The YODA Project
Research Proposal Review

The following page contains the final YODA Project review approving this proposal.

The YODA Project
Research Proposal Review - Final
(Protocol #: 2020-4244)

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 researchers have provided greater clarity about the kind of data requested and its use within the larger analysis.

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 YODA Project
Research Proposal Review - Revisions Requested
(Protocol #: 2020-4244)

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?

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. 'This is a proposal for an important systematic review and network meta-analysis to compare the cardiovascular and renal effectiveness of second-line antidiabetic drugs in patients with Type 2 diabetes mellitus. However, very little detail is offered when it comes time to pre-specifying the methods, both in the submitted proposal and in the PROSPERO registration. The authors should consider providing more detail, including whether there are any inclusion / exclusion criteria that will be applied to the trial sample populations, what terms/codes will be used to define the main outcome and predictor variables, and specifics as per the statistical analysis. The purpose of the proposal is to allow an investigator peer-reviewing a completed study manuscript to determine whether "the authors did what they had said they would do". But as written, the methods are so vague that no individual decision is pre-specified.'

2. 'The statistical analytic plan is somewhat thin as written, but that does not preclude the investigators from conducting the analysis.'

3. 'There is a lack of detail in the methods section - does this group have experience with IPD meta-analysis?'

4. 'The use of an odds ratio for the pooled analysis of CANVAS & CANVAS-R is not statistically sound given the very different durations of the studies which will lead to very different probability estimates for experiencing outcome events. Unclear why the analytic proposal unnecessarily deviates from the time to event framework.'

Principal Investigator

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General Information

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  First Name: Shaun
Last name: Lee Wen Huey
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Primary Affiliation: Monash University Malaysia
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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_ruth.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_1.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. 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
2. NCT01989754 - 28431754DIA4003 - A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2 Diabetes

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

Research Proposal

Project Title

Cardiorenal outcomes of second-line antidiabetic drugs in patients with Type 2 diabetes: a systematic review and network meta-analysis

Narrative Summary:

The rise in new antidiabetic drugs have provided clinicians with more choices to tailor Type 2 diabetes mellitus pharmacotherapy according to patient characteristics. In comparison to older second-line antidiabetic drugs like sulphonylurea, these drugs have comparable glycaemic control and better side effect profile. Additionally, some of these these drugs confer cardiorenal benefits in cardiovascular outcome trials. This study aims to compare efficacy and cardiorenal effectiveness of second-line antidiabetic drugs after metformin using systematic review and network meta-analysis.

Scientific Abstract:

Background
The rise in new antidiabetic drugs have provided clinicians with more choices to tailor Type 2 diabetes mellitus pharmacotherapy according to patient characteristics. In comparison to older second-line antidiabetic drugs like sulphonylurea, these drugs have comparable glycaemic control and better side effect profile. Additionally, some of these drugs confer cardiorenal benefits in cardiovascular outcome trials. The comparative effectiveness these drugs remain unclear.
Objective
To compare the cardiovascular and renal effectiveness of second-line antidiabetic drugs in patients with Type 2 diabetes mellitus.
Study Design
EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials will be searched for RTCs reporting cardiovascular and renal outcomes.
Participants
Patients with Type 2 diabetes mellitus
Main Outcome Measure(s)
Cardiovascular outcomes including MACE, myocardial infarction, stroke, cardiovascular death, cardiovascular mortality, all-cause mortality, unstable angina, heart failure, transient ischemic attack,
Renal outcomes including renal composite outcome, development of end-stage renal disease, decline in eGFR, dialysis, kidney transplantation, renal death, loss of kidney function, acute kidney injury.

Statistical Analysis
Network meta-analysis and pairwise meta-analysis will be conducted. Statistical heterogeneity in effects between studies calculating by the I² index. Publication bias will be assessed using funnel plot. Statistical analysis will be carried in R statistical software.

Brief Project Background and Statement of Project Significance:

Diabetes mellitus is a metabolic disorder currently affecting 463 million adults worldwide. Among them, 90% are Type 2 Diabetes Mellitus (T2DM) patients(1). In comparison to healthy populations, T2DM patients are at higher risk for cardiovascular and renal problems which might lead to disabilities and deaths. Lifestyle changes and metformin are the first line treatments to achieve glycaemic control. However, most T2DM patients require a combination of drugs to keep their blood glucose within the recommended limit. While traditional oral antidiabetic drugs are useful in keeping blood glucose in control, they are often characterized by their limited beneficial effects

on long term outcomes including cardiovascular and renal effects. In the last two decades, the rise in approval of oral antidiabetic drugs by United States Food and Drug Administration (FDA) has provided us with more choices to tailor therapies according to patient characteristics(2). These include drugs like dipeptidyl peptidase-4 (DPP-4) inhibitor, sodium-glucose co-transporter-2 (SGLT2) inhibitor, glucagon-like peptide-1 (GLP-1) receptor agonist, bile acid sequestrants and dopamine-2 agonists. Previous reviews focused on the cardiovascular outcomes of respective drug class and there is limited number of reviews that look at both the cardiovascular and renal outcomes of these drugs as a whole. Additionally previous systematic reviews have not included some of the more recent cardiovascular and renal outcome trials(3,4).

Specific Aims of the Project:

To compare the cardiovascular and renal effectiveness of second-line antidiabetic drugs in patients with Type 2 diabetes mellitus using systematic review and network meta-analysis.

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
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:

Data source: EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials
Trials included: NCT02128932, NCT01720446, NCT02692716, NCT01394952, NCT01179048, NCT01147250, NCT02465515, NCT01144338, NCT00968708, NCT00790205, NCT01107886, NCT01243424, NCT01897532, NCT02065791, NCT01131676, NCT01730534, NCT00968812, NCT00377676, NCT01959529, NCT00700856, NCT00174993, NCT00379769, NCT00069784, NCT00145925, NCT00954447, NCT01167881, NCT00856284, NCT00622284, NCT01106677
Inclusion: Patients with Type 2 diabetes, patients with outcome of interest, more than 1000 patients per trial, randomized controlled trial, patients on background therapy of metformin.

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

Cardiovascular outcomes including MACE, myocardial infarction, stroke, cardiovascular death, cardiovascular mortality, all-cause mortality, unstable angina, heart failure, transient ischemic attack, Renal outcomes including renal composite outcome, development of end-stage renal disease, decline in eGFR, dialysis, kidney transplantation, renal death, loss of kidney function, acute kidney injury.

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

history of cardiovascular disease, history of chronic kidney disease, study follow-up period

Statistical Analysis Plan:

Network meta-analysis and pairwise meta-analysis will be conducted. Odds ratios will be calculated using binary outcome in numbers. Statistical heterogeneity between studies will be calculated using I² index. Publication bias will be assessed using funnel plot. Statistical analysis will be carried in R statistical software.
Software Used:
R
Project Timeline:

8/02/2020-1/03/2020 Formal screening of search results against eligibility criteria
1/03/2020-31/04/2020 Data request
01/04/2020-01/06/2020 Data extraction
01/06/2020-1/07/2020 Data analysis

01/07/2020-1/09/2020 Drafting manuscript
01/10/2020 First submitted for publication
01/10/2020 Results reported back to the YODA Project

Dissemination Plan:

Potentially suitable journals: Journal of Diabetes Obes Metab

Bibliography:

1. IDF Diabetes Atlas 9th edition 2019. Diabetesatlas.org. 2019.
2. What are the direct medical costs of managing Type 2 Diabetes Mellitus in Malaysia?. Med J Malaysia. 2019;72(5):271-277.
3. Grenet G, Ribault S, Nguyen G, Glais F, Metge A, Linet T et al. GLUcose COntrol Safety & Efficacy in type 2 DIabetes, a systematic review and NETwork meta-analysis. PLOS ONE. 2019;14(6):e0217701.
4. Fei Y, Tsoi M, Cheung B. Cardiovascular outcomes in trials of new antidiabetic drug classes: a network meta-analysis. Cardiovascular Diabetology. 2019;18(1).

Supplementary Material:

https://yoda.yale.edu/sites/default/files/prospero_ruth_100220_sr_nma_cardiorenal_antidiabetic.pdf