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General Information

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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?: Twitter

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_do.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_fja_signed-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 Mellitus

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

Research Proposal

Project Title

A Data-Zone Scoring System to Assess the Generalizability of Canagliflozin to Individual Patients

Narrative Summary:

Utilizing clinical trial inclusion/exclusion criteria to determine applicability to patients is limited by trial subjects being unevenly distributed across these criteria. We will characterize participants in the CANVAS trial by their baseline characteristics in a novel manner to develop a schema to evaluate the applicability of canagliflozin to non-trial patients.

We will define the data-rich zone of CANVAS based on a composite metric of participant characteristics, and not on inclusion/exclusion criteria. For each individual, a composite z-score will be calculated to quantify composite deviation from the average. This will be compared to the same score for real-world patients.

Scientific Abstract:

Background: Evaluating applicability of clinical trials to specific patients is difficult. Using only inclusion and exclusion criteria does not account for participants being heterogeneous across these criteria. It is possible for patients to fit trial parameters yet be poorly represented by the majority of trial participants. Conversely, patients excluded based on a parameter could still closely resemble the trial population in other respects. Most clinicians find it difficult to recall all inclusion criteria and may apply results more broadly than appropriate based on headline results.

Objective:
The objective of this project is to define the “data-free”, “data-limited” and “data-rich” zones for trial participants for the CANVAS trial, which could guide who to treat with the SGLT2 inhibitor canagliflozin.

Study Design:
A mathematical framework will be developed to quantify the difference between an individual participant and the theoretical average CANVAS trial participant. This difference, termed the Trial Score, will stratify participants into the “data-rich” (less than the 90th percentile), “data-limited” (90th and the 97.5th), and “data-free” zone (beyond 97.5th percentile).

Participants:
The participants of the CANVAS and CANVAS-R trial

Main Outcome Measure:
The distribution of Trial Scores across the CANVAS participants. The CANVAS Trial Score will also be calculated for de-identified patients to describe how real-world patients compare to the trial participants.

Statistical Analysis:
Statistical analysis will be done using R.

Brief Project Background and Statement of Project Significance:

Canagliflozin is a sodium–glucose cotransporter 2 inhibitor (SGLT2) that reduces glycemia, body weight, and albuminuria in people with diabetes (Neal et al., 2017). It has also been shown to reduce blood pressure in individuals with elevated risk of cardiovascular disease (Neal et al., 2017). The CANVAS and CANVAS-R trials (NCT01032629 and NCT01989754) were landmark trials that helped to establish the utility of canagliflozin for reduction of cardiovascular and renal complications in those with type 2 diabetes. The proposed study will evaluate the generalizability of the CANVAS trials to individual patients by assigning each participant a Trial Score, a numerical score that succinctly characterizes the participants baseline characteristics. The Trial Score for each participant is their distance in multidimensional space to the theoretical mean trial participant.
The results of this project will enhance the knowledge of precision medicine and assist clinicians in their decision-

making processes. Utilization of a trial score can aid the clinician in determining if a specific drug will be efficacious in the patients they care for. Further study of how clinicians can implement and apply a scoring system such as the Trial Score in everyday practice is needed such as how this method can be integrated within the electronic medical record.

The Trial Score is not meant to be prescriptive, but rather to help the clinician and patient have an informed discussion about the applicability of a clinical trial. Its use would allow a clinician to determine, in a quantifiable manner, how pertinent a trial is to a specific patient, and provide a framework to understand how other trials or populations overlap with the trial in question. Overall, the trial score can convey to clinicians whether their patients are well represented by the trial and whether these patients would benefit from the treatment.

Previous research has been conducted on the SPRINT (Systolic Blood Pressure Intervention) Trial in which baseline characteristics were used to generate a trial score for each participant and compare these data to an NHANES population and participants from the ACCORD-BP Trial (Laffin et al., 2018). The participants who fell in the data-rich zone for both ACCORD-BP and SPRINT responded well to intensive blood pressure control (Laffin et al., 2018).

Furthermore, a trial score web calculator was developed for the SPRINT Trial as a tool for clinical decision making and as available as an application (Laffin & Alenghat, 2019). The Trial Score Calculator can be found here: https://alenghatlab.shinyapps.io/SPRINT_TSC/

Specific Aims of the Project:

1. Analyze data from the Canagliflozin CANVAS trials and assign trial scores to each participant
2. Sort participants into data-rich, data-limited and data-free zones
3. Apply trial score to a real world population

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
Develop or refine statistical methods
Research on comparison group
Research on clinical prediction or risk prediction

Research Methods

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

All participants included in the CANVAS and CANVAS-R trials will be included.

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

The main outcome is the distribution of Trial Scores across the CANVAS participants. A secondary outcome is, using the CANVAS Trial Score, the distribution across real-world de-identified patients.

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

Once the Trial Score is developed it will be assessed as a predictor of outcomes in both the canagliflozin and placebo arms of the trial.

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

Continuous variables from the baseline characteristics will be used to calculate the trial score
Categorical variables will not be included.

Statistical Analysis Plan:

1) Identify the variables to use in the score
a) Only continuous, baseline variables
b) Variables should be fairly common/routine parts of a patient's assessment in real world
c) Variables should be sufficiently distinct from each other in how they describe patient
d) Variables ideally would be available in all the planned populations to be analyzed
e) Aim for 10 or less variables
2) Compute z-scores for each variable, for each patient
3) Compute the trial score (unweighted and weighted by the variable's association with the primary outcome) for each participant
4) Show the distribution of trial scores across the population
5) Determine how the trial score impacts outcome over the whole population
6) Determine if the trial scores (both versions) predict response to treatment allocation
Steps 5 and 6 will be conducted with univariable logistic regression with Trial Score as the independent variable and the trial primary outcome (with or without treatment allocation) as the dependent variable.
Software Used:
RStudio

Project Timeline:

Project Start Date: June 1, 2020
Analysis Completion Date: August 15, 2020
Manuscript Drafted: September 1, 2020
Submitted Manuscript: September 15, 2020

Dissemination Plan:

Dissemination will occur with a manuscript for publication hopefully in one of the following journals: Circulation: Heart Failure, Circulation, JAHA, JACC: Heart Failure, European Journal of Preventive Cardiology, JAMA Cardiology, Diabetes, Diabetes Care, Journal of Endocrinology, The Journal of Clinical Endocrinology and Metabolism

Bibliography:

Laffin LJ, Besser SA, Alenghat FJ. (2018) A data-zone scoring system to assess the generalizability of clinical trial results to individual patients. European Journal of Preventive Cardiology doi: 10.1177/2047487318815967. PMID: 30477321.

Laffin LJ, Alenghat FJ. The SPRINT Trial Score web calculator. (2019) European Journal of Preventive Cardiology doi: 10.1177/2047487319857210. PMID: 31189381.

Neal B, Perkovic V, Mahaffey KW, et al. (2017) Optimizing the analysis strategy for the CANVAS Program: a prespecified plan for the integrated analyses of the CANVAS and CANVAS-R trials. Diabetes Obes Metab