Principal Investigator

First Name: Wesley
Last Name: Kerr
Degree: MD PhD
Primary Affiliation: UCLA
E-mail: wesley1610@gmail.com
Phone number: 3108256681
Address: 710 Westwood Plaza Suite 1-240

City: Los Angeles
State or Province: CA
Zip or Postal Code: 90095
Country: USA
SCOPUS ID: 8938253400

General Information

Key Personnel (in addition to PI):
First Name: John
Last name: Stern
Degree: MD
Primary Affiliation: UCLA
SCOPUS ID: 7402955488

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/system/files/scanned_from_a_xerox_multifunction_printer_0.pdf
https://yoda.yale.edu/system/files/scan.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. NCT00210782 - CAPSS-272 - A Double-blind Trial Comparing the Efficacy, Tolerability and Safety of Monotherapy Topiramate Versus Phenytoin in Subjects With Seizures Indicative of New Onset Epilepsy
2. NCT00113815 - TOPMATPEP3001 - A Randomized, Double-Blind, Placebo-Controlled, Fixed Dose-Ranging Study to Assess the Safety, Tolerability, and Efficacy of Topiramate Oral Liquid and Sprinkle Formulations as an Adjunct to Concurrent Anticonvulsant Therapy for Infants (1-24 Months of Age) With Refractory Partial-Onset Seizures
3. NCT00230698 - TOPMAT-EPMN-104 - Topiramate (RWJ-17021-000) Monotherapy Clinical Trial in Patients With Recently Diagnosed Partial-Onset Seizures
4. NCT00236704 - YTC - Topiramate Clinical Trial in Primary Generalized Tonic-Clonic Seizures
5. NCT00236756 - YL - A Double-Blind Trial of Topiramate in Subjects With Lennox-Gastaut Syndrome.

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

Research Proposal

Project Title

Real time monitoring of individual response to antiseizure medication treatment during clinical trials

Narrative Summary:

This analysis aims to use statistical theories to limit the time that participants in clinical trials take medications that they are assigned. The goal of this would be to improve participant safety by reducing exposure to ineffective medications. Shortening the duration of trial participation also can improve trial efficiency.
While these theories can apply to many episodic conditions, we chose to explore these statistical theories in seizures.

Scientific Abstract:

Background: Clinical trials of patients with seizures typically involve static treatment assignments where patients are required to stay on the same medication regimen for a specified period of time, irrespective of seizure count. Objective: We use statistical theory to demonstrate that both number of seizures and time on treatment matter. In canonical trials, patients could consider discontinuing trial treatment if seizure frequency doubled. There is one proposal to wait until the number of prerandomization seizures occur and use the time to this endpoint as a measure of effectiveness (French et al. Neurology 2015). Our proposal is that a daily estimate of seizure frequency can be statistically compared to the individual patient's baseline or prerandomization seizures. If there is statistical confidence that the treatment has not benefitted the patient, even after just one week, then the patient should be eligible to either exit the trial or change treatment arms. Study Design: We will re-analyze daily seizure-count information from clinical trials to show the benefits and cautions of applying these theories. In this way we can compare (1) canonical trial design, (2) time to prerandomization seizures, and (3) real-time seizure frequency estimation. Participants include patients with seizures. Main Outcome Measures include time spent on ineffective therapy and false positive discontinuation. Statistical Analysis includes modeling seizure processes as Poisson or negative binomial distributions.

Brief Project Background and Statement of Project Significance:

Seizures affect 3.4 million people in the United States alone. In addition to direct costs of healthcare for seizures, seizures have a profound impact on patient independence by limiting employment opportunities and mobility including driving. Unfortunately, despite many antiseizure medications, around 30% of patients with seizures continue to have seizures despite medications. Therefore, further clinical trials and more treatments are needed to improve the care of these patients.

Our theoretical approach has the potential to reduce the risk to patients of enrolling in trials as well as reduce the cost of trials, which may assist with recruitment. They also may improve the statistical power of trials to detect meaningful differences. To examine the benefits and limitations of our approach, we will apply our theories to actual clinical trial data to show how these trials could be done more efficiently where patients can have fewer seizures and be on ineffective treatments for less time. This benefits both the patient and the trial by reducing the time needed to monitor patients on each treatment. In our statistical design, we chose the Poisson process and negative binomial processes as models for seizures because prior literature has shown that they best match the time course of seizures recorded in seizure diaries.

Specific Aims of the Project:

Aim 1) Sensitivity, Specificity, and Negative/Positive Predictive Value of statistical prediction of response on each day of trial participation. Aim 2) Variation in these contingency table parameters with respect to changes in chosen statistical parameters. Aim 3) Reproduction of the primary and secondary end points for the trial based on

truncated trial participation.

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
Develop or refine statistical methods
Research on clinical trial methods

Research Methods

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

Any participant with seizures is eligible. We require that the number of seizures that occurred in a pre-randomization baseline phase be reported, with ideally daily or weekly seizure counts during that time. After randomization, we need ideally daily, but can use weekly, seizure counts as well as treatment assignments. Exclusion criteria include patients for whom only total aggregate seizure counts are available. To maximize applicability to a broad range of trials, we will include all eligible trials with the appropriate daily (or weekly) seizure counts in Yoda or Vivli (attached application).

Main Outcome Measure and how it will be categorized/defined for your study:

The main outcome measure will be the number of days each patient was continued on therapy after lack of response was determined. Secondary outcome measures include false-positive rate of the determination of non-responder, as well as number of adverse effects that occurred after determination of non-response, as well as statistical parameters to optimize the models of the data.

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

The daily (or weekly) seizure frequency estimate will be the main predictor of response. We will use Poisson or negative binomial statistics combined with a Bayesian approach to determine the likelihood of lack of seizure frequency improvement by 25, 50, or 75%. When the certainty of non-response is high enough (e.g. 95% or 99%), we will propose the patient discontinue that treatment.

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

The number of days spent on therapy after non-response could be predicted, defined by the total treatment period minus the number of days needed to determine non-response for each individual patient. The false-positive and false-negative prediction rate for our approaches. The number of adverse effects that were reported after non-response was determined. The number mandatory observation days in our statistical prediction, and other parameters regarding the statistical models (e.g. number of samples in the negative binomial).

Statistical Analysis Plan:

The pre-randomization seizure count will be modeled using Poisson and Negative Binomial statistics to make a Bayesian prior distribution for the estimate of seizure frequency on an individual-patient basis (Chiang et al. Epilepsia Open 2018). For each day (or week) with reported seizure count, the post-randomization estimate of seizure frequency will be re-estimated. These two distributions will be compared to determine a likelihood that seizure frequency had reduced by 25, 50, or 75% on treatment. Actual treatment assignment or other confounding factors will not contribute to this estimate. Additional sensitivity analysis will include a ROC of certainty of non-response compared to sensitivity and specificity, the number of mandatory observation days prior to allowing treatment discontinuation, the influence of high or low pre-randomization seizure frequency, the influence of potential clustering of seizures, and optimal parameters in the Poisson and Negative Binomial models.

This statistical plan can be stated another way as follows. We will use individual-level, daily seizure counts to estimate the likelihood of response to the assigned treatment in the trial. We model seizure counts as Poisson or negative binomial processes. Based on this model, we will use a Bayesian approach to estimate the likelihood that seizure frequency has responded to treatment. Response will be defined as 25, 50, or 75% reduction in seizure

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frequency. When a participant's likelihood of response is less than a threshold (e.g. 5% or 1%), we will simulate discontinuing participation in the trial. We will repeat the primary and secondary outcome analysis of the trial based on these truncated participation records to evaluate the effect of this early discontinuation on trial outcomes.

We will include all trials where individual-level seizure counts were available for patients at regular intervals prior to the completion of the trial. The ideal trial would include a daily seizure diary, but other acceptable reporting schemes include weekly seizure counts prior to completion of the trial. We also require reporting of individual-level baseline seizure count. In our paradigm, each individual patient's seizure data is analyzed separately. This maintains the independence of individual trials. Due to our focus on improving trials overall, we will report statistics on an individual trial level, as well as a group level using meta-analysis techniques. For example, we will report the number of days spent on an ineffective treatment past when lack of efficacy was determined for each patient, as well as summary statistics by trial.

Due to the flexible nature of the duration of observation for each patient in our analysis, we will include all patients with data available from both the baseline period and the treatment period. If patients are lost to follow-up or otherwise discontinue participation in the trial, only data prior to discontinuation will be included. Missing data will not be imputed. For trials with titration periods, we will analyze data on each medication dose separately and keep the titration period separate from the treatment observation period.
Software Used:
R

Project Timeline:

Anticipated start date: 10/2021. Data organization 10/2021-01/2022. Poisson modeling of trials 02 to 05/2022. Publication preparation and submission 06/2022-07/2022. Negative Binomial modeling of trials 06-09/2022. Publication preparation and submission 09/2022-10/2022.

Dissemination Plan:

We intend to publish all research findings in peer-reviewed journals. Pending results, we can present these results at the American Epilepsy Society conference as well as the American Academy of Neurology. The peer- review journals that we will consider include but are not limited to Neurology, Epilepsia, Epilepsy Research, Epilepsy & Behavior, Seizure, Neurotherapeutics, and CNS drugs.

Bibliography:

French, J.A., et al., Time to prerandomization monthly seizure count in perampanel trials: A novel epilepsy endpoint. Neurology, 2015. 84(20): p. 2014-20.
Chiang, S., et al., Epilepsy as a dynamic disease: A Bayesian model for differentiating seizure risk from natural variability. Epilepsia Open, 2018. 3(2): p. 236-246.

Supplementary Material:

https://yoda.yale.edu/sites/default/files/vivlirequest210927_0.pdf