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 #: 2024-0972)

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 #: 2024-0972)

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?	Unsure, further clarification from requestor is needed
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:

1. The researcher's aim is "To derive bounds for the true treatment effect in cases of broken blinding, even when the key conditions are not met." By what criteria will the researchers determine that blinding is broken?
2. The researchers mention a "belief variable" but it is unclear from the proposal how this can be derived if it has not been directly measured within the trial. Please add further clarification.
3. The selection of the trials that will be analyzed requires additional information. At this stage, it is unclear if the identified trials will be appropriate for the proposed analyses. Perhaps this makes more sense as a two-stage analysis: 1) determine which proportion of selected trials are suitable (and reporting on this finding) and 2) conducting the proposed analyses on the suitable trials (and reporting on these findings). Please clarify.

Principal Investigator

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Degree: Ph.D.
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State or Province: Isreal
Country: Isreal

General Information

Key Personnel (other than PI):
First Name: Rachel
Last name: Axelrod
Degree: M.A.
Primary Affiliation: Department of Statistics and Operations Research, Tel Aviv University, Israel
SCOPUS ID:
Requires Data Access? Yes

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: Israel Science Foundation
How did you learn about the YODA Project?: Internet Search

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/11/YODA-data-agreement-4.pdf
https://yoda.yale.edu/wp-content/uploads/2024/11/YODA-data-agreement-Daniel.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. NCT01381900 - 28431754DIA3014 - A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, 18-Week Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Alone or in Combination With a Sulphonylurea
2. NCT01340664 - 28431754DIA2003 - A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin
3. NCT02025907 - 28431754DIA4004 - A Randomized, Double-blind, Placebo Controlled, 2-arm, Parallel-group, 26-week, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin and Sitagliptin Therapy
4. NCT00650806 - 28431754OBE2001 - A Randomized, Double-Blind, Placebo-Controlled,

Parallel-Group, Dose-Ranging Study to Investigate the Safety and Efficacy of JNJ-28431754 in Nondiabetic Overweight and Obese Subjects

5. NCT02243202 - 28431754OBE2002 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Investigate the Safety and Efficacy of the Co-administration of Canagliflozin 300 mg and Phentermine 15 mg Compared With Placebo for the Treatment of Non-diabetic Overweight and Obese Subjects
6. NCT02065791 - 28431754DNE3001 - A Randomized, Double-blind, Event-driven, Placebo-controlled, Multicenter Study of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Subjects With Type 2 Diabetes Mellitus and Diabetic Nephropathy
7. NCT01032629 - 28431754DIA3008 - A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus
8. NCT04614948 - VAC31518COV3009 - A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older
9. NCT04505722 - VAC31518COV3001 - A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older
10. NCT01369355 - CNTO1275CRD3003 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Subjects With Moderately to Severely Active Crohn's Disease
11. NCT01369342 - CNTO1275CRD3002 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Crohn's Disease (UNITI-2)
12. NCT01369329 - CNTO1275CRD3001 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Crohn's Disease Who Have Failed or Are Intolerant to TNF Antagonist Therapy (UNITI-1)
13. NCT00771667 - C0743T26 - A Phase 2b, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Ustekinumab Therapy in Subjects With Moderately to Severely Active Crohn's Disease Previously Treated With TNF Antagonist Therapy
14. NCT00269854 - C0168T16 - A Placebo-Controlled, Dose-Ranging Study Followed by a Placebo-Controlled, Repeated-Dose Extension of Anti-TNF Chimeric Monoclonal Antibody (cA2) in the Treatment of Patients With Active Crohn's Disease
15. NCT01190839 - REMICADECRD3001 - Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing REMICADE (Infliximab) and Placebo in the Prevention of Recurrence in Crohn's Disease Patients Undergoing Surgical Resection Who Are at Increased Risk of Recurrence
16. NCT00236665 - TOPMAT-OBHT-001 - A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of the Efficacy and Safety of Topiramate in the Treatment of Obese Patients With Mild to Moderate Essential Hypertension
17. NCT00236613 - TOPMAT-OBES-001 - A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel Group, Dose-Response Study to Assess the Efficacy and Safety of Topiramate in the Treatment of Patients With Obesity
18. NCT00231660 - TOPMAT-OBDM-002 - A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Efficacy and Safety of Topiramate in the Treatment of Obese, Type 2 Diabetic Patients Treated With Metformin
19. NCT00231647 - TOPMAT-OBD-202 - A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Study to Assess the Efficacy and Safety of Topiramate OROS Controlled-Release in the Treatment of Obese, Type 2 Diabetic Subjects Managed With Diet or Metformin
20. NCT00642278 - 28431754DIA2001 - A Randomized, Double-Blind, Placebo-Controlled, Double-Dummy, Parallel Group, Multicenter, Dose-Ranging Study in Subjects With Type 2 Diabetes Mellitus to Evaluate the Efficacy, Safety, and Tolerability of Orally Administered SGLT2 Inhibitor JNJ-28431754 With Sitagliptin as a Reference Arm

21. NCT00207766 - C0168T26 - ACCENT II - A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNF Chimeric Monoclonal Antibody (Infliximab, Remicade) in the Long Term Treatment of Patients With Fistulizing CROHN'S Disease
22. NCT00207662 - C0168T21 - ACCENT I - A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNFa Chimeric Monoclonal Antibody (Infliximab, Remicade) in the Long-term Treatment of Patients With Moderately to Severely Active Crohn's Disease

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

Research Proposal

Project Title

Estimating Reliable Treatment Effects Despite Blinding Failures in Clinical Trials

Narrative Summary:

Many drugs and vaccines affect medical outcomes through both physiological and behavioral mechanisms. Clinical trials typically use blinding to isolate the physiological effects, but this process often fails, leading to inaccurate treatment effect estimates. Previous research suggests that, despite unblinding, treatment effect estimates can still be estimated under certain conditions. In this work, we propose a new method to estimate treatment effect bounds when these conditions are unmet and illustrate the method with a clinical trial with broken blinding.

Scientific Abstract:

Background:
Drugs and vaccines can influence outcomes through both physiological and non-physiological pathways. For example, Canagliflozin, used for type 2 diabetes, may lead to higher HbA1c levels if patients become less diligent about diet and exercise. Clinical trials aim to measure physiological effects, often using blinding to eliminate behavioral influences. Previous research has identified key conditions, such as measuring a "belief variable," to help estimate treatment effects accurately, even when blinding fails.

Objective:
To derive bounds for the true treatment effect in cases of broken blinding, even when the key conditions are not met.

Study Design:
This is a statistical methodological study. We will demonstrate the application of the proposed bounds and sensitivity analysis using real clinical trial data.

Participants:
We aim to analyze one or two clinical trials that meet two criteria: (1) The treatment potentially has a non-physiological effect, and (2) blinding is imperfect due to strong side effects or notable treatment effects.

Primary and Secondary Outcome Measures:
The treatment effect is defined as the causal contrast
E(Y^{a=1,m}) vs. E(Y^{a=0,m}), where
E denotes expectation, Y is the outcome (e.g., weight loss), a is the treatment arm, and m is the "message indicator," which reflects the participant's belief about their treatment assignment.

Statistical Analysis:
We will use Linear Programming techniques and sensitivity analysis to construct bounds for the treatment effect.

Brief Project Background and Statement of Project Significance:

It is well known that medications and vaccines can affect desired medical outcomes through physiological mechanisms. However, they may also influence outcomes through behavioral pathways [1,2,3]. For example, individuals treated with insulin may justify consuming more food because they perceive the insulin injection as a safeguard against hyperglycemia [1,4], potentially leading to an underestimation of insulin's effect on weight loss.

To isolate the physiological effect of a treatment and eliminate behavioral influences, clinical trials typically use a "blinding" procedure, where participants are unaware of their treatment assignment. Ideally, the control group receives a placebo with side effects similar to those of the actual treatment. However, several studies have shown that blinding is often unsuccessful, with participants correctly guessing their treatment group [5,6]. This unblinding can occur due to an ineffective placebo choice [9] or because the treatment itself produces noticeable effects.

[10] developed a method to separate physiological and behavioral effects using a "belief variable," which reflects an individual's belief about whether they received the actual treatment. This method is only valid under two conditions: (1) the "Y dismissible component condition" is met, ensuring no common causes between the belief variable and the outcome, and (2) the belief variable is measured during the study. However, in many trials, one or both conditions are not met. For example, personality traits like optimism may influence both the belief about receiving the treatment and the likelihood of engaging in behaviors that affect the outcome, such as exposure to infectious agents [11].

This project aims to improve the accuracy of treatment effect estimates by addressing behavioral confounders in clinical trials for both vaccines and drugs. We will develop methods to separate physiological and behavioral effects even when blinding is imperfect, and when the belief variable or the "Y dismissible component condition" is not available. The findings will enhance the reliability of treatment efficacy estimates and improve the understanding of real-world treatment effects, ultimately informing both scientific research and public health.

Specific Aims of the Project:

This project aims to provide partial identification of the physiological treatment effect in two key settings: (1) when the Y dismissible component condition is violated, and (2) when the belief variable is unmeasured. For the first setting, we derive bounds using two strategies. The first strategy employs the linear programming approach developed in [12], which generates nonparametric, valid, and tight bounds, evaluated without any assumptions. The second strategy incorporates assumptions about monotone relationships between the unmeasured variable, the belief variable, and the outcome.

When the belief variable is unmeasured, we propose a sensitivity analysis approach to address potential biases.

To summarize, our main objectives are:

To demonstrate how unmeasured common causes can impact clinical trial results, using real examples and directed acyclic graphs.
To develop a framework--based on bounds or sensitivity analysis--to distinguish between physiological and behavioral effects, even when the belief variable is unmeasured or common causes are present.
To apply our methods to real data and estimate bounds for the true physiological effects.

Study Design:

Methodological research

What is the purpose of the analysis being proposed? Please select all that apply.

Develop or refine statistical methods

Research on clinical trial methods

Research Methods

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

We will include clinical trials that are highly likely to meet the following conditions:

The treatment has a non-physiological effect, such as diabetes medications (e.g., Canagliflozin, JNJ-28431754), drugs for Crohn's Disease (e.g., Remicade), hypertension treatments (e.g., Topiramate), or the COVID-19 vaccine (e.g., Ad26.COV2.S).
The trial experienced broken blinding due to strong or unique side effects or a pronounced treatment effect.
For our final analysis, we will focus on 1-3 clinical trials that demonstrate the greatest difference between the treatment effect estimated using standard methods (which do not account for behavioral effects) and the treatment effect estimated using our proposed method.

Inclusion/Exclusion Criteria for Each Trial
Inclusion criteria: All participants who met the study's eligibility requirements, complied with the protocol, and received the required treatment doses.
Exclusion criteria: Participants who did not meet the eligibility requirements, failed to comply with protocol procedures, or did not receive the required treatment doses.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Canagliflozin and JNJ-28431754 (Diabetes Treatment):
Primary Outcome: Change in Glycosylated Hemoglobin (HbA1c) from baseline to Week 18/26.
Secondary Outcome: Percent change in body weight from baseline to Week 18.

Ad26.COV2.S (COVID-19 Vaccine):
Primary Outcome: Number of participants with the first occurrence of molecularly confirmed moderate to severe/critical COVID-19 in seronegative participants, with onset at least 14 days after the second vaccination.

Ustekinumab/Infliximab/Remicade (Crohn's Disease Treatment):
Primary Outcome: Number of participants achieving clinical remission at Week 44 or clinical response at Week 6/4.

Topiramate (Hypertension Treatment):
Primary Outcome: Percent change in body weight and/or sitting diastolic blood pressure from baseline.

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

The main predictor in all studies is the treatment arm (A), categorized into two groups:
Treatment (A=1): Subjects who received the active treatment being tested (Canagliflozin, Ad26.COV2.S, Ustekinumab/Infliximab/Remicade, or Topiramate).

Control (A=0): Subjects who received the placebo.

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

Side Effects / Adverse Events (S):
The presence of side effects or adverse events will be categorized into two groups:
Yes (S=1): Subjects who reported adverse events.
No (S=0): Subjects who did not report adverse events.
All selected trials include "safety" in their title, so we expect this variable to be present in the data. The exact definition of adverse events will depend on the specific trial data.
Other Variables:
Additional variables collected in the clinical trials, such as age, sex, and comorbidities, will be used to stratify the main outcome measure. Alternatively, these variables may be used to estimate the inverse probability of treatment weighting (IPTW) and incorporated into the final analysis.

Statistical Analysis Plan:

This is a statistical methodology study, not a reanalysis aimed at deriving new medical insights. Our goal is to demonstrate our novel methods using real clinical data.

We will estimate treatment effectiveness by comparing the main outcome for each treatment arm. For binary outcomes (e.g., infection status in the Ad26.COV2.S/Ustekinumab/Infliximab/Remicade trials), we will calculate the rate difference or rate ratio. For continuous outcomes (e.g., HbA1c in the Canagliflozin/Topiramate trials), we will calculate the mean difference or mean ratio.

Our focus is on scenarios where direct estimation of treatment effects is biased due to unobserved common causes. To address this, we will provide two alternatives for estimating directly the treatment effects: bounds and a sensitivity analysis framework. These methods are based on conditional expectations of the outcome in each treatment arm. For binary outcomes, the expectation is the event rate (e.g., infection rate). For continuous outcomes, the expectation is the mean (e.g., mean HbA1c).

Regarding missing data, if the proportion of missing outcomes is low, we will exclude subjects with missing data and perform a complete case analysis. As a sensitivity analysis, we will impute missing outcomes using the Multivariate Imputation by Chained Equations (MICE) algorithm (implemented in the R mice package). If the proportion of missing data is high, we will prioritize imputation.

We are requesting multiple clinical trials due to uncertainty about which trial will best meet the two conditions outlined in the Data Source section. Since we do not plan to conduct a meta-analysis, no special methods are required to combine datasets.

Our primary aim is to present a new estimation method, not to make statistical inferences. However, we will compute non-parametric confidence intervals using the bootstrap method.

Software Used:

RStudio

Project Timeline:

Estimated start date: January 2025
Estimated analysis completion: March 2025
Estimated manuscript submission: June 2025

Dissemination Plan:

We plan to submit our research findings to one of the top peer-reviewed journals in biostatistics, i.e.,

statistics for biological and medical research. Examples of these journals are Biometrics, Biostatistics, and Statistical Methods in Medical Research.

Bibliography:

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10. Stensrud, Mats J., Daniel Nevo, and Uri Obolski. “Distinguishing immunologic and behavioral effects of vaccination.” *Epidemiology* 35, no. 2 (2024): 154-163.

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