Research Data Request: Real time monitoring of individual response to antiseizure medication treatment during clinical trials

Vivli ID: 00007161

Comments from the Vivli Team

PI noted in chat on 6/4/2021: “We will not code based on MedDRA so MedDRA training is not applicable. Safety will be improved by reduced time spent in trial.”

Research Team

Lead Investigator and Statistician

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Education or Qualifications

University of Pennsylvania, Biological Basis of Behavior, Biological Mathematics BA
University of California, Los Angeles, MD
University of California, Los Angeles, PhD in Biomathematics
Eisenhower Health, Preliminary Intern
University of California, Los Angeles, Neurology Residency

Dr. Kerr currently serves as a biostatistical reviewer for the journal Neurology for 12 manuscripts to date. Dr. Kerr logs his peer review activities on Publons: https://publons.com/researcher/1344842/wesley-t-kerr/.

Prior peer-reviewed manuscripts where Dr. Kerr has served as the statistician by PMID due to character limits: 33621828, 33601302, 33545649, 33388672, 32875486, 31874358, 31474213, 31238807, 30940048, 30884437, 30064848, 29414562, 5669805, and others.

Conflicts of Interest and Plan for Management

None

Additional Researchers

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Education or Qualifications

Wesleyan University, BA in Molecular Biology/Biochemistry
Wesleyan University, MA in Physical Biochemistry
Mount Sinai School of Medicine, MD
Beth Israel Medical Center, Internship
University of California, Los Angeles, Neurology Residency and Clinical Neurophysiology/Epilepsy Fellowship
Board Certified Neurologist & Epileptologist
AAN & AES Member

Conflicts of Interest and Plan for Management

Consultant for UCB

Research Proposal

General

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

Narrative summary explaining the relevance of the project to science and public health

This analysis aims to use statistical theories to limit the time that participants in clinical trials take medications that they are assigned to. 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. 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.

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.

Aims/Objectives and Hypotheses

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.

Purpose of Analysis

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations
Research that confirms or validates previously conducted research on treatment effectiveness
Research that confirms or validates previously conducted research on treatment safety
Participant-level data meta-analysis
Summary-level data meta-analysis

Study Design

Brief Description

We will use daily individual seizure counts to estimate the likelihood that a participant will respond to assigned treatment in a clinical trial using statistical theory. The statistical models include parameters that can influence these predictions including minimum duration of therapy and number of independent trials for a negative binomial distribution. If participant was highly unlikely to respond to the assigned treatment, then the participant could terminate that treatment earlier than planned. We will evaluate the influence of this early termination on the conclusions of the trial.

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).

Outcome Elements Categorization/Definitions

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.

While a shorter time of observation on ineffective treatment is expected to reduce adverse effects on specific medication, we will not report or code specific adverse effects based on MedDRA. Instead, we will focus on seizure count, time on therapy, and if efficacy could be determined prior to reporting of an adverse effect.

Main Predictor / Independent Variable

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

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).

Project Timeline

Target Analysis Start Date
10/1/21
Estimated Analysis Completion Date
6/30/23
Dissemination and Publication Plan

Plan
We intend to publish all research findings in peer-reviewed journals as well as Bioarchiv pending acceptance in other 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.

Peer reviewed publication and potentially Bioarchiv

Citations

Statistical Analysis Plan

General 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 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. The 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.

Countries where analysis will be conducted

USA

Funding

General

Government Funding
NO

Employment Contracts
NO

Additional Contracts or Consultancies
NO

Commercial Funding
NO

Other Information

Requested Studies
A Randomized, Double-blind, Placebo-controlled, Multicenter, Parallel-group Study to Evaluate the Efficacy and Safety of Brivaracetam in Subjects (≥16 to 80 Years Old) With Partial Onset Seizures

https://search.vivli.org/myDataRequestDetailsRO/InProgress/8c241338-2846-432d-99f8-4a205425222/Studies
An International, Randomized, Double-blind, Parallel-group, Placebo-controlled, Flexible Dose Study: Evaluation of the Safety and Efficacy of Brivaracetam in Subjects (≥ 16 to 70 Years Old) Suffering From Localization-related or Generalized Epilepsy.

PI: UCB
Sponsor: UCB Pharma SA
Study ID: NCT000504881
IRP/Approver: Wellcome Trust
Data Request ID: 00007161
Sponsor ID: N01358
Data Contributor: UCB
IPD Uploaded:

A Multi-center, Double-blind, Parallel-group, Placebo Controlled, Randomized Study: Evaluation of the Efficacy and Safety of Brivaracetam in Subjects (≥ 16 to 70 Years Old) With Partial Onset Seizures.

PI: UCB
Sponsor: UCB
Study ID: NCT00490035
IRP/Approver: Wellcome Trust
Data Request ID: 00007161
Sponsor ID: N01252
Data Contributor: UCB
IPD Uploaded:

A Multicenter, Double-Blind, Randomized Conversion to Monotherapy Comparison of Two Doses of Lamotrigine for the Treatment of Partial Seizures

PI: GlaxoSmithKline
Sponsor: GlaxoSmithKline
Study ID: NCT00464269
IRP/Approver: Wellcome Trust
Data Request ID: 00007161
Sponsor ID: N01057
Data Contributor: GlaxoSmithKline
IPD Uploaded:

A Double-blind, Multicenter, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Adjunctive Treatment With 3000 mg/Day (Pediatric Target Dose of 60 mg/kg/Day) Oral Levetiracetam (LEV) (166, 250, and 500mg Tablets), in Adult and Pediatric Subjects (4-65 Years) Suffering From Idiopathic Generalized Epilepsy With Primary Generalized Tonic-clonic (PGTC) Seizures.

PI: UCB
Sponsor: UCB
Study ID: NCT00160550
IRP/Approver: Wellcome Trust
Data Request ID: 00007161
Sponsor ID: N01061
Data Contributor: UCB
IPD Uploaded:

A Multicenter, Double-blind, Randomized, Parallel Group, Positive-controlled Trial Comparing the Efficacy and Safety of Levetiracetam (1000 to 3000 mg/Day Oral b.i.d.) to Carbamazepine (400 to 1200 mg/Day Oral b.i.d.), Used as Monotherapy for up to a Maximum of 121 Weeks in Subjects (≥ 16 Years) Newly or Recently Diagnosed as Suffering From Epilepsy, and Experiencing Partial or Generalized Tonic-clonic Seizures

PI: UCB
Sponsor: UCB
Study ID: NCT00150735
IRP/Approver: Wellcome Trust
Data Request ID: 00007161
Sponsor ID: N01061
Data Contributor: UCB
IPD Uploaded:

A Multicenter, Double-blind, Double-dummy, Randomized, Positive-Controlled Study Comparing the Efficacy and Safety of Lacosamide (200 to 600 mg/Day) to Controlled Release Carbamazepine (400 to 1200 mg/Day), Used as Monotherapy in Subjects (≥ 16 Years) Newly or Recently Diagnosed With Epilepsy and Experiencing Partial-onset or Generalized Tonic-clonic Seizures.

PI: UCB
Sponsor: UCB
Study ID: NCT01243177
IRP/Approver: Wellcome Trust
Data Request ID: 00007161
Sponsor ID: SP0003
Data Contributor: UCB
IPD Uploaded:
A Multicenter, Double Blind, Randomized, Placebo Controlled, Parallel Group Study to Investigate the Efficacy and Safety of Lacosamide as Adjunctive Therapy in Subjects With Epilepsy ≥4 Years to <17 Years of Age With Partial Onset Seizures

PI:
- Sponsor: UCB Pharma
- Study ID: NCT01921205
- IRP/Approver: Welcome Trust
- Data Request ID: 00007161
- Sponsor ID: SP0969
- Data Contributor: UCB

A Double-Blind Trial of Topiramate in Subjects With Lennox-Gastaut Syndrome.

PI:
- Sponsor: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
- Study ID: NCT00236756
- IRP/Approver: Johnson & Johnson
- Data Request ID: 00007161
- Sponsor ID: CR005464
- Data Contributor: Johnson & Johnson

A Randomised, Double-blind, Placebo-controlled, Parallel-group, Multicentre Study to Determine the Efficacy and Safety of 2 Doses of Retigabine Immediate Release (900 mg/Day and 600 mg/Day) Used as Adjunctive Therapy in Adult Asian Subjects With Drug-resistant Partial-onset Seizures.

PI:
- Sponsor: GlaxoSmithKline
- Study ID: NCT01648101
- IRP/Approver: Wellcome Trust
- Data Request ID: 00007161
- Sponsor ID: RTG114855
- Data Contributor: GlaxoSmithKline

A Multi-Center, Open-label, Randomized Study to Evaluate the Long Term Effectiveness of Levetiracetam as Monotherapy in Comparison With Oxcarbazepine in Subjects With Newly or Recently Diagnosed Partial Epilepsy

PI:
- Sponsor: UCB
- Study ID: NCT01498822
- IRP/Approver: Welcome Trust
- Data Request ID: 00007161
- Sponsor ID: N01367
- Data Contributor: UCB

A Randomized, Open-label, Parallel Group, Multi-center, Comparative, Phase IV Trial of Levetiracetam (LEV) Versus Topiramate (TPM) as Adjunctive Therapy to Evaluate Efficacy and Safety in Subjects With Refractory Partial Onset Seizures

PI:
- Sponsor: UCB Korea Co., Ltd.
- Study ID: NCT01229735
- IRP/Approver: Welcome Trust
- Data Request ID: 00007161
- Sponsor ID: N01353
- Data Contributor: UCB

Topiramate Clinical Trial in Primary Generalized Tonic-Clonic Seizures

PI:
- Sponsor: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
- Study ID: NCT00236704
- IRP/Approver: Johnson & Johnson
- Data Request ID: 00007161
- Sponsor ID: CR005455
- Data Contributor: Johnson & Johnson

A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Phase 3 Study to Determine the Efficacy and Safety of Retigabine (1200 mg/Day) Used as Adjunctive Therapy in Refractory Epilepsy Patients With Partial-Onset Seizures

PI:
- Sponsor: GlaxoSmithKline
- Study ID: NCT00220415
- IRP/Approver: Welcome Trust
- Data Request ID: 00007161
- Sponsor ID: VRX-RET-E22-301
- Data Contributor: GlaxoSmithKline

Topiramate (RWJ-17021-000) Monotherapy Clinical Trial in Patients With Recently Diagnosed Partial-Onset Seizures

PI:
- Sponsor: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
- Study ID: NCT00230698
- IRP/Approver: Johnson & Johnson
- Data Request ID: 00007161
- Sponsor ID: CR002503
- Data Contributor: Johnson & Johnson

A Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel Group Trial to Investigate the Efficacy and Safety of SPM 927 (200mg/Day and 400mg/Day) as Adjunctive Therapy in Subjects With Partial Seizures With or Without Secondary Generalization

PI:
- Sponsor: UCB
- Study ID: NCT00220415
A Double-blind Trial Comparing the Efficacy, Tolerability and Safety of Monotherapy Topiramate Versus Phenytoin in Subjects With Seizures Indicative of New Onset Epilepsy
PI:
Sponsor: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Study ID: NCT00210782
IPD Uploaded:

A Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel Group Trial to Investigate the Efficacy and Safety of SPM 927 (400mg/Day and 600mg/Day) as Adjunctive Therapy in Subjects With Partial Seizures With or Without Secondary Generalization
PI:
Sponsor: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Study ID: NCT00136019
IPD Uploaded:

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
PI:
Sponsor: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Study ID: NCT00113815
IPD Uploaded:

A Multicenter, Double-Blind, Randomized, Parallel-group Evaluation of LAMICTAL Extended-release Adjunctive Therapy in Subjects With Partial Seizures
PI:
Sponsor: GlaxoSmithKline
Study ID: NCT00104416
IPD Uploaded:

A Multicenter, Double-blind, Randomized, Parallel-group Evaluation of LAMICTAL Extended-Release Adjunctive Therapy in Patients With Primary Generalized Tonic-Clonic Seizures
PI:
Sponsor: GlaxoSmithKline
Study ID: NCT00043901
IPD Uploaded:

A Multi-Center, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Evaluation of Lamotrigine Adjunctive Therapy in Subjects With Primary Generalized Tonic-Clonic Seizures
PI:
Sponsor: GlaxoSmithKline
Study ID: NCT001777139
IPD Uploaded:

Valproate Dose Reduction and Its Clinical Evaluation by Introducing Lamotrigine in Japanese Women With Epilepsy - Single Arm, Multicenter, and Open-label Study -
PI:
Sponsor: GlaxoSmithKline
Study ID: NCT02100644
IPD Uploaded:

A Multicentre, Open-label, Long-term, Safety, Tolerability, and Efficacy Study of Retigabine Immediate-release (IR) in Asian Adults With Partial Onset Seizures (Extension of Study RTG114655)
PI:
Sponsor: GlaxoSmithKline
Study ID: NCT01777139
IPD Uploaded:
A Multi-center, Uncontrolled, Open-label, Evaluation of Lamotrigine Monotherapy on Newly Diagnosed Typical Absence Seizures in Children and Adolescents

PI:
Sponsor: GlaxoSmithKline
Study ID: NCT01431976
IRP/Approver: Wellcome Trust
Data Request ID: 00007161
Sponsor ID: 115377
Data Contributor: GlaxoSmithKline
IPD Uploaded:

A Multi-center, Uncontrolled, Open-label, Evaluation of Lamotrigine Monotherapy in Newly Diagnosed Epilepsy or Recurrent Epilepsy (Currently Untreated)

PI:
Sponsor: GlaxoSmithKline
Study ID: NCT01431963
IRP/Approver: Wellcome Trust
Data Request ID: 00007161
Sponsor ID: 115376
Data Contributor: GlaxoSmithKline
IPD Uploaded:

A Multi-centre, Open-Label, Long-Term, Safety and Tolerability Study of Retigabine Immediate Release (IR) in Adults With Partial-Onset Seizures (Extension of Study RGB113905)

PI:
Sponsor: GlaxoSmithKline
Study ID: NCT00310388
IRP/Approver: Wellcome Trust
Data Request ID: 00007161
Sponsor ID: LEP103944
Data Contributor: GlaxoSmithKline
IPD Uploaded:

Lamotrigine Extended-Release in Elderly Patients With Epilepsy

PI:
Sponsor: GlaxoSmithKline
Study ID: NCT00310388
IRP/Approver: Wellcome Trust
Data Request ID: 00007161
Sponsor ID: LEP103944
Data Contributor: GlaxoSmithKline
IPD Uploaded:

A Multicenter, Open-Label, Long-Term, Safety, Tolerability and Efficacy Study of Retigabine in Adult Epilepsy Patients With Partial-Onset Seizures (Extension of Study VRX-RET-E22-302)

PI:
Sponsor: GlaxoSmithKline
Study ID: NCT00310388
IRP/Approver: Wellcome Trust
Data Request ID: 00007161
Sponsor ID: LEP103944
Data Contributor: GlaxoSmithKline
IPD Uploaded:

A Multicenter, Open-label, Long-term, Safety, Tolerability and Efficacy Study of Retigabine in Adult Epilepsy Patients With Partial-onset Seizures (Extension of Study VRX-RET-E22-301)

PI:
Sponsor: GlaxoSmithKline
Study ID: NCT00310388
IRP/Approver: Wellcome Trust
Data Request ID: 00007161
Sponsor ID: LEP103944
Data Contributor: GlaxoSmithKline
IPD Uploaded:

An Open-label, Double Conversion Study to Characterize the Pharmacokinetics of Lamotrigine When Switching Patients With Epilepsy on LAMICTAL Immediate-release to Extended-release Formulation and Vice Versa

PI:
Sponsor: GlaxoSmithKline
Study ID: NCT00264615
IRP/Approver: Wellcome Trust
Data Request ID: 00007161
Sponsor ID: LEP103944
Data Contributor: GlaxoSmithKline
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Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Phase 3 Study - Determine Efficacy and Safety of Two Doses of Retigabine (900 Mg/Day and 600 Mg/Day) Used as Adjunctive Therapy in Refractory Epilepsy Patients With Partial-Onset Seizures

PI:
Sponsor: GlaxoSmithKline
Study ID: NCT00264615
IRP/Approver: Wellcome Trust
Data Request ID: 00007161
Sponsor ID: LEP103944
Data Contributor: GlaxoSmithKline
IPD Uploaded:

A Multicenter, Open-Label Conversion of Valproate Monotherapy to Lamotrigine Monotherapy in Patients With Epilepsy

PI:
Sponsor: GlaxoSmithKline
Study ID: NCT00043914
IRP/Approver: Wellcome Trust
Data Request ID: 00007161
Sponsor ID: LAM40013
Data Contributor: GlaxoSmithKline
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Attached Files

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