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 #: 2021-4620)

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 #: 2021-4620)

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?	Unsure, further clarification from requestor is needed
4. Recommendation for this data request:	Not Approve

Comments:

This is an interesting question and centers around the potential effects of discontinuation of therapy. The investigators request to use multiple clinical trials (active treatment v. placebo followed by open label use of therapy). My question is how many patients will they actually have that received active treatment in the randomized phase and then discontinued during the open label period. The corollary is what statistical analysis have they done to look at power/sample size.

Request is to use data to determine the clinical impact of a period of antipsychotic discontinuation following antipsychotic reinstatement. The proposal could be strengthened by providing more information on the statistical analysis plan, including what methods will be used to meta-analyze the data from the 7 different trials, and whether additional covariates will be used for risk-standardization.

This study will require considerable statistical sophistication to adjust for unscheduled drop-out periods, loss to followup, use of additional medication and other common problems in trials of anti-psychotic drugs. The section on statistical methods would benefit from greater detail.

Principal Investigator

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General Information

Key Personnel (in addition to PI):

First Name: Robin
Last name: Murray
Degree: PhD
Primary Affiliation: King's College London
SCOPUS ID:

First Name: David
Last name: Taylor
Degree: PhD
Primary Affiliation: King's College London
SCOPUS ID:

First Name: Sameer
Last name: Jauhar
Degree: PhD
Primary Affiliation: King's College London
SCOPUS ID:

First Name: Joseph
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Degree: MRCPsych
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SCOPUS ID:

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?: Internet Search

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_rm.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019dt.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019dt_0.pdf
https://yoda.yale.edu/system/files/yoda_coi_robmcc.pdf
https://yoda.yale.edu/system/files/jn_coi_nelft_21092021.pdf

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_sj_0.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. NCT00086320 - R076477-SCH-301 - A Randomized, Double-blind, Placebo-controlled, Parallel-group Study With an Open-label Extension Evaluating Paliperidone Extended Release Tablets in the Prevention of Recurrence in Subjects With Schizophrenia
2. NCT00650793 - R076477-SCH-703 - 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 Treatment of Subjects With Schizophrenia - Open Label Phase
3. NCT00111189 - R092670PSY3001 - 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
4. NCT00752427 - R076477-SCH-702 - 24 week extension of NCT00085748: A Randomized, 6-Week Double-Blind, Placebo-Controlled Study With an Optional 24-Week Open-Label Extension to Evaluate the Safety and Tolerability of Flexible Doses of Paliperidone Extended Release in the Treatment of Geriatric Patients With Schizophrenia
5. NCT00078039 - R076477-SCH-303 - Trial Evaluating Three Fixed Dosages of Paliperidone Extended-Release (ER) Tablets and Olanzapine in the Treatment of Patients With Schizophrenia
6. NCT00085748 - R076477-SCH-302 - A Randomized, 6-Week Double-Blind, Placebo-Controlled Study With an Optional 24-Week Open-Label Extension to Evaluate the Safety and Tolerability of Flexible Doses of Paliperidone Extended Release in the Treatment of Geriatric Patients With Schizophrenia
7. NCT00645307 - R076477-SCH-701 - 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

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

Research Proposal

Project Title

The effects of antipsychotic discontinuation and reinstatement

Narrative Summary:

Discontinuation and associated relapse are often proposed to have long term negative effects. This, however, is based upon naturalistic data and it is not possible to determine whether discontinuation has a causally important long-term effect. In the current study we intend to examine data from trials in which after a period in which subjects are randomised to placebo or active antipsychotic treatment they are subsequently all treated with antipsychotics in an open label fashion. We will examine whether the period of antipsychotic discontinuation has any impact on longer term outcomes during the open label period, we will also examine the effect that rate of discontinuation has on outcomes.

Scientific Abstract:

Background:Discontinuation of antipsychotics in individuals with schizophrenia is associated with a relapse of psychotic symptoms. Discontinuation and associated relapse are often proposed to have long term deleterious

effects over and above the acute relapse. This, however, is primarily based upon naturalistic data and it is therefore not possible to determine whether discontinuation has a causal long-term effect.
Objective:To determine the clinical impact of a period of antipsychotic discontinuation following antipsychotic reinstatement
Design:Examine data from trials in which after a period of randomisation to placebo or active antipsychotic treatment, participants are subsequently treated with antipsychotics in an open label fashion. We will examine whether the initial period of antipsychotic discontinuation has an impact on longer term outcomes during the open label period.
Participants:Individuals with schizophrenia who have been randomised to placebo or antipsychotic treatment in a randomised controlled trial and subsequently followed up during open label antipsychotic treatment.
Outcome Measures:Symptom severity measured using the PANSS. Cognitive symptoms measured by the BACS. Motor side effects measured by the AIMS. Akathisia measured by the Barnes Akathisia Scale. Metabolic side effects indexed by weight and measures of blood sugar and lipids.
Statistical Analysis:The above outcome measures will act as dependent variables, while randomisation group will act as the primary predictor variable, with baseline scores included as a covariate in a general linear model

Brief Project Background and Statement of Project Significance:

Discontinuation of antipsychotics in individuals with schizophrenia is associated with a relapse of psychotic symptoms. Discontinuation and associated relapse are often proposed to have long term deleterious effects over and above the acute relapse. This, however, is based upon naturalistic data and it is therefore not possible to determine whether discontinuation has a causal long-term effect. There are very few randomised controlled trials that have examined this issue and the evidence from these has been conflicting with one suggesting that antipsychotic discontinuation may have some long-term benefits (1). In the current study we intend to examine data from trials in which following a period in which individuals are randomised to placebo or active antipsychotic treatment, they are subsequently treated with antipsychotics in an open label fashion. We will examine whether the period of antipsychotic discontinuation has any impact on longer term outcomes during the open label period.

Specific Aims of the Project:

To determine the clinical impact of a period of antipsychotic discontinuation following antipsychotic reinstatement

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
Confirm or validate previously conducted research on treatment effectiveness

Research Methods

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

Data sources will be randomised controlled trials of antipsychotics in the treatment of schizophrenia. All studies in which subjects enter an open label period of follow up following a period of randomisation to placebo vs active treatment will be included.

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

Outcome measures will include the following:
Positive and Negative Syndrome Scale: Total score and subscales (positive, negative, general)
Barnes Akathisia Rating Scale
Brief Assessment of Cognition in Schizophrenia
Abnormal Involuntary Movement Scale
Simpson Angus Scale
Schizophrenia Quality of Life Scale
Clinical Global Impression
Personal and Social Performance Scale
Laboratory markers of metabolic side effects
Weight

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

The main predictor variable is the group to which the participant is randomised during the double blind period of the trial

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

Demographic variables including age and gender, and drug half life will be examined to see if any associations differ across these variables

Statistical Analysis Plan:

A general linear model will be used to determine whether the predictor variable (randomisation group) is associated with any of the outcome variables at the end of the open label period.
Software Used:
R
Project Timeline:

3 months – data cleaning
2 months -data analysis
4 months- manuscript preparation

Dissemination Plan:

Findings will be disseminated via publication in clinical journals (e.g. JAMA Psychiatry, Lancet Psychiatry) and presentation at scientific conferences (e.g. Schizophrenia International Reserach Society)

Bibliography:

1. Wunderink L, Nieboer RM, Wiersma D, Sytema S, Nienhuis FJ (2013): Recovery in Remitted First-Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation or Maintenance Treatment Strategy: Long-term Follow-up of a 2-Year Randomized Clinical Trial. JAMA Psychiatry. 1–8.

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