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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 research methods award ME-2021C2-22365
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/03/SV_57KskaKADT3U9Aq-R_5rPSeAKyHTyqyb3.pdf
https://yoda.yale.edu/wp-content/uploads/2024/04/Guanbo-Wang-YODA-COI_April-2024-.pdf
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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

1. NCT00267969 - C0743T08 - A Phase 3, Multicenter, Randomized, Double-blind, Placebo Controlled Trial Evaluating the Efficacy and Safety of Ustekinumab (CNTO 1275) in the Treatment of Subjects With Moderate to Severe Plaque-type Psoriasis
2. NCT00543725 - TMC278-TIDP6-C215 - A Phase III, Randomized, Double-blind Trial of TMC278 25mg q.d. Versus Efavirenz 600mg q.d. in Combination With a Background Regimen Containing 2 Nucleoside/Nucleotide Reverse Transcriptase Inhibitors in Antiretroviral-naive HIV-1 Infected Subjects.
3. NCT00540449 - TMC278-TIDP6-C209 - A Phase III, Randomized, Double-blind Trial of TMC278 25 mg q.d. Versus Efavirenz 600mg q.d. in Combination With a Fixed Background Regimen Consisting of Tenofovir Disoproxil Fumarate and Emtricitabine in Antiretroviral-naive HIV-1 Infected Subjects
4. NCT00454584 - C0743T12 - A Phase 3, Multicenter, Randomized Study Comparing CNTO 1275 and Etanercept for the Treatment of Moderate to Severe Plaque Psoriasis
5. NCT02431247 - TMC114FD2HTX3001 - WK48 - A Phase 3, Randomized, Active-controlled, Double-blind Study to Evaluate Efficacy and Safety of Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (D/C/F/TAF) Once Daily Fixed Dose Combination Regimen Versus a Regimen Consisting of Darunavir/Cobicistat Fixed Dose Combination Coadministered With Emtricitabine/Tenofovir Disoproxil Fumarate Fixed Dose Combination in Antiretroviral Treatment-naive Human Immunodeficiency Virus Type 1 Infected 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. 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
9. NCT02019472 - CNTO136ARA3005 - A Multicenter, Randomized, Double-blind, Parallel Group Study of Sirukumab Monotherapy Compared With HUMIRA® Monotherapy Administered Subcutaneously, in Subjects With Active Rheumatoid Arthritis
10. NCT01604343 - CNTO136ARA3002 - A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study of CNTO 136 (Sirukumab), a Human Anti-IL-6 Monoclonal Antibody, Administered Subcutaneously, in Subjects With Active Rheumatoid Arthritis Despite DMARD Therapy
11. NCT02207231 - CNTO1959PSO3001 - Phase 3, Multicenter, Randomized, Double-blind, Placebo and Active Comparator-controlled Study Evaluating the Efficacy and Safety of Guselkumab in the Treatment of Subjects With Moderate to Severe Plaque-type Psoriasis
12. NCT03090100 - CNTO1959PSO3009 - A Phase 3, Multicenter, Randomized, Double-blind Study Evaluating the Comparative Efficacy of CNTO 1959 (Guselkumab) and Secukinumab for the Treatment of Moderate to Severe Plaque-type Psoriasis
13. NCT02207244 - CNTO1959PSO3002 - A Phase 3, Multicenter, Randomized, Double-blind, Placebo and Active Comparator-controlled Study Evaluating the Efficacy and Safety of Guselkumab for the Treatment of Subjects With Moderate to Severe Plaque-type Psoriasis With Randomized Withdrawal and Retreatment
14. NCT00091910 - CR004114 (EPO-ICU-002) - A Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of Epoetin Alfa in Critically Ill Subjects
15. - EPO-2 /// PR98-15-014 - Efficacy in the rHuEPO (Epoetin Alfa) in the Critically Ill Patient: A Randomized, Double Blind, Placebo-Controlled trial
16. NCT00036439 - C0168T37 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
17. NCT00096655 - C0168T46 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
18. 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

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

Research Proposal

Project Title

Combining clinical trials with external data: applications in the YODA database

Narrative Summary:

Clinical trials are widely considered the optimal study design to evaluate the effectiveness of treatments for any given condition of interest. In recent years, there has been growing interest in developing strategies to combine clinical trials with other sources of data (e.g., other trials or observational sources such as registries) to extend inferences in a manner that might not be otherwise be possible using a single trial alone (1-5). Among the most encouraging applications of such study designs is to compare treatments that were in fact evaluated in separate studies, which would maximize what can be learned from completed trials, and also potentially mitigate concerns surrounding the cost and time required to conduct new trials (6-9). Despite such promise, however, analyses arising from combining clinical trials may be subject to biases that may not be present when using data from a singular trial. For example, systematic differences between the demographic features of study participants of one trial, as compared to an external trial, must be handled in a principled fashion in such analyses. Here, we propose the development of a set of causal methods across a variety of study designs that may be utilized when a clinical trial data is combined with other trials, and illustrate these methods across a range of clinical trial examples sourced from YODA.

Scientific Abstract:

Background: In recent years, there has been increasing interest in combining clinical trials with external sources of data, including other clinical trials and observational sources, to conduct causal inference tasks that might benefit from pooling data derived from multiple sources. We propose developing methods in causal inference to validly estimate treatment effects from such data structures.

Study design: We consider study designs where clinical trials are combined with other trials to improve the statistical precision with which treatment effects have been estimated in the index clinical trial (e.g., incorporation of external controls). We will also develop causal methods to combine clinical trials with other trials with the purpose of comparing the effect of treatments that were evaluated in separate studies. To illustrate the proposed methods, we will draw on a wide range of clinical trials sourced from YODA, which can be combined under a set of basic data structures that can be used to estimate the effect of different treatments. For example, we will consider combining the NCT00267969 (PHOENIX I, 2008) and NCT00454584 (ACCEPT, 2010) trials conducted to evaluate the treatment of moderate to severe plaque psoriasis. Specifically, we consider a comparison of the treatments studied in PHOENIX I (ustekinumab and placebo) and the treatments studied in ACCEPT (etanercept and ustekinumab).

Participants: Participants across the applied examples will be defined by the eligibility criteria of the trials under consideration. For example, the participants in PHOENIX I and ACCEPT were individuals who were: (1) aged 18 years or older; (2) had a diagnosis of moderate to severe plaque psoriasis

diagnosed at least 6 months prior; (3) candidates for phototherapy or systemic treatment; (4) individuals with a psoriasis area-and-severity index (PASI) of 12 or greater; (5) had disease affecting 10% or more of the body surface area at their baseline.

Primary and Secondary Outcome Measure(s): The main outcome measures chosen will reflect a common outcome that was studied in the trials that are being combined. In combining the PHOENIX and ACCEPT trials, we will focus on the common primary endpoint of clinical response to treatment as defined by a ≥ 75% improvement in the 12-week PASI score.

Statistical analysis: We will apply estimators based on outcome modeling with standardization inverse probability weighting, and doubly robust methods to facilitate the treatment comparisons of interest. These estimators could be used in a joint analysis of the PHOENIX and ACCEPT trials, for instance to improve statistical precision (e.g., pooling the common ustekinumab arms across trials), or comparing treatments that did not feature in the same trial (e.g., comparing etanercept 50mg twice weekly as found in ACCEPT to the placebo arm of the PHOENIX trial).

Brief Project Background and Statement of Project Significance:

In recent years there has been growing interest in combining clinical trials with external sources of data (e.g., other trials and increasingly rich and available sources of real-world observational data) to generate causal inferences that may not be possible with trial data alone (1-9). Studies that have used combined trial data have borrowed strength from external non-trial participants to obtain more precise effect estimates (10-12). Other designs have made treatment comparisons across different studies, for example when a treatment arm from the index clinical trial is compared to a treatment arm sourced from external data (13, 14). Strategies to aggregate data in this manner have become increasingly common in evaluations of drug efficacy, and have featured in a growing number of medications receiving provisional approval by regulatory agencies such as the US Food and Drug Administration (4) and European Medicines Agency (15).

The putative advantages of combining clinical trials with external sources of data include increased study power, reduced trial enrollment requirements, possible detection of treatment efficacy or harm signals during earlier phases of drug or device evaluation, and conduct of post-marketing surveillance (7-9, 11, 12). However, designs that use such composite data structures are vulnerable to biases including confounding and selection bias, arising within and between the appended datasets. Here, we propose the development of a suite of formal causal inference methods to validly estimate average treatment effects when clinical trial data are combined with external data (e.g., other trials). We will cover a basic set of data structures that might facilitate cross-trial treatment comparisons, and derive candidate estimators such as outcome modeling with standardization (16-19), inverse probability weighting (17, 18, 20), and doubly robust methods (21) that are commonly implemented in epidemiology. To illustrate our methods, we will apply these estimators in a wide variety of clinical trials sourced from YODA. The importance of such methods is underscored by the current need by healthcare providers, regulators, and researchers to have a formal causal apparatus with which to conduct and evaluate such studies in the literature.

Specific Aims of the Project:

AIM 1: Develop novel causal methods to improve statistical precision when estimating average treatment effects combining a clinical trial with another trial that shares at least one treatment arm.

AIM 2: Develop novel causal methods to estimate average treatment effects when combining a clinical trial with external data (e.g., another trial), with the primary purpose of comparing treatments that were evaluated in separate studies.

Study Design:

Other

Study Design Explanation:

Analysis of combined trials

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

Develop or refine statistical methods

Research on clinical trial methods

Research on comparison group

Research Methods

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

In the list of YODA trials requested, we have specifically paired trials that could be used for Aims 1 and/or 2. For example, let us consider the NCT00267969 (PHOENIX I, 2008)(22) and NCT00454584 (ACCEPT, 2010)(23) trials. PHOENIX I and ACCEPT had the same eligibility criteria, including: (1) age 18 years or older; (2) individuals with a diagnosis of moderate to severe plaque psoriasis diagnosed at least 6 months prior; (3) individuals who were candidates for phototherapy or systemic treatment; (4) individuals with a psoriasis area-and-severity index (PASI) of 12 or greater; (5) individuals with disease affecting 10% or more of the body surface area at their baseline; and (6) exclusion of individuals with nonplaque psoriasis, known previous diagnosis of cancer, and recent serious infection. Thus, the study population across the PHOENIX I and ACCEPT trials would be defined precisely by their trial eligibility criteria.

In another example, let us consider the Active Ulcerative Colitis Trials I and II (NCT00036439 and NCT00096655)(24). Once again, the trials had essentially the same eligibility criteria, defined by: (1) age 18 years or older); (2) endoscopy and biopsy-proven ulcerative colitis; (3) active disease with a Mayo disease score of 6-12, constituting moderate to severe disease; (4) no history of Crohn’s disease or indeterminate colitis; and (5) no history of past use of biologic therapy. For the studies that we have applied for through YODA, we will conduct pairwise analyses of trials that were studied the same population of study participants, as determined by trial eligibility.

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

The main outcome measures chosen will reflect a common outcome that was studied in the trials that are being combined. For example, in combining the PHOENIX and ACCEPT trials, we will focus on the common primary endpoint, that is, clinical response to treatment as defined by a ≥ 75% improvement in the 12-week PASI score. In combining the ACT I and ACT II trials, we will focus on the common primary endpoint of a clinical response to treatment at 8 weeks, defined as a decrease in total Mayo disease score of ≥ 3 and at least ≥ 30% decrease from baseline. There may also be secondary outcomes of interest that are available across trials. For example, in PHOENIX and ACCEPT, one might also be interested in comparing the proportion of study participants who achieved a physician’s global assessment score of 1 or 0 (indicating either minimal or absence of disease) 12 weeks following randomization.

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

We will classify treatment strategies in each trial according to the treatments that were randomized. For instance, in the PHOENIX trial, study participants were randomized to: (1) Ustekinumab 45mg at week 0 and week 4; (2) Ustekinumab 90mg at week 0 and week 4; or (3) placebo. In the ACCEPT trial, study participants were randomized to: (1) etanercept 50mg twice weekly; (2) Ustekinumab 45mg at week 0 and week 4; or (3) Ustekinumab 90mg at week 0 and week 4. In our other example, both ACT I and ACT II randomized study participants to: (1) intravenous infliximab (5mg/kg) at weeks 0, 2, 4, 6, 14, and 22; (2) intravenous infliximab (10mg/kg) at weeks 0, 2, 4, 6, 14, and 22; or (3) placebo at weeks 0, 2, 4, 6, 14, and 22.

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

As part of the development, implementation, and evaluation of our proposed causal methods, we will require variables that might capture systematic imbalances between the populations of the two trials under consideration (e.g., age, sex, disease severity, race, use of previous treatments, and medical comorbidities). These variables can be found in Table 1 in most clinical trials.

Statistical Analysis Plan:

Across Aims 1 and 2, we will apply estimators based on outcome modeling with standardization (16-19), inverse probability weighting (17, 18), and doubly robust methods (21) to facilitate the treatment comparisons of interest. For example, when considering the PHOENIX and ACCEPT trials, one question of immediate clinical interest is the treatment comparison between initiation of a placebo (as found in the PHOENIX trial) versus initiation of etanercept 50mg twice weekly (as evaluated in the ACCEPT trial). When considering the ACT I and II trials, we could be interested in improving the statistical precision of any of the treatment comparisons in ACT I (e.g., intravenous infliximab 5mg/kg versus placebo) by incorporating placebo controls from ACT II in the analysis. In these examples, we would apply variants of the aforementioned estimators – which will require adjusting for systematic imbalances in the composition of these trials – to obtain an effect estimate for the treatment comparison. Nonparametric bootstrapping will be used to obtain 95% confidence intervals.

Software Used:

R

Project Timeline:

In the first twelve months following data acquisition, we will identify the most promising trials with the patient-level data required for our analyses (e.g., PHOENIX and ACCEPT; ACT I and ACT II). We aim to clean and harmonize the data and will endeavor to complete the preliminary analyses within 12 months. Pursuant to an extension of the 12-month data use agreement, we will continue to work on refining the causal methods and apply them to other datasets that we have applied for through YODA.

Dissemination Plan:

The results of our work will be used for the purposes of dissertation writing (by Dr. Lawson Ung), with a view to publication in the peer-reviewed literature (e.g., epidemiology and clinical journals) and research meetings. We hope to reach a broad audience comprising public health researchers, trialists, clinicians, and statisticians.

Bibliography:

1. Pocock SJ. The combination of randomized and historical controls in clinical trials. J Chronic Dis. 1976;29(3):175-88.
2. van Rosmalen J, Dejardin D, van Norden Y, Löwenberg B, Lesaffre E. Including historical data

in the analysis of clinical trials: Is it worth the effort? Stat Methods Med Res. 2018;27(10):3167-82.
3. Gray CM, Grimson F, Layton D, Pocock S, Kim J. A Framework for Methodological Choice and Evidence Assessment for Studies Using External Comparators from Real-World Data. Drug Safety. 2020;43(7):623-33.
4. US Food and Drug Administration. Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products Bethesda, Maryland: US FDA,; 2023 [Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products.
5. European Medicines Agency. Guideline on clinical trials in small populations Amsterdam, Netherlands: EMA; 2006 [Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-trials-small-populations_en.pdf.
6. Hall KT, Vase L, Tobias DK, Dashti HT, Vollert J, Kaptchuk TJ, et al. Historical Controls in Randomized Clinical Trials: Opportunities and Challenges. Clinical Pharmacology & Therapeutics. 2021;109(2):343-51.
7. Rahman R, Ventz S, McDunn J, Louv B, Reyes-Rivera I, Polley MC, et al. Leveraging external data in the design and analysis of clinical trials in neuro-oncology. Lancet Oncol. 2021;22(10):e456-e65.
8. Tan K, Bryan J, Segal B, Bellomo L, Nussbaum N, Tucker M, et al. Emulating Control Arms for Cancer Clinical Trials Using External Cohorts Created From Electronic Health Record-Derived Real-World Data. Clinical Pharmacology & Therapeutics. 2022;111(1):168-78.
9. Tan WK, Segal BD, Curtis MD, Baxi SS, Capra WB, Garrett-Mayer E, et al. Augmenting control arms with real-world data for cancer trials: Hybrid control arm methods and considerations. Contemporary Clinical Trials Communications. 2022;30:101000.
10. Dron L, Golchi S, Hsu G, Thorlund K. Minimizing control group allocation in randomized trials using dynamic borrowing of external control data – An application to second line therapy for non-small cell lung cancer. Contemp Clin Trials Commun. 2019;16:100446.
11. Thorlund K, Dron L, Park JJH, Mills EJ. Synthetic and External Controls in Clinical Trials – A Primer for Researchers. Clin Epidemiol. 2020;12:457-67.
12. Ventz S, Khozin S, Louv B, Sands J, Wen PY, Rahman R, et al. The design and evaluation of hybrid controlled trials that leverage external data and randomization. Nature Communications. 2022;13(1):5783.
13. Gökbuget N, Dombret H, Ribera JM, Fielding AK, Advani A, Bassan R, et al. International reference analysis of outcomes in adults with B-precursor Ph-negative relapsed/refractory acute lymphoblastic leukemia. Haematologica. 2016;101(12):1524-33.
14. Carrigan G, Whipple S, Capra WB, Taylor MD, Brown JS, Lu M, et al. Using Electronic Health Records to Derive Control Arms for Early Phase Single-Arm Lung Cancer Trials: Proof-of-Concept in Randomized Controlled Trials. Clin Pharmacol Ther. 2020;107(2):369-77.
15. Sharpless NE, Doroshow JH. Modernizing Clinical Trials for Patients With Cancer. JAMA. 2019;321(5):447-8.
16. Dahabreh IJ, Robertson SE, Tchetgen EJ, Stuart EA, Hernán MA. Generalizing causal inferences from individuals in randomized trials to all trial-eligible individuals. Biometrics. 2019;75(2):685-94.
17. Dahabreh IJ, Robertson SE, Steingrimsson JA, Stuart EA, Hernán MA. Extending inferences from a randomized trial to a new target population. Statistics in Medicine. 2020;39(14):1999-2014.
18. Dahabreh IJ, Haneuse SJA, Robins JM, Robertson SE, Buchanan AL, Stuart EA, et al. Study Designs for Extending Causal Inferences From a Randomized Trial to a Target Population. Am J Epidemiol. 2021;190(8):1632-42.
19. Robins J. A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect. Mathematical Modelling. 1986;7(9):1393-512.
20. Dahabreh IJ, Robertson SE, Hernán MA. On the relation between g-formula and inverse probability weighting estimators for generalizing trial results. Epidemiology. 2019;30(6):807-12.
21. Bang H, Robins JM. Doubly robust estimation in missing data and causal inference models. Biometrics. 2005;61(4):962-73.
22. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of

ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet. 2008;371(9625):1665-74.
23. Griffiths CE, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med. 2010;362(2):118-28.
24. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis. New England Journal of Medicine. 2005;353(23):2462-76.