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 #: 2021-4836)

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:

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)
1 Church Street, Suite 200, New Haven, CT 06510

The YODA Project
Research Proposal Review - Revisions Requested
(Protocol #: 2021-4836)

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:

"The investigators have submitted a data request to use data from two trials as part of a systematic review and meta-analysis of double-blind randomized controlled trials to characterize adverse events associated with acetylcholinesterase inhibitor use. There is too little detail about aims and methods, and the same form of words is copied three times. We have a number of questions:

1. One of the trials requested seems off topic - it has nothing to do with acetylcholinesterase inhibitors. Please clarify the relevance or need for your analyses.
2. Will the investigators be using IPD or just the summary data (IPD are requested, but the purpose is described as 'summary-level data meta-analysis')?
3. Will the investigators be conducting a broad search of the literature to identify trials? Selecting just these two for analysis seems limited, but no additional trials are mentioned.
4. What adverse events will be studied? There is no pre-specification. At various points in the proposal, terms used include 'adverse events', 'psychiatric adverse events', and 'neuropsychiatric symptoms like headache or dizziness'. Please pre-specify.
5. Related to the prior point, how will 'symptom clusters' be defined? Please pre-specify.
6. Would recommend pre-specifying which other variables will be used to stratify analyses, beyond sex and age.
7. Please specify what 'specific diseases' and 'previous illnesses of participants' will be studied.

Much more detail is needed, as the goal of proposals submitted to the YODA Project for data re-use are to enable outside investigators/peer reviewers to have a reasonable sense of what will be done with the data so that a finished project can be assessed against what was proposed."

Principal Investigator

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General Information

Key Personnel (in addition to PI):
First Name: Nadine
Last name: Bittner
Degree: Master of Science
Primary Affiliation: Charité - Universitätsmedizin Berlin
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?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_21.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. NCT00638690 - COU-AA-301 - A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy
2. GAL-INT-3 - Long Term Safety and Efficacy of Galantamine in the treatment of Alzheimer'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

Adverse events of acetylcholinesterase inhibitors - systematic review and meta-analysis of double-blind randomized controlled trials

Narrative Summary:

Dementias are increasingly developing into a serious health problem. With proof of effectiveness, the acetylcholinesterase inhibitors donepezil, rivastigmine, galantamine and the NMDA antagonist memantine are currently approved in Germany for the treatment of mild to moderate Alzheimer's dementia and are used in clinical practice. Acetylcholinesterase inhibitors often produce different adverse events such as neuropsychiatric symptoms like headache or dizziness. The aim of this systematic review and meta-analysis is to quantify the risk of acetylcholinesterase inhibitors to cause common adverse events compared to placebo and other medications.

Scientific Abstract:

Background: Dementias are increasingly developing into a serious health problem. With proof of effectiveness, the acetylcholinesterase inhibitors donepezil, rivastigmine, galantamine and the NMDA antagonist memantine are currently approved in Germany for the treatment of mild to moderate Alzheimer's dementia and are used in clinical practice.
Objective: In 2016, 53.5 million defined daily doses (million DDD) of the group of cholinesterase inhibitors and 27.5 million DDD of the NMDA receptor antagonist memantine were prescribed in Germany. With regard to psychiatric adverse drug reactions, information can be found sporadically in the specialist information.
Acetylcholinesterase inhibitors often produce different adverse events such as neuropsychiatric symptoms like headache or dizziness.
Study Design: The aim of this systematic review and meta-analysis is to quantify the risk of acetylcholinesterase inhibitors to cause common adverse events compared to placebo and other medications.
Main Outcome measures: consequently we aim to answer these questions:
1. Which adverse events appear the most during therapy with acetylcholinesterase inhibitors and how is the risk compared to placebo and alternative treatments?
2. Are there differences between different acetylcholinesterase inhibitors regarding the occurence of adverse events during therapy?
3. Are there differences between patients populations or different diseases regarding the occurence of adverse events during therapy with acetylcholinesterase inhibitors?
Statistical Analysis: We perform pairwise meta-analyses, calculating odds ratios (OR) with 95% confidence intervals (CI) and respective pvalues for each symptom or symptom cluster.

Brief Project Background and Statement of Project Significance:

Dementias are increasingly developing into a serious health problem. With proof of effectiveness, the acetylcholinesterase inhibitors donepezil, rivastigmine, galantamine and the NMDA antagonist memantine are currently approved in Germany for the treatment of mild to moderate Alzheimer's dementia and are used in clinical practice.
In 2016, 53.5 million defined daily doses (million DDD) of the group of cholinesterase inhibitors and 27.5 million DDD of the NMDA receptor antagonist memantine were prescribed in Germany. With regard to psychiatric adverse drug reactions, information can be found sporadically in the specialist information.
Acetylcholinesterase inhibitors often produce different adverse events such as neuropsychiatric symptoms like headache or dizziness. The aim of this systematic review and meta-analysis is to quantify the risk of acetylcholinesterase inhibitors to cause common adverse events compared to placebo and other medications.

Specific Aims of the Project:

1. Which adverse events appear the most during therapy with acetylcholinesterase inhibitors and how is the risk compared to placebo and alternative treatments?
2. Are there differences between different acetylcholinesterase inhibitors regarding the occurence of adverse events during therapy?
3. Are there differences between patients populations or different diseases regarding the occurence of adverse events during therapy with acetylcholinesterase inhibitors?

What is the purpose of the analysis being proposed? Please select all that apply.
Summary-level data meta-analysis
Summary-level data meta-analysis pooling data from YODA Project with other additional data sources

Research Methods

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

PubMed, Web of Science, ClinicalTrials.gov

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

Prespecified primary and secondary outcomes are psychiatric adverse events (PAE) and withdrawal of therapy due to PAE, respectively.

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

Dosage, frequency and duration of application/intake of acetylcholinesterase inhibitors, specific disease, sex, age, previous illnesses of participants.

Statistical Analysis Plan:

Statistical analyses are carried out using Review Manager 5.3.18 and/or R since RevMan will not be available. We perform pairwise meta-analyses, calculating odds ratios (OR) with 95% confidence intervals (CI) and respective p-values for each symptom or symptom cluster.
Software Used:
R
Project Timeline:

Actual start date: 01/01/2021
Analysis completion date: 31/10/2021
Date manuscript drafted: 15/01/2022 and submitted for publication 31/01/2022
Anticipated completion date: 30/04/2022

Dissemination Plan:

PubMed, Web of Science, ClinicalTrials.gov
Search dates: to 31 of May 2021
Before the final analysis the search will be re-run in order to identify further studies for inclusion.
Potentially suitable journals for submission would be: PLoS ONE, Hypertension, Psychological Review, Psychological Medicine, Depression and Anxiety, Human Psychopharmacology-Clinical and Experimental

Bibliography:

European database of suspected adverse drug reaction reports. Secondary European database of suspected adverse drug reaction reports 2020. http://www.adrreports.eu/en/index.html.
FDA Adverse Event Event Reporting System (FAERS) Public Dashboard. . Secondary FDA Adverse Event Event Reporting System (FAERS) Public Dashboard. 2020. https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-repor...
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