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General Information

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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: PCORI

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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

Associated Trial(s): NCT01106625 - 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 Glycemi

NCT01064414 - A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, 26-Week, Multicenter Study With a 26-Week Extension, to Evaluate the Efficacy, Safety and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabete
NCT01081834 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin as Monotherapy in the Treatment of Subjects With Type 2 Diabetes Mellitus Inadequately Co
NCT01106677 - A Randomized, Double-Blind, Placebo and Active-Controlled, 4-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 Inadequ
NCT00968812 - A Randomized, Double-Blind, 3-Arm Parallel-Group, 2-Year (104-Week), Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-28431754 Compared With Glimepiride in the Treatment of Subjects With Type 2 Diabetes Mellitus
NCT01106651 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Compared With Placebo in the Treatment of Older Subjects With Type 2 Diabetes Mellitus In
NCT01106690 - 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 Glycemi
NCT01137812 - A Randomized, Double-Blind, Active-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Versus Sitagliptin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Con
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Making Better Use of Randomized Trials: Assessing Applicability and Transporting Causal Effects

Narrative Summary:
Use of randomized clinical trials (RCTs) to inform clinical and policy decisions—even when trials are impeccably designed and conducted—requires the application of trial results to patients who differ from trial participants in significant ways. We propose to develop and evaluate methods for assessing the applicability of RCT results and transporting trial results to broader target populations. A stakeholder panel of patients, clinicians, methodologists, guideline developers, and representatives of federal agencies will participate in the design and conduct of this project.

Scientific Abstract:
Background;
Use of RCTs to inform clinical and policy decisions, even when trials are impeccably designed and conducted, requires the application of trial results to patients who differ from trial participants in significant ways.
Objective;
Our first aim is to develop methods for assessing the applicability of RCTs and transporting causal effects from RCTs to target populations; describe methods for assessing the robustness of inferences based on these methods. Second, to evaluate the performance of methods developed in Aim 1 in simulation studies that will reflect real-world data. Third, to empirically assess the methods developed under Aims 1 and 2 in high-impact clinical topics.
Study Design;
Our approach combines causal inference theory, computer simulation studies, and empirical analyses of trial and observational data on high-impact clinical areas. This comprehensive approach is designed to address the research gaps identified in Section A.3.
Participants;
Participants include any that meet the inclusion criterion for their respective RCT. This methods study will be compiling a database of RCTS with at least 100 participants to perform the specified methods on.
Main Outcome Measure(s);
The main outcomes measures include any primary or secondary outcomes specified in the protocol of the respective RCT, and will be extrapolated during the analysis.

Statistical Analysis;
The PS is the probability of being treated conditional on pre-treatment covariates. We will use logistic regression fit with standard
maximum likelihood methods to estimate the PS.

Brief Project Background and Statement of Project Significance:
The randomized clinical trial (RCT) is widely recognized as the preferred study design for assessing the efficacy of treatments and treatment policies. The advantages of RCTs stem from randomization (which renders the compared treatment groups “similar”), but also from the use of a priori specified criteria to select patients for participation, and the use of carefully planned followup procedures for ascertaining outcomes. In addition, randomization justifies simple, assumption-free approaches for the statistical analysis of trial data.2 However, for practical and ethical reasons, RCTs cannot be conducted in all target populations where specific interventions are considered for use.3 Moreover, stringent selection criteria and patients’ reluctance to participate in trials render RCT populations unrepresentative of those seen in clinical practice (e.g., women, ethnic/racial minorities, the elderly, and patients with multiple comorbidities are often underrepresented). Numerous systematic studies have demonstrated that most trials lack external validity and enroll patients who differ in various important characteristics compared with patients to whom trial findings are applied. Study design-based approaches for improving the external validity of RCTs include the conduct of randomized experiments in representative samples (“population-based survey experiments”) and pragmatic trials (large trials with simple inclusion criteria and treatment protocols). Survey experiments are exceedingly rare for medical interventions because of their limited feasibility in clinical care settings. Pragmatic trials, despite their strengths, do not fully address issues of generalizability because questions about the effectiveness of interventions in populations different from those enrolled in a pragmatic trial always arise (e.g., how do the results of a large simple trial conducted in Europe apply in the U.S.?) and because they are logistically challenging to conduct. Furthermore, inclusion criteria that aim to make trial samples representative of a population may not be the most efficient way for addressing certain research questions (e.g., for confirmatory studies of heterogeneity of treatment effects, HTE, it is often more efficient to sample participants in a way that maximizes the study’s statistical power to detect between-subgroup differences). In fact, it has been argued that representativeness in “designed” epidemiological studies (including RCTs) that address causal relationships should be avoided in most cases.12-14 After all, even if patients invited to participate in a trial are representative of the target population, those who consent to randomization may still be unrepresentative of the target. Thus, even when RCTs have high internal validity, “real world” decisions always have to rely on the extrapolations results to a target population. Use of RCTs to inform clinical and policy decisions, even when trials are impeccably designed and conducted, requires the application of trial results to patients who differ from trial participants in significant ways.

Specific Aims of the Project:
Our long-term objective is to optimize the translation of clinical trial results into clinical practice.
By leveraging advances in causal inference and considerable existing data resources we will achieve the following specific aims:
Aim 1: Develop methods for assessing the applicability of RCTs and transporting causal effects from RCTs to target
populations; describe methods for assessing the robustness of inferences based on these methods.
Aim 2: Evaluate the performance of methods developed in Aim 1 in simulation studies that will reflect real-world data.
Aim 3: Empirically assess the methods developed under Aims 1 and 2 in two high-impact clinical topics: (a) thrombolysis
for the treatment of acute ischemic stroke; and (b) revascularization strategies for chronic coronary artery disease (CAD).

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:
To address Aim 1 we will perform the following tasks:
(1) compile a dataset of RCTs;
(2) design observational studies corresponding to the RCTs;

(3) analyze the RCT data;
(4) analyze the observational data;
(5) compare the results of RCT and observational data analyses and synthesize findings across topics. We detail the
methods for each of these tasks below.
Task 1, Compile a dataset of RCTs: We have obtained individual patient data from 30 RCTs* in cerebrovascular and cardiovascular disease (see preliminary work, Box 1). We have collected details of the patient selection criteria through associated publications and we have been able to reconstruct the original papers' analysis plans and (numerically) reproduce their results.
We will expand our database by including non-cerebrovascular/cardiovascular trials and using a sample size cut-off of 500 enrolled patients. During the funding period we will continue to monitor our sources (NHLBI, NIDDK and Trials) to identify any new studies that meet our criteria. Furthermore, we have identified additional sources of RCT databases.
* the trials requested through the YODA Project are in addition to the 30 identified RCTS

Main Outcome Measure and how it will be categorized/defined for your study:
We will also evaluate and report the distribution of predicted risk in treated and untreated patients, in the observational and
randomized data. We will summarize predicted baseline risk using non-parametric estimates of the empirical distribution of outcome risk and descriptive statistics (mean, median, minimum, maximum, and 25th and 75th percentile). We will also compare the ratio of the outcome risk in the extreme quartiles, the median-to-mean risk ratio, and use Pearson's median skewness coefficient.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
When information on the predicted response for individuals is not reliable, our methods may still be able to provide answers for the target population and its subgroups: Some of the proposed methods do not rely on modeling response to treatment and may be useful when predictive outcome modeling is not feasible, e.g., due to the low number of events in the trial or the lack of background information on outcome predictors. These methods rely instead on the predicted probability of participating in the trial (and thus have a greater number of outcomes equal to the number of participants in the trial) and can be used to obtain population and subgroup-specific estimates of the treatment effect in the target population. Importantly, because the two approaches rely on different statistical modeling assumptions (even though the underlying structural models are the same), they can be used as stability analyses for addressing the same research question when data are available for implementing both.

Statistical Analysis Plan:
Transporting causal effects: We will transport causal effects using (1) probability of participation-based estimators (both IPPW and stratification); (2) outcome-model based estimators; (3) and doubly robust estimators, with a focus on the best performing estimators identified in simulation studies (Aim 2).
(a) Empirical evaluation of methods across trials: for groups of trials of sufficiently similar interventions, comparators, outcomes, and patient population we will use each trial as a possible "target" population. We will then apply probability of participation- and outcome model-based, and doubly robust estimators in the remaining trials to transport their effects to the target (the left-one-out trial). Importantly, this analysis allows for formal empirical evaluation because in the left-out trial we can estimate treatment effects using information on the actual exposure and outcome data, and we can compare this estimate with the "transported" estimates. This analysis is somewhat weakened by the fact that trials on the same topic area are not identical, but we believe that trials deemed similar enough to be included in the same meta-analyses are at least as similar between them, as each of them is similar to an observational study representing a target population.44,93 Results from these analyses will be interpreted qualitatively, with reference to the particular characteristics of the trials and in view of the results of our simulations.
(b) Assessment of performance using both randomized trials and observational studies: We will apply the same methods to transport the effects from each randomized study to a common target population represented by the registry data. Again, comparisons will be interpreted qualitatively, with reference to the particular characteristics of the trials and target populations, and in view of the results of the simulation studies in Aim 2. Analyses will examine (1) the average causal effect in the overall target population (in all analyses); (2) the average causal effect on the treated (when transporting results to target populations represented by observational data; this causal effect is equal with the average causal effect in the overall population when transporting results to target populations represented by an observational study as in (a) above); (3) the conditional average causal effect in subgroups of the population (in all analyses). For analyses focusing on conditional average effects, we will examine the effect in

subgroups defined by sex (male vs. female), age (above or below median in the trial), and race/ethnicity (depending on data availability; to be determined at the protocol stage of each analysis). Comparisons between subgroups will be based on formal interaction tests and estimates of relative treatment effects (comparing subgroups); results will be reported in a standardized manner. If additional exploratory analyses are undertaken they will be reported in full (for descriptive purposes).

Project Timeline:
Table 3: Project deliverables and delivery dates. Stakeholder calls are not included in this table.
Finalize list of participants
Finalized list of stakeholder partners (including those currently marked as TBN).
November 30, 2015
Develop a toolbox for assessing applicability and transporting causal effects
Formulate an overarching framework for assessing applicability and transporting causal effects from trials to populations. Develop estimators for transporting causal effects that rely on different modeling assumptions, describe methods for sensitivity analysis. Manuscripts to disseminate the framework.
October 31, 2016
Establish DUAs
Signed DUAs for all RCT and observational datasets to be used for Aim 3.
October 31, 2016
Evaluate proposed methods in simulation studies
Completed simulation studies comparing alternative methods for assessing applicability and alternative estimators for transporting causal effects from trials to target populations. Manuscripts describing the simulation studies.
October 31, 2017
Empirical analyses for trials of acute stroke – applicability
Completed analyses on the applicability of randomized clinical trials of stroke thrombolysis to the target population (OSR). Manuscript describing the analyses.
October 31, 2017

Dissemination Plan:
This study combines characteristics of studies of observational data, RCT analyses, and evidence syntheses. We will report our findings according to rigorous reporting standards, as applicable. Immediately available avenues for dissemination: Although PCORI guidelines specify that we are not expected to undertake dissemination efforts for the proposed work, we believe that our research team is well positioned
to disseminate research findings widely and across different research communities. Dahabreh is the Associate Director of the AHRQ-funded Brown Evidence-based Practice Center (EPC), one of 11 centers funded by the AHRQ to conduct rigorous systematic reviews (of both RCT and observational evidence), which are used to inform healthcare policy and clinical practice guideline development. Through his affiliation with the EPC program Dahabreh can disseminate our findings to a group of leading researchers (and other EPC investigators) engaged in the evaluation of clinical research evidence. For example, from September 2013, Dahabreh will be leading an cross-EPC workgroup aiming to develop guidance for the integration of observational and RCT evidence. Please see page 21 of ResearchPlan_Dahabreh.

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PCORI Research Plan – Improving Methods
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