The YODA Project
Research Proposal Review

The following page contains the final YODA Project review approving this proposal.

The Yale University Open Data Access (YODA) Project
Yale University Center for Outcomes Research and Evaluation (CORE)
1 Church Street, Suite 200, New Haven, CT 06510

The YODA Project
Research Proposal Review - Final
(Protocol #: 2021-4712)

Reviewers:

- ☒ Nihar Desai
- ☒ Cary Gross
- ☐ Harlan Krumholz
- ☐ Richard Lehman
- ☒ Joseph Ross

Review Questions:	**Decision:**
1. Is the scientific purpose of the research proposal clearly described?	Yes
2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health?	Yes
3. Can the proposed research be reasonably addressed using the requested data?	Yes, or it's highly likely
4. Recommendation for this data request:	Approve

Comments:

The YODA Project
Research Proposal Review

Revisions were requested during review of this proposal.
The following pages contain the original YODA Project review and the original submitted proposal.

The Yale University Open Data Access (YODA) Project
Yale University Center for Outcomes Research and Evaluation (CORE)
1 Church Street, Suite 200, New Haven, CT 06510

The YODA Project
Research Proposal Review - Revisions Requested
(Protocol #: 2021-4712)

Reviewers:

- ☒ Nihar Desai
- ☒ Cary Gross
- ☐ Harlan Krumholz
- ☐ Richard Lehman
- ☒ Joseph Ross

Review Questions:	**Decision:**
1. Is the scientific purpose of the research proposal clearly described?	No
2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health?	Unsure, further clarification from requestor is needed
3. Can the proposed research be reasonably addressed using the requested data?	Yes, or it's highly likely
4. Recommendation for this data request:	Not Approve

Comments:

Investigators have proposed a project to apply "statistical theory to demonstrate that both number of seizures and time on treatment matter". I found the purpose of this project very difficult to discern. Perhaps the authors could clarify? It seems they are modeling past daily/weekly seizure burden to determine how long someone needs to be on treatment to discern non-effect, but that is not obvious. Instead, the main outcome is described as "The main outcome measure will be the number of days each patient was continued on therapy after lack of response was determined". But the investigators are analyzing clinical trial data, where all patients randomized to inclusion are expected to adhere to whatever treatment was assigned for the duration of the trial. Additional clarification would help.

Principal Investigator

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General Information

Key Personnel (in addition to PI):
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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. 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). Objective: We use statistical theory to demonstrate that both number of seizures and time on treatment matter. Study Design: We will re-analyze daily seizure-count information from clinical trials to show the benefits and cautions of applying these theories. 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.
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/vivlirequest.pdf