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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?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/untitled.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. NCT00887198 - COU-AA-302 - A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Asymptomatic or Mildly Symptomatic Patients With Metastatic Castration-Resistant Prostate Cancer
3. NCT00924469 - COU-AA-201-DFCI - A Phase 2 Open-Label, Randomized, Multi-center Study of Neoadjuvant Abiraterone Acetate (CB7630) Plus Leuprolide Acetate and Prednisone Versus Leuprolide Acetate Alone in Men With Localized High Risk Prostate Cancer
4. NCT01088529 - COU-AA-203 - A Randomized, Open-Label, Neoadjuvant Prostate Cancer Trial of Abiraterone Acetate Plus LHRHa Versus LHRHa Alone
5. NCT01424930 - 212082PCR2008 - An Open-Label Study to Determine the Short-Term Safety of Continuous Dosing of Abiraterone Acetate and Prednisone in Modified Fasting and Fed States to Subjects With Metastatic Castration-Resistant Prostate Cancer
6. NCT01314118 - 212082PCR2005 - A Multicenter, Open-label, Single-arm, Phase 2 Study of Abiraterone Acetate Plus Prednisone in Subjects With Advanced Prostate Cancer Without Radiographic Evidence of Metastatic Disease
7. NCT01695135 - ABI-PRO-3001 - A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (JNJ-212082) Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy
8. NCT02236637 - 212082PCR4001 - A Prospective Registry of Patients With a Confirmed Diagnosis of Adenocarcinoma of the Prostate Presenting With Metastatic Castrate-Resistant Prostate Cancer
9. NCT00473512 - COU-AA-001 - A Phase I/II Open Label Study of the 17?-Hydroxylase/ C17,20 Lyase Inhibitor, Abiraterone Acetate in Patients With Prostate Cancer Who Have Failed Hormone Therapy
10. NCT00485303 - COU-AA-004 - A Phase II Open Label Study of CB7630 (Abiraterone Acetate) and Prednisone in Patients With Advanced Prostate Cancer Who Have Failed Androgen Deprivation and Docetaxel-Based Chemotherapy
11. NCT01685983 - 212082PCR2007 - A Phase 2 Open Label Study of Abiraterone Acetate (JNJ-212082) and Prednisolone in Patients With Advanced Prostate Cancer Who Have Failed Androgen Deprivation and Docetaxel-Based Chemotherapy.
12. NCT00474383 - COU-AA-003 - A Phase II Open Label Study of CB7630 (Abiraterone Acetate) in Patients With Advanced Prostate Cancer Who Have Failed Androgen Deprivation and Docetaxel-Based Chemotherapy
13. NCT00473746 - COU-AA-002 - Phase I/II Open Label Dose Escalation Study of the 17?-Hydroxylase/ C17,20-Lyase Inhibitor, Abiraterone Acetate in Hormone Refractory Prostate Cancer
14. NCT01795703 - JNJ-212082-JPN-202 - A Phase II Study of JNJ-212082 (Abiraterone Acetate) in Metastatic Castration-Resistant Prostate Cancer Patients Who Have Received Docetaxel-based Chemotherapy
15. NCT00544440 - COU-AA-BMA - An Observational Study of Continuous Oral Dosing of an Irreversible CYP17 Inhibitor, Abiraterone Acetate (CB7630), in Castration-Resistant Prostate Cancer Patients Evaluating Androgens and Steroid Metabolites in Bone Marrow Plasma
16. NCT01867710 - 212082PCR2023 - A Randomized Phase 2 Study Evaluating Abiraterone Acetate With Different Steroid Regimens for Preventing Symptoms Associated With Mineralocorticoid Excess in Asymptomatic, Chemotherapy-naïve and Metastatic Castration-resistant Prostate Cancer (mCRPC) Patients
17. NCT01715285 - 212082PCR3011 - A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Subjects With High-Risk, Metastatic Hormone-naive Prostate Cancer (mHNPC)

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

Research Proposal

Project Title

Design and validation of an external control arm using prior clinical trials and real-world data

Narrative Summary:

There is increasing interest in using data from outside of clinical trials to replace or support controls within trials.

However the methodological development underpinning these "external control arms" is unclear. The rationale for this project is to develop and external control arm for clinical trials of patients with prostatic cancer and test the viability of such an approach given prostatic-specific details such as endpoint variability in PFS, OS, and relevant prognostic factors.

Scientific Abstract:

Background: In recent years, there has been a growing interest in "externally controlled" trials (ECT). ECT have the potential to provide more accurate treatment effect estimates and reduce the current false positive rates .
Objective: We will discuss designs and interpretable metrics of bias and statistical efficiency of ECT and compare ECT performance to randomized and single-arm designs.
Study Design: We will specify an ECT design that leverages information from real-world data (RWD) and prior clinical trials to reduce bias associated with interstudy variations of the enrolled populations.
Participants: We will use a collection of clinical studies in prostatic cancer and RWD from patients treated with the current standard of care to evaluate ECTs. Statistical Analysis: Modeling and validation will be based on a "leave one out" scheme, with iterative selection of a single-arm from one of the studies, for which we will estimate treatment effects using the remaining studies as external control. This aims to produce interpretable and robust estimates on ECT bias and type I errors. We aim to develop a model-free approach to evaluate ECTs based on collections of clinical trials and RWD for prostatic cancer,
Main Outcome Measure(s): We aim to quantify possible inflated false positive error rates of standard single-arm trials in comparison with using external control data.

Brief Project Background and Statement of Project Significance:

Project's background: General approach to design and evaluation of the ECT: To design an ECT, estimate the sample size for a targeted power, and evaluate relevant operating characteristics, our approach is the following. First, define the patient population for the ECT. Next, identify a set of prognostic factors associated with the outcome of interested and estimated the prevalence in the study population. Finally, specify the control therapy and identify available datasets (trials and RWD) using that therapy and extract relevant outcomes and patients' characteristics.
As described below, to validate the ECT design, the control arm of each study is compared (using adjustment methods) to an external control that is defined by the remaining available data for patients that received the same control treatment. In these comparisons the treatment effect is zero by construction, which facilitates interpretability of the validation analyses and produce bias and variability summaries for ECT's treatment effect estimates, and type I error rates estimates.
If the ECT design maintains (approximately) the targeted type I error rate, determine the sample size required for ECT, single arm trial and RCT for a targeted probability of treatment discovery at a pre-defined treatment effect.
Project's significance: These project aims to provide new insights of the use of ECT designs in prostatic cancer. We aim to proof if ECT should be preferred to single-arm studies and to verify if there is a reduction of the false positive error rates when using ECT.

Specific Aims of the Project:

1. Develop an external control arm using data from prior trials and data abstracted from electronic health records from normal clinical care
2. Assess the total explained variance in OS and PFS from known prognostic factors
3. Analyze the sources of inter-trial variability in outcomes

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
Participant-level data meta-analysis
Participant-level data meta-analysis pooling data from YODA Project with other additional data sources
Develop or refine statistical methods
Research on clinical trial methods

Research Methods

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

We will include collections of clinical trials with prostatic neoplasms patients.
Patients on the control arm will be added analyzed. However we will like to access (if possible) to patients on the treatment arm to study more the demographics and differences in patient populations.
We will plan to pool data from the YODA Project with other additional real world data sources (without study identifiers), abstracted from patients undergoing treatment for newly diagnosed prostatic cancer at the Dana-Farber Cancer Institute (Boston, MA). Such data will be uploaded to the secure platform.

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

Overall Survival (time to event and censoring, or relevant dates) and Progression-free survival (time to event and censoring, or relevant dates)

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

prostate-specific antigen (PSA) or any of its derivatives

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

Age (continuous), Sex, performance status, Long interspersed element (LINE-1) methylation status, Sampling density indicates the ratio of transrectal ultrasound the prostate (TRUS)

Statistical Analysis Plan:

Terminology and Notation: The binary variable A indicates the assignment of a patient to the experimental treatment, A=1, or to the control arm, A=0, and Y denotes the outcome. We focus on binary endpoints, such as survival at 12 months from enrollment (OS12) and expand the discussion to time-to-event outcomes. The vector X indicates a set of pre-treatment patient characteristics including known or likely prognostic factors.
We evaluate whether characteristics X are sufficient to obtain unbiased treatment effect estimates or not, and use Pr?(Y=1?A=a,X) to indicate the probability of a positive response to treatment a given the pre-treatment characteristics X.
Externally Controlled Trial (ECT) design: The ECT uses the study data and external data to conduct inference on treatment effects. More specifically, we estimate -for a hypothetical randomized study- the average treatment effect by averaging the conditional outcome probabilities with respect to a distribution Pr_X (x). Possible definitions for Pr_X(x) used by existing adjustment methods are the distribution of patient characteristics X in the single arm study, Pr_SAT (x), or the distribution of X in the external (historical) control, Pr_HC (x). We considered adjustment methods, all based on the usual hypothesis of no unmeasured confounders, to estimate average treatment effects: direct standardization, matching, inverse probability weighting and marginal structural methods. These methods use different reweighting schemes to obtain estimates of TE_Ave.
Model-free evaluation of the ECT design: We will evaluate the ECT design by mimicking the comparison of an ineffective experimental arm to an external control. Hypothetical ECT experimental arms are generated from data of the Standard of care (SOC) arm of one the included studies and "rea world" datasets. For each study, we will iterate the following three steps to generate ECTs:
We randomly selected n patients (without replacement) from the SOC arm of the study and use the clinical profiles X and outcomes Y of these patients as experimental arm of the ECT. Here n is the number of enrolled patients. The SOC arms of the remaining studies are then used as the external control. We then estimated the treatment effect comparing the "experimental" arm and the external control using one of the candidate adjustment methods and test the null hypothesis of no-benefit at target type I error rate of 10%. We the repeat the steps several times with different sets of n randomly selected patients. For each study, we also conduct steps with n equal to the sample size of the SOC arm. A similar model-free evaluation allows one to evaluate the operating characteristics of ECTs in presence of positive treatment effects, by reclassifying in step (a) - randomly and with fixed probability - negative individual outcomes into positive.
We will compare the ECT against a single-arm trial and RCT designs in the setting of prostatic cancer patients and evaluate if the ECT design can provide unbiased treatment effects estimates. We used the following criteria to compare designs:

(a) bias and variability of treatment effect estimates,
(b) deviations of Type I error rates from targeted control of false positive results, and
(c) the sample size to achieve a targeted power.
Software Used:
R

Project Timeline:

Data curation: 2 months (merging data, quality checks, harmonizing data)
Exploratory data analysis: 1 month (identifying confounding variables and evaluating prognostic effects of these confounding variables)
Validation analysis: 1 month (validation and building of a synthetic control cohort and simulations to evaluate the robustness of our method)
Drafting introduction and literature review: 2 months
Writing up results: 2 months
Editing, proof reading and last changes of the manuscript: 1 month
Expected completion date: 9 months

Dissemination Plan:

We aim to obtain one methodological publication for a medical or oncology journal, such as the Journal of Clinical Oncology or Clinical Cancer Research.

Bibliography:

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