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 #: 2016-1038)

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 #: 2016-1038)

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:

1. The proposal focuses on meta-analyzing control-arm data from anti-epilepsy clinical trials conducted among children, generating a placebo response-effect estimate. While this is important and will be of great use to science and future drug development efforts, more information is needed on what additional trials have been identified for inclusion in the meta-analysis, whether individual participant-level data (IPD) are available from these trials, whether this data will be uploaded to the secure data sharing platform to be analyzed along with the data made available from Janssen via the YODA Project or if summary analyses from the Janssen data will be exported from the platform and then combined with the other data, and if IPD are not available from other trials, whether summary-level data would suffice for meta-analysis. In addition, please pre-specify likely predictor variables of interest (sex, race, seizure disorder type, etc.).

2. The dissemination plan is vague and there are no references. I think we need further detail on the number of other pediatric epilepsy trials being sought and the details of the proposed meta-analytic methods. It is important that they cite similar studies, and commit themselves to full publication of their methods and their eventual findings in a peer-reviewed journal. If their approach is wholly novel then perhaps it should be set out for comment in a journal such as Trials or PLOS One, prior to the work being done.

Principal Investigator

First Name: Deanne
Last Name: Dilley
Degree: MPH (Statistics)
Primary Affiliation: UCB Biosciences
E-mail: datasharing.coordinator@ucb.com
Phone number: 919-767-2555
Address: 8010 Arco Corporate Drive

City: Raleigh
State or Province: NC
Zip or Postal Code: 27617
Country: USA
SCOPUS ID: 55252035800

2016-1038

General Information

Key Personnel (in addition to PI): **First Name:** Anthony
Last name: Daniels
Degree: BS
Primary Affiliation: UCB

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

yoda_project_coi_form_for_data_requestors_2016_t_daniels.docx.pdf
yoda_project_coi_form_for_data_requestors_2016_d_dilley.docx.pdf
certification_of_training_on_data_use_agreement_d_dilley.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

Associated Trial(s): A double-blind, randomized trial of topiramate as adjunctive therapy for partial-onset seizures in children
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Development of historical control using placebo data from pediatric epilepsy studies

Narrative Summary:
In the development of new drugs, pharmaceutical companies need to conduct clinical studies in the pediatric population for a medications approved for the same indication in adults. To prove that the new treatment works in children, there needs to be a standard to which the new medication can be compared to show it performs better than no treatment. To limit the number of pediatric subjects exposed to placebo, it is proposed to perform a combined analysis of the placebo responses observed in completed studies in children with epilepsy to create a historical control for reference in future studies.

Scientific Abstract:
Background
Clinical studies in the pediatric population are often more difficult to enroll than those conducted in adults; especially in the population of children younger than 4 years of age and ethical questions about exposing children to placebo.

Objective
The goal of this project is to create a historical control using the data from pediatric subjects for several anti-epileptic drugs (eg, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate) that could be used as a comparator to future drugs.

Study Design
A meta-analysis design is proposed to combine the results from multiple studies

Participants
Subjects from clinical studies that meet the following criteria:

• Randomized and placebo-controlled
• Has at least one of the main outcomes with aggregate statistics reported:
• Information is available on the number of treatment arms in the study and subjects randomized to each arm and corresponding dosages
• Subjects <18 years of age
• Specific indication (partial-onset seizures, generalized seizures)
• Type of therapy: adjunctive or monotherapy

Main Outcome
The main outcomes are the reduction in seizure frequency compared to baseline and percent reduction in seizure frequency from baseline (responder status)

Statistical Analysis Plan
A meta-analysis design is proposed to combine the results from multiple studies. If participant-level data for applicable studies is available, modeling and simulation exercises may also be employed. A Bayesian framework will be also be considered and evaluated.

Brief Project Background and Statement of Project Significance:
Clinical studies in the pediatric population are often more difficult to enroll than those conducted in adults; especially in the population of children younger than 4 years of age. To limit the number of pediatric subjects exposed to placebo in future studies, it is proposed to perform a meta- analysis of the placebo responses observed in completed studies in children with epilepsy (especially those with partial-onset seizures) to create a historical control (a group of patients who were observed at some time in the past or for whom data are available through records) for reference in future studies.

The significance of this analysis is that it could possibly reduce the number of pediatric subjects required to be randomized to the placebo arm of clinical studies, and would minimize the exposure of a larger number of pediatric subjects with potentially life-threatening seizures to placebo. In addition, leveraging historical control placebo response may shorten development timelines, allowing quicker access to additional treatment options for epilepsy in the pediatric population.

Specific Aims of the Project:
The goal of this proposal is to summarize the placebo response in pediatric patients randomized to placebo in, randomized, controlled studies of anti-epileptic drugs in children with epilepsy (particularly partial-onset seizures).

What is the purpose of the analysis being proposed? Please select all that apply. Participant-level data meta-analysis
Participant-level data meta-analysis will pool data from YODA Project with other additional data sources

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
Data will be obtained on subjects randomized to the placebo arm of randomized controlled studies. Specifically the analysis will focus on clinical studies that meet the following criteria:

• The study is randomized and placebo-controlled
• The study has at least one of the following efficacy endpoints as primary with aggregate statistics reported:
a. Reduction in seizure frequency compared to baseline
b. Percent reduction in seizure frequency from baseline (responder status)
• Information is available on the number of treatment arms in the study and subjects randomized to each arm and corresponding dosages
• Study includes subjects <18 years of age
• Specific indication (partial-onset seizures, generalized seizures)
• Type of therapy: adjunctive or monotherapy

Main Outcome Measure and how it will be categorized/defined for your study:
There are two primary endpoints of interest in this study.

1. The percent (%) reduction in seizure frequency from baseline (continuous variable)

2. Responder status (yes/no) where responder is defined as subjects with ?50% reduction in seizure frequency from baseline

The effect measure of interest is the placebo rate for the two efficacy endpoints.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
The proposed analysis is to perform a meta-analysis of placebo response based on endpoints from completed clinical trial. The main predictor/independent variable is treatment (placebo).

Other Variables of Interest may be defined once all available data is collected from YODA and data sources outside of YODA (eg, demographic information).

Statistical Analysis Plan:
Studies to be used in the analysis will include pediatric epilepsy trials previously conducted by UCB and other pharmaceutical companies. If aggregate data for efficacy endpoints from the requested studies is received, a meta-analysis design is proposed to combine the results from multiple studies as a weighted average. The result of combing study results to form a new placebo historical control may increase

the statistical power (over individual studies) and may, improve estimates of the size of the effect. An estimate of the combined placebo historical control for each endpoint will be evaluated using a fixed effect model. The inverse of the estimates' variance will be used as the study weight. Heterogeneity of studies will be investigated.

If participant-level data for applicable studies is available, modeling and simulation exercises may also be employed. A Bayesian framework will be also be considered and evaluated.

Project Timeline:
It is estimated that this project can be completed within a one year timeframe and will consist of the following

timeframes: requesting and collection of data, completion of analysis, summarization of data, and submission of data to Regulatory Authorities.

Dissemination Plan:
After analysis is completed, the results would be published in a journal available to the public.

Bibliography:
Not Applicable