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General Information

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

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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): NCT00307684 - An Open International Multicentre Long-Term Follow Up Study to Evaluate Safety of Prolonged Release OROS Methylphenidate in Adults With Attention Deficit Hyperactivity Disorder
NCT00326300 - An Open-Label, Dose-Titration, Long-Term Safety Study to Evaluate CONCERTA (Methylphenidate HCL) Extended-release Tablets at Doses of 36 mg, 54 mg, 72 mg, 90 mg, and 108 mg Per Day in Adults With Attention Deficit Hyperactivity Disorder
NCT00246220 - A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study To Evaluate the Safety And Efficacy Of Prolonged Release OROS Methylphenidate Hydrochloride (18, 36 and 72 mg/Day), With Open-Label Extension,
NCT01009047 - A Randomized, Multicenter, Double-Blind, Active-Controlled, Flexible-Dose, Parallel-Group Study of the Efficacy and Safety of Prolonged Release Paliperidone for the Treatment of Symptoms of Schizophrenia in Adolescent Subjects, 12 to 17 Ye
NCT00645099 - A Prospective Randomized Open-label 6-Month Head-To-Head Trial to Compare Metabolic Effects of Paliperidone ER and Olanzapine in Subjects With Schizophrenia
NCT00518323 - A Randomized, Multicenter, Double-Blind, Weight-Based, Fixed-Dose, Parallel-Group, Placebo-Controlled Study of the Efficacy and Safety of Extended Release Paliperidone for the Treatment of Schizophrenia in Adolescent Subjects, 12 to 17 Yea
NCT01606228 - An Open-Label Prospective Trial to Explore the Tolerability, Safety and Efficacy of Flexibly-Dosed Paliperidone ER among Treatment-Naive and Newly Diagnosed Patients with Schizophrenia
NCT00334126 - A Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy

and Safety of Paliperidone ER Compared to Quetiapine in Subjects With an Acute Exacerbation of Schizophrenia
NCT00645307 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study With an Open-Label Extension Evaluating Extended Release OROS® Paliperidone in the Prevention of Recurrence in Subjects With Schizophrenia - Open Label Phase
NCT00650793 - A Randomized, DB, PC and AC, Parallel Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Dosages of Extended Release OROS Paliperidone (6, 9, 12 mg/Day) and Olanzapine (10 mg/Day), With Open-Label Extension, in the T
NCT00589914 - A Randomized, Double-Blind, Parallel-Group, Comparative Study of Flexible Doses of Paliperidone Palmitate and Flexible Doses of Risperidone Long-Acting Intramuscular Injection in Subjects With Schizophrenia
NCT00604279 - A Randomized, Open-Label, Parallel Group Comparative Study of Paliperidone Palmitate (50, 100, 150 mg eq) and Risperidone LAI (25, 37.5, or 50 mg) in Subjects with Schizophrenia
NCT00590577 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (25 mg eq., 100 mg eq., and 150 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia
NCT00111189 - A Randomized Double-blind Placebo-controlled Parallel Group Study Evaluating Paliperidone Palmitate in the Prevention of Recurrence in Patients With Schizophrenia. Placebo Consists of 20% Intralipid (200 mg/mL) Injectable Emulsion
NCT00210548 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (50 mg eq., 100 mg eq., and 150 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia
NCT00101634 - A Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (25 mg eq, 50 mg eq, and 100 mg eq) of Paliperidone Palmitate in Patients With Schizophrenia
NCT00391222 - A Randomized, Double Blind, Placebo and Active Controlled Parallel Group Study to Evaluate the Efficacy and Safety of Risperidone Long-acting Injectable (LAI) for the Prevention of Mood Episodes in the Treatment of Subjects With Bipolar I
NCT00034749 - The Efficacy and Safety of Risperidone in Adolescents With Schizophrenia: a Comparison of Two Dose Ranges of Risperidone
NCT00076115 - Research on the Effectiveness of Risperidone in Bipolar Disorder in Adolescents and Children (REACH): A Double-Blind, Randomized, Placebo-Controlled Study of the Efficacy and Safety of Risperidone for the Treatment of Acute Mania in Bipola
NCT00132678 - A Randomized, Double-blind, Placebo-controlled Study to Explore the Efficacy and Safety of Risperidone Long-acting Intramuscular Injectable in the Prevention of Mood Episodes in Bipolar 1 Disorder, With Open-label Extension
NCT00094926 - A Prospective, Randomized, Double-blind, Placebo-controlled Study of the Effectiveness and Safety of RISPERDAL CONSTA Augmentation in Adult Patients With Frequently-relapsing Bipolar Disorder
NCT00714688 - A Multicentre, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study to Evaluate Efficacy and Safety of Prolonged Release (PR) OROS Methylphenidate (54 and 72 mg/Day) in Adults With Attention Deficit/Hyperactivi
NCT00866996 - A Multi-center Randomized Parallel Group Study Evaluating Treatment Outcomes of Concerta (Extended Release Methylphenidate) and Strattera (Atomoxetine) in Children With Attention-deficit/Hyperactivity Disorder
NCT00269815 - Long-term Safety and Effectiveness of OROS (Methylphenidate HCl) in Children With ADHD
NCT00397033 - A Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Two Dosages of Paliperidone ER in the Treatment of Patients With Schizoaffective Disorder
NCT00412373 - A Randomized, Double-blind, Placebo-controlled, Parallel- Group Study to Evaluate the Efficacy and Safety of Flexible-dose Paliperidone ER in the Treatment of Patients With Schizoaffective Disorder
NCT00236444 - Risperidone in the Prevention of Relapse: a Randomized, Double-blind, Placebo-controlled Trial in Children and Adolescents With Conduct and Other Disruptive Behavior Disorders
NCT00236470 - Risperidone in the Treatment of Children and Adolescents With Conduct and Other Disruptive Behavior Disorders - an Open Label Follow-up Trial of CR002020
NCT00250354 - The Safety And Efficacy Of Risperidone Versus Placebo In Conduct Disorder In Mild, Moderate And Borderline Mentally Retarded Children Aged 5 To 12 Years
NCT00266552 - The Safety And Efficacy Of Risperidone Versus Placebo In Conduct Disorder and Other Disruptive Behavior Disorders In Mild, Moderate And Borderline Mentally Retarded Children Aged 5 To 12 Years
NCT00253201 - Efficacy, Tolerability and Safety of Galantamine in the Treatment of Alzheimer's Disease
NCT00253227 - Galantamine in the Treatment of Alzheimer's Disease: Flexible Dose Range Trial
NCT00216502 - Long Term Treatment With Galantamine In Dementia

NCT00799409 - The ABC Study: A Double-Blind, Randomized, Placebo-Controlled, Crossover Study Evaluating the Academic, Behavioral, and Cognitive Effects of CONCERTA on Older Children With ADHD
NCT00799487 - Double-Blind, Randomized, Placebo-Controlled, Crossover Study Evaluating the Academic, Behavioral and Cognitive Effects of CONCERTA on Older Children With ADHD (The ABC Study)
NCT00249132 - A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients
NCT00253162 - The Efficacy And Safety Of Flexible Dose Ranges Of Risperidone Versus Placebo Or Haloperidol In The Treatment Of Manic Episodes Associated With Bipolar I Disorder.
NCT00378092 - A Prospective Study of the Clinical Outcome Following Treatment Discontinuation After Remission in First-Episode Schizophrenia
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Detection of uninformative clinics during the trial of a new drug using statistical and machine learning techniques

Narrative Summary:
Major Depressive Disorder affects 350 million people worldwide . Remission rates with standard therapies are 30-50% . No treatments with new mechanisms of action have been approved. For treatments that are effective, 50% of clinical trials fail . A key determinant of this failure is the high variability in subjective clinical ratings and large placebo response rates.
The detection of uninformative centers at an early stage could lead to more efficient drug testing as noise level due to placebo response could be controlled.It is of great significance to find ways to recognize clinical centers which have a high probability of providing inaccurate data about the effect of drug and placebo.

Scientific Abstract:
Background: Major Depressive Disorder affects 350 million people worldwide. No treatments with new mechanisms of action have been approved this century.
For treatments that are effective, 50% of clinical trials fail.
Objective: The detection of uninformative centers at an early stage could lead to more efficient drug testing. It is significant to find ways to recognize clinical centers which have a high probability of providing inaccurate data about the effect of drug and placebo.
Study Design: The study is meta-analysis. Based on the results obtained from different clinical centers, a pattern is expected to be found which lead to classification of the centers into informative and uninformative. Standard machine learning and statistical techniques will be used.
Participants: Major Depressive Disorder patients.
Main Outcome Measure: Hamilton Depression Rating Score.
Statistical Analysis: 1. A multivariate logistic analysis to test statistical relationship between two placebo predictor variables (HAMD-17 score at baseline (P) and HAMD-17 score at the end of the study (F)) and the probability of detecting a signal of a clinically relevant treatment effect; 2. The posterior probability of the difference (P ? F) will be used for ranking the centers according to their performance within each individual trial; 3. Use standard machine learning techniques to identify and learn patterns in data which determine whether the data is informative or not with all the biometric and demographic features of the patient and along with the HAMD data, etc.

Brief Project Background and Statement of Project Significance:
Major Depressive Disorder (MDD) affects 350 million people worldwide and is now the world's second leading cause of disability . Remission rates with standard therapies are 30-50% . Despite the significant unmet need, no treatments with new mechanisms of action have been approved this century. Over the last ten years the probability of success for new MDD drugs entering human testing has been 7.2% . Historically, for treatments that are known to be effective, up to 50% of clinical trials fail . A key determinant of this failure is the high variability in subjective clinical ratings and large placebo response rates.

The detection of uninformative centers at an early stage could lead to more efficient drug testing as the noise level in the data due to placebo response could be controlled. This would mean more reliable results in a shorter time-

frame, and with a smaller number of subjects. It is thus of great significance to find ways to recognize clinical centers which have a high probability of providing inaccurate data about the effect of drug and placebo.

Specific Aims of the Project:
The aim of the project is to detect uninformative centers at an early stage to lead to more efficient drug testing.

Our hypothesis is that poor quality endpoint data at a site level differs systematically from the general trial data, for example in variability, correlation between assessments or non-plausible placebo response trajectories generated in a given center. These systematic differences would allow detection of sites with poor quality data during the conduct of the trial. The aim of this study would be to develop a quantitative methodology to detect sites contributing poor quality data.
Blinded data from previous Major Depressive Disorder (MDD) trial will be divided into a training set and a test set to assess whether outlier sites can be detected and to determine the accuracy of such predictions. Our aim is to classify each recruitment center on an ongoing basis during patient accrual as informative or non-informative.

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
Research that confirms or validates previously conducted research on treatment effectiveness
Summary-level data meta-analysis
Summary-level data meta-analysis uses only data from YODA Project
Participant-level data meta-analysis
Participant-level data meta-analysis uses only data from YODA Project

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
We focus on placebo-controlled trials in ‘Major Depressive Disorder’ as these are the most common types of registration trial. We are interested in Clinical study Data for 'Major Depressive Disorder’ studies.

Main Outcome Measure and how it will be categorized/defined for your study:
The difference in Hamilton Depression Rating Scale (HAMD) score at the beginning and at the end of the studies will be analyzed. The HAMD score is a measure of depression, and the change in the score during a clinical trial is a measure of effectiveness of drug/placebo. Our study will find whether the change in HAMD scores in different clinics are consistent.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
We want to focus our study on “Major Depressive disorder”. For our analysis, we estimate that at least 5000-7000 data points may be necessary. For independent variables, we need biometric and demographic data, like age, gender, body mass index, disease history, smoking, drinking or other lifestyle.

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

Statistical Analysis Plan:
Signal detection: 1. A multivariate logistic analysis to test statistical relationship between two placebo predictor variables (HAMD-17 score at baseline (P) and HAMD-17 score at the end of the study (F)) and the probability of detecting a signal of a clinically relevant treatment effect (the difference between end-of-study HAMD-17 score of active treatment andplacebo); 2. A probabilistic threshold derived from an ROC curve analysis to classify clinical centers as informative.
Non linear longitudinal modeling: Estimating treatment effect by associating a weighting factor to the data collected at clinical centers. The weight will be defined by the posterior probability of detecting a clinically relevant difference between active treatment and placebo at that center.
Dealing with missing data: Different strategies such as “Missing Not At Random”, “Missing At Random” will be employed. The best strategy will be chosen based on statistical measures such as p-values.
Detecting outliers: To detect an outlier, we have to define what is normal”. The normal may be defined as 11 < final HAMD < 20. There can be other information about what is normal. We know older people should recover slower

than younger people. If a clinic shows otherwise results, its data may be questionable. We can assign probabilities based on few more tests like this. If the data fails all the tests, or fails half of them or passes all of them.
Machine learning: Use standard machine learning techniques to identify and learn patterns. To classify each centre directly by plotting the HAMD scores of all patients for each centre. Uninformative and informative centres may exhibit different distributions.

Project Timeline:
Anticipated project start date: After we get the data from YODA Project
Analysis completion date: 4 or 5 months after we get the data
Date manuscript drafted: 6 months after we get the data
First submitted for publication: 8 months after we get the data
Date results reported back to YODA Project: 8 months after we get the data

Dissemination Plan:
Results of the study will be made available through publication in a peer-reviewed journal or presentation at a relevant scientific conference.

Bibliography:
1. Clin Pharmacol Ther. 2008 Sep;84(3):378-84. doi: 10.1038. Model-based approach and signal detection theory to evaluate the performance of recruitment centers in clinical trials with antidepressant drugs. Merlo-Pich E(1), Gomeni R.
2. Neuropsychopharmacology. 2015 Apr 21. doi: 10.1038. A Novel Methodology to Estimate the Treatment Effect in Presence of Highly Variable Placebo Response. Gomeni R(1), Goyal N(2), Bressolle F(1), Fava M(3).
3. Eur J Pharm Sci. 2009 Jan 31;36(1):4-10. doi: 10.1016. Modelling placebo response in depression trials using a longitudinal model with informative dropout. Gomeni R(1), Lavergne A, Merlo-Pich E.

Supplementary Material: supplementary_material.docx