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)
195 Church Street, 5th Floor, New Haven, CT 06510

The YODA Project
Research Proposal Review - Final
(Protocol #: 2022-4854)

Reviewers:

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

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:

No additional 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)
195 Church Street, 5th Floor, New Haven, CT 06510

The YODA Project
Research Proposal Review - Revisions Requested
(Protocol #: 2022-4854)

Reviewers:

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

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?	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:	Not Approve

Comments:

1. For the outcome measures of interest, the data request states, "Outcome measures of interest include PANSS, CGI-S, PSP, adverse events, and hospitalization."
a. Are "PANSS, CGI-S, PSP, adverse events, and hospitalization" examples of the outcomes that will be considered? If this is not an outcome specific evaluation, perhaps that is worth clarifying.
b. Are there certain outcomes that are 'primary' vs. 'secondary'?

2. Additional information regarding these approaches with proper references would clarify the statistical analysis. Will new methods be developed? Are there references that could be included for either of these overarching methods.

Principal Investigator

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Key Personnel (in addition to PI):

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Degree: PhD
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Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
Project Funding Source: This work has been funded by NIMH (R01MH126856) and PCORI (ME-2020C3-21145)
How did you learn about the YODA Project?: Internet Search

Conflict of Interest

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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

1. NCT00589914 - R092670PSY3006 - 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
2. NCT00604279 - R092670PSY3008 - 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
3. NCT00210717 - R092670PSY3002 - A Randomized, Double-Blind, Parallel Group, Comparative Study of Flexibly Dosed Paliperidone Palmitate (25, 50, 75, or 100 mg eq.) Administered Every 4 Weeks and Flexibly Dosed RISPERDAL CONSTA (25, 37.5, or 50 mg) Administered Every 2 Weeks in Subjects With 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

Combining data sources to identify effect moderation for personalized mental health treatment

Narrative Summary:

Identifying effect moderators is crucial for personalized delivery of treatment and prevention interventions, but doing so is incredibly difficult using standard study designs. This work will synthesize, extend, and apply methods for identifying effect moderators when multiple studies are available, with a particular focus on the complexities in mental health research.

Scientific Abstract:

Background: Identifying effect moderators is crucial for personalized delivery of treatment and prevention interventions, but doing so is incredibly difficult using standard study designs.

Objective: This work will synthesize, extend, and apply methods for identifying effect moderators when multiple studies are available, with a particular focus on the complexities in mental health research.

Study Design: This work will synthesize, extend, and apply methods for identifying effect moderators when multiple studies are available, with a particular focus on the complexities in mental health research. The methods will apply broadly and will be illustrated in an example: estimating the effects of medication treatment for schizophrenia (using 3 randomized controlled trials). In addition, we will synthesize experimental data with non-experimental data from the Duke University and Johns Hopkins Health System electronic health record.

Participants: Adult patients with schizophrenia

Main Outcome Measure(s): For schizophrenia studies, key outcomes of interest include PANSS, CGI-S, PSP, adverse events, and hospitalization.

Statistical Analysis: The work will: 1) Extend moderation methods for scenarios with multiple randomized experiments, and 2) Develop methods for using data from combined datasets with both experimental and non-experimental designs to identify effect moderation. Two types of methods will be developed. First, machine learning methods (developed already in the single study setting to estimate the conditional additive treatment effect as a function of covariates) will be extended to cases with multiple trials. Second, a Bayesian meta-analysis approach using individual level patient data will also be used.

Brief Project Background and Statement of Project Significance:

Determining “what works for whom” is a key goal in prevention and treatment across a variety of areas, including mental health. By understanding which individuals benefit most from which treatments we have the possibility of directing scarce resources to those who will most benefit, and of reducing the “churn” of individuals attempting multiple treatments before finding the one that works for them. Identifying effect moderators—factors that relate to the size of treatment effects--is crucial for delivery of treatment and prevention interventions, but doing so is incredibly difficult using standard study designs. By developing methods to take full advantage of both experimental and non-experimental data this work has the potential to move towards personalized mental health, thus improving how we prevent and treat mental health challenges in the population.

Specific Aims of the Project:

Aim 1: Develop methods to identify effect heterogeneity using multiple randomized experiments.

Aim 2: Develop methods to identify effect heterogeneity using data from combined datasets with both experimental and non-experimental studies.

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 Methods

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

We will be analyzing data on Vivli. The four other studies that will be used on Vivli include NCT01153009, NCT01140906, NCT00672620, and NCT00635219.

Male or female; Age >= 18; schizophrenia according to DSM-IV; baseline PANSS total score 60-120; BMI >= 15 kg/m^2; interventions including paliperidone palmitate and risperidone LAI

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

Outcome measures of interest include PANSS, CGI-S, PSP, adverse events, and hospitalization

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

We will consider effect moderators and confounders that are collected across the RCTs and EHR data. Possible effect moderators include co-occurring disorders such as fibromyalgia, coronary artery disease, diabetes, obesity, hypertension, and other mental health conditions (bipolar, anxiety, PTSD); demographics such as age, race, and gender; height, weight, and BMI; information on substance use, including drugs and alcohol; and indicators of severity of disease.

Statistical Analysis Plan:

Our proposed project spans a broad spectrum that includes on one end the situation where putative effect moderators have been specified and on the other end the situation where effect moderation is assumed to be via some unknown function of a set of covariates. We use Bayesian parametric models to handle the former case and nonparametric machine learning methods to handle the latter case. In addition, to deal with the problem that RCTs are generally not powered to test moderation effects, we propose to combine data from multiple studies: multiple RCTs, and RCTs plus non-experimental
electronic health records (EHR) data. Our work builds on Bayesian meta-analysis with individual participant-level data (IPD) and extends existing machine learning methods for effect modeling (developed for the single study setting) to handle multiple studies.
Software Used:
RStudio
Project Timeline:

Anticipated project start date: 1/1/2022
Analysis completion date: 5/31/2025
We plan to write multiple manuscripts over the course of project. We aim to submit first publication using the YODA data in the early 2023.

Dissemination Plan:

First, the newly developed methods will be disseminated through journal articles, conference talks, and a website to both statistical and medical audience. Second, we will develop (and publish in journals relevant to mental health researchers) several tutorials to provide general guidance on how to use the methods to combine data sources when examining effect moderation. Third, we will disseminate the methods through teaching at Johns Hopkins, Duke, and more broadly.

Bibliography:

Riley RD, Lambert PC, and Abo-Zaid G, (2010). Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ: British Medical Journal, p. 340:c221.

Hong H, Fu H, Price KL, and Carlin BP. (2015). Incorporation of individual patient data in network meta-analysis for multiple continuous endpoints, with application to diabetes treatment. Statistics in Medicine, 34(20), 2794-2819.

Seo M, White IR, Furukawa TA, Imai H, Valgimigli M, Egger M, Zwahlen M, Efthimiou O. (2021). Comparing methods for estimating patient-specific treatment effects in individual patient data meta-analysis. Statistics in Medicine, 40(6):1553-1573.

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