials of epilepsy called Time to Event designs. In a traditionally designed trial, participants go through baseline, titration, and maintenance phases with pre-specified static durations. In a Time to Event trial, these phases can be shortened if an individual participant meets certain safety or effectiveness criteria. However, Time to Event designs have not been broadly adopted for prospective trials. In this work, we will use data from past trials to address key concerns with the Time to Event design.

Scientific Abstract:

Background: The design of randomized controlled trials of adjunct treatments for epilepsy have not changed in decades, but there are increasing challenges with participant recruitment and trial conduct. Time to Event designs aim to improve participant recruitment and trial conduct by reducing exposure to ineffective treatments, while also providing sufficient data to establish efficacy and safety. Re-analyses of prior trials have demonstrated that Time to Event designs may reproduce the primary efficacy conclusions, especially the design of Time to Prerandomization Seizure Count (T-PSC).

Objective: We propose to evaluate the Time to Event design on as many trials of treatments for epilepsy as possible to facilitate use on a prospective trial. The aims of this project seek to address key concerns regarding this design.
Study Design: This study re-evaluates prior trials with the Time to Event design with the goal of replication of the primary efficacy and safety conclusions as compared to the full-length trials. Additionally, we perform analyses regarding the sensitivity of Time to Event designs to factors including low baseline seizure count, titration periods, predictability of long-term response, and others to be identified.
Participants: Patients with uncontrolled epileptic seizures.
Primary & Secondary Outcome Measure(s): The primary outcome efficacy and safety measures match the primary outcome measures of the original included trials, except that they are calculated using data from before the Time to Event endpoint. This includes differences in the median percent seizure frequency reduction, 50% responder rate, and frequency of adverse events on active treatment compared to placebo. Secondary outcome measures include the reduction in time (and cost) when using the Time to Event endpoint, as compared to the full-length trial; as well as the predictability of long-term seizure efficacy from Time to Event information.
Statistical Analysis: The statistical analysis of each individual trial matches the original statistical analysis, except for only using seizure diary and adverse event data that occurred before the Time to Event endpoint. This will be supplemented by survival statistics applied to the Time to Event data. For illustration and to demonstrate the relative effect size (and thereby statistical power) of this approach, we will use mixed-effects generalized linear models to perform meta-analyses across trials. We will use rolling averages (e.g., loess techniques) and mixed-effects polynomial generalized linear models to illustrate patterns in the outcomes with respect to specific parameters (e.g., prerandomization seizure count).

Brief Project Background and Statement of Project Significance:

Epilepsy is the third most common cause of neurological disability and death globally, but a third of patients are failed by antiseizure medications (ASMs). Parallel assignment Randomized placebo-Control Trials (RCTs) for epilepsy have been the mainstay of trials for regulatory approval of new ASMs for decades. In traditionally designed RCTs, patients with high seizure burden may remain on placebo or ineffective treatment for at least 5 months, even if seizures are frequent. Participants randomized to placebo had a 5.8-fold increased risk of death, therefore it is critical to reduce participants? exposure to ineffective treatments. These risks of participating in RCTs also contributes to trial recruitment issues.
The fundamental clinical research question this work addresses is if a Time-to-Event design can shorten participants? exposure to placebo or ineffective treatment while also achieving the dual goals of evaluating treatment efficacy and safety. In a Time-to-Event design, participants receive treatment until they reach specific efficacy or safety endpoints. This proposal is important and original because it directly addresses concerns that have been barriers to adoption of the most promising Time-to-Event design, known as time to pre-randomization seizure count (T-PSC). In T-PSC, participants receive treatment until their post-randomization seizure count exceeds the average monthly PSC experienced during baseline. The expected societal impact is to have sufficient ad hoc evidence to promote T-PSC as a safe and effective primary efficacy endpoint in prospective RCTs to evaluate this design. The expected impact of this research on patient care and human health is to reduce trial participants risk of death, trial cost, and improve participant recruitment. The rationale of this project is that by making RCTs safer, cheaper, and more efficient, we enable further development of novel treatments for epilepsy to reduce the impact of seizures and adverse effects of treatment on quality of life and mortality through all causes including Sudden Unexpected Death in Epilepsy (SUDEP).

Specific Aims of the Project:

This project aims to evaluate Time to Event designs for clinical trials of patients with epilepsy who have continued seizures. Based on prior re-analyses of clinical trials, the time to pre-randomization seizure count (T-PSC) design is promising, but there are concerns that, if resolved, would increase utility.
Aim 1: We hypothesize that observation until T-PSC reproduces the group- and individual-level

conclusions regarding efficacy with effect size, Cohen's Kappa, and Spearman's Rho greater than 80%.
Aim 2: T-PSC determines efficacy based on fewer seizures, but this may limit statistical power for patients with low baseline seizure frequency.
Aim 3: We hypothesize that the inclusion of titration/dose-finding phases underestimates efficacy with Time to Event designs.
Aim 4: We hypothesize that adverse events observed during the blinded phase of trials primarily occur before T-PSC.
Aim 5: We hypothesize that the seizure response seen before Time to Event endpoints is predictive of long-term seizure response in an open-label extension.
Aim 6: We hypothesize that there are other Time to Event designs that may address limitations in the T-PSC design.

What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

New research question to examine treatment safety

Confirm or validate previously conducted research on treatment effectiveness

Confirm or validate previously conducted research on treatment safety

Preliminary research to be used as part of a grant proposal

Participant-level data meta-analysis

Meta-analysis using data from the YODA Project and other data sources

Research on clinical trial methods

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

The goal of the research is to evaluate the Time to Event methodology in patients with epilepsy, as compared to the full-length trial. For each individual trial, we will match the inclusion and exclusion criteria used within the original publication evaluating the efficacy and safety of treatment.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

The main seizure efficacy outcome elements are the traditional dual primary outcomes for clinical trials of treatments for epilepsy: median percent reduction in seizure frequency (MPR; US Food and Drug Administration [FDA]) and 50% responder rate (50RR; European Medicines Agency [EMA]). Percent reduction in seizure frequency for each individual is defined by 100% minus the average seizure frequency during titration and maintenance divided by average seizure frequency during prerandomization baseline. The median of this percent reduction is compared across groups traditionally using a rank ANCOVA. The 50% responder rate is the percent of individuals for which percent reduction in seizure frequency is 50% or greater, when calculated using seizures from maintenance only compared to prerandomization baseline. To evaluate the safety of treatment, we compare the rate of adverse events that occurred within each treatment arm. Of note, we will not evaluate for new, unreported adverse events. Instead, this analysis will focus on if the previously identified adverse events can be observed with a Time to Event design.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

The main predictor/independent variable of future seizure efficacy and safety of treatment are the previous entries from seizure diaries and reported adverse events. We will use the provided diary and adverse events as defined by each individual trial.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

There are numerous secondary outcome elements to this research. We can apply multiple statistical techniques to evaluate the group- and individual-level agreement of these co-primary seizure efficacy metrics when calculated with a Time to Event design, as compared to the full-length trials. For Time to Event designs, time before reaching the time to event endpoint is a quantitative metric for the efficacy of treatment using survival statistics including log rank and Cox Proportional Hazards. Additionally, we can separately analyze the time needed to make conclusions regarding seizure efficacy and safety with Time to Event designs compared to full-length trials, which also inform considerations of cost.
Other than the other clinical variables included in the original trial analysis, we do not propose to evaluate novel associations of gender, age groups, and ethnic groups.

Statistical Analysis Plan:

Here is a general description of the statistical analysis plan based on each individual aim. Further details can be found in the attached parallel proposal with Vivli, which does not have a character limit.
Aim 1: The dual primary seizure efficacy outcomes for each trial will be calculated as specified in the original publications of the trials: median percent reduction in seizure frequency (MPR) using a rank ANCOVA with stratification, 50% responder rate (50RR) with CMH tests or mixed-effects logistic regression. We will add mixed effects Cox-Proportional Hazards of the time before reaching T-PSC. Additionally, we will evaluate individual level correspondence at T-PSC versus the full-length trial with Spearman?s Rho (MPR) and Cohen?s Kappa (50RR). For illustration, we will used mixed-effects generalized linear models to combine across trials using the World Health Organization Defined Daily Dose to combine across dosages of different medications.
Aim 2: For 50RR, we will use mixed-effects meta-analytic logistic regression with linear and polynomial terms for prerandomization seizure count (PSC). For MPR, we will evaluate multiple mixed-effects meta-analytic regression techniques including linear, log-linear, and rank regressions. We specifically will evaluate associations between average and standard deviation of seizure frequency in different trial phases with similar mixed-effects meta-analytic generalized-linear models.
Aim 3: For trials with a titration or dose-finding phase, we will calculate the dual primary outcomes of each trial in 3 situations: (1) when the Time to Event endpoint starts with the first treatment dose and all data before the Time to Event endpoint contributes to the outcome, (2) when the Time to Event endpoint starts on the first day of the official maintenance phase and only data from maintenance before the Time to Event endpoint contributes to the outcome, and (3) when the Time to Event endpoint starts on the first day of the official maintenance phase and data from both maintenance and titration contribute to the outcome. We will compare the magnitude and effect size of the primary outcomes in these situations to the full-length trial.
Aim 4: On a per-trial basis as well as meta-analytically across trials using mixed-effects modeling, we will evaluate the frequency with which each reported adverse effect started or occurred, as compared to the T-PSC for each patient. We will focus on adverse effects and categories of adverse effects as reported in the original publication of each trial, as well as adverse effects that appear on the FDA or EMA package label of each medication. Based on these data, we will categorize adverse effects as occurring uniformly before T-PSC (early), both before and after T-PSC (mid), and uniformly after T-PSC (late).
Aim 5: We will use survival-based statistics including Kaplan-Meier plots and Cox Proportional Hazards to evaluate the degree to which seizure efficacy observed before Time to Event endpoints is predictive of long-term seizure efficacy seen later in the blinded trial and in the open-label extension, as well as sensitivity analyses for this.

Aim 6: We will use generalized-linear models to design and evaluate other Time to Event designs that seek to improve upon T-PSC (e.g., binomial regression of seizure-free days, negative binomial regression, clustering terms, periodicity terms). In addition, we will evaluate potential applications of Time to Event designs to the baseline phase.

Software Used:

R

Project Timeline:

This project is a continuation of a project which has used data from both YODA and Vivli. There is specific funding for Aims 1 through 4 from the current date through June 30th, 2025. The funding at the University of Pittsburgh begins July 1st, 2023. Based on progress on analyses from the Vivli data, we aim to to complete Aims 1 & 3 by the end of 2023 including analysis completion, drafting the manuscript, submission, and reporting back to YODA. We will work concurrently on Aim 2 with the goal of completion by March 2024. We aim to complete Aim 4 by June 2024. We will conduct the other aims based on the time and data access permitting.

Dissemination Plan:

We intend to publish all research findings in peer-reviewed journal as well as Bioarchiv pending acceptance in other journals. Pending results, we can present these results at conferences including the American Epilepsy Society, American Academy of Neurology, Epilepsy Pipeline, and Epilepsy Therapies & Diagnostic Devices. The peer-reviewed journals that we will consider include but are not limited to Neurology, Epilepsia, Epilepsy Research, Epilepsy & Behavior, Seizure, Neurotherapeutics, and CNS drugs.

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