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Requires Data Access? Unknown

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?: Scientific Publication

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2023/08/COI-FORM-GR.pdf
https://yoda.yale.edu/wp-content/uploads/2023/04/coi-form-HL.pdf
https://yoda.yale.edu/wp-content/uploads/2018/09/sv_6m4tghhxg7w7uxe-r_1er9tru33pc2n8t.pdf
https://yoda.yale.edu/wp-content/uploads/2014/10/coi_form_im.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. 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
4. NCT02236637 - 212082PCR4001 - A Prospective Registry of Patients With a Confirmed Diagnosis of Adenocarcinoma of the Prostate Presenting With Metastatic Castrate-Resistant Prostate Cancer
5. 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
6. 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.
7. 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
8. 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
9. NCT01591122 - ABI-PRO-3002 - A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (JNJ-212082) Plus Prednisone in Asymptomatic or Mildly Symptomatic Patients With Metastatic Castration-Resistant Prostate Cancer
10. NCT02257736 - 56021927PCR3001 - A Phase 3 Randomized, Placebo-controlled Double-blind Study of JNJ-56021927 in Combination With Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone in Subjects With Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer (mCRPC)

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

Research Proposal

Project Title

Evaluation of G-computation and conformal prediction to provide early signs of efficacy in single arm trial with time to event outcomes

Narrative Summary:

Phase II trials are often conducted using a single arm without comparative treatment and suffer from short follow-up times. Endpoints often reported in this context are the response measured using RECIST criteria based on the variation in the Sum of Longest Diameters (SLD) of the target lesions and the Prostate Specific Antigen (PSA) response in prostate cancer.

This study proposes to evaluate the use of conformal prediction to estimate for each patient the range of plausible variation in SLD and PSA level values that would have been observed under SoC, providing a point of comparison. Additionally, the use of G-computation will be explored based on the variation in SLD/PSA level.

Scientific Abstract:

Background : Phase II oncology trials are often single arm without comparative treatment and suffer from short follow-up times. An endpoint often reported and more suitable with short follow-up times is the response measured using RECIST criteria based on the variation in the Sum of Longest Diameters (SLD) of the target lesions at a given time. External control arm efficacy analysis based on this endpoint could be better powered and inform the decision to move to the next phase. Additionally, [Loiseau2022] suggests that G-computation increases statistical power compared to propensity based methodologies while controlling for type I error. Relying on G-computation to estimate treatment efficacy using change in SLD as endpoint could therefore be more informative in early phases.
Conformal prediction emerged as a framework that allows for the construction of prediction intervals with guaranteed error bounds for a given outcome variable. Conformal prediction provides a measure of uncertainty around the predictions. In a setting of a phase II trial, conformal prediction could be used to predict for each patient what would have been the range of plausible change in SLD values whether he received comparative treatment. This could provide a point of comparison for each patient and potentially drive inclusion criteria of a phase III.
Objective :
- Evaluate G-computation directly applied to the largest reduction of the SLD and compare it with propensity score based estimators.
- Study the use of Conformal prediction to provide a point of comparison for each patient included in the single arm trial.
Study Design : A pool of clinical trials that share a common treatment (Abiraterone acetate + prednisolone) will be used in this study. The outcomes of interest to compute the treatment effect will be the change in SLD and the PSA level.
To evaluate the relevance of relying on conformal prediction the following approach will be used. Given one trial A, we will consider all the patients under Abiraterone acetate + prednisolone in the pool of trials PA, excluding the one considered, and restrict to the set of patients that share inclusion/exclusion criteria. All the patients in PA will be used to derive a model to predict the change in SLD. Conformal prediction will then be used to produce intervals for the predictions that are guaranteed to contain the ground truth with 95% probability. The model will then be applied on the Abiraterone acetate + prednisolone arm of the trial A to assess that the coverage of the methodology is as expected.
To evaluate the relevance of external control arm methodologies applied on SLD/PSA changes, and more particularly G-computation, we will rely on internal replication study [Loiseau2022].
Participants : Individual data from all the trials specified.
Primary and Secondary Outcome Measure(s): Change from baseline in SLD and in PSA level.
Statistical Analysis: To assess the relevance of conformal prediction, we will compute the coverage (how many time the observed change in SLD/PSA falls into the predicted range of plausible values), the MSE, MAE and the width of the confidence interval.
To compare the different estimators of treatment effect on the change in SLD/PSA, we will compute the MSE, the MAE and the confidence interval width. We will also assess the ability of the methodology to reproduce the results of the original trial on hard endpoints.

Brief Project Background and Statement of Project Significance:

There is a growing interest in complementing a single arm with historical data. This is particularly true for Phase II trials conducted in oncology which often rely on a single arm testing the active treatment and lack of comparator. A white paper written by Medidata and FDA scientists was presented in a Friends of Cancer Research meeting in December 2018 and demonstrates the interest of both regulators and private companies in this question.

Our work proposes to address one of the main limitations of this kind of methodology, the small number of events observed (progressions and deaths) in the single arm trials by providing analysis on an intermediate outcome (PSA/SLD change from baseline) and assess the relevance of this approach and could extend its use.
Additionally, we propose a more personalized approach to the external control arm by providing for each patient a range of plausible values under SoC relying on conformal prediction. This could open help selection of patients likely to maximize the benefit at an early stage.
Additionally, data is often spread and due to RGPD in Europe, pooling single arm trial data and real word data can be impossible. Therefore we evaluate the impact of relying on federated learning to deal with this limitation.

Specific Aims of the Project:

The objective of the project is to assess the relevance of the conformal prediction framework to provide an individual estimate of the counterfactual outcome, i.e. what would have been the range of plausible change in PSA/SLD values whether the patients received the SoC treatment instead of the treatment under assessment. Additionally, we will assess the ability of G-computation in an ECA setting applied to change in PSA/SLD values to perform an estimation of efficacy in agreement with the estimate of the randomized trial on the hard endpoint.

Study Design:

Methodological research

Research Methods

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

Given one trial A, we will consider all the patients under Abiraterone acetate + prednisolone in the pool of clinical trials PA, excluding the one considered, and restrict to the set of patients that share similar background therapy and inclusion/exclusion criteria in order to comply with the positivity assumption required for causal inference.

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

The study will focus on treatment effects on the change from baseline in SLD and change from baseline in PSA level.

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

All the characteristics available at baseline will be considered for model training and validation.

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

na

Statistical Analysis Plan:

A pool of clinical trials that share a common treatment (Abiraterone acetate + prednisolone) will be used in this study. The outcomes of interest to compute the treatment effect will be the change in SLD and the PSA level.
To evaluate the relevance of relying on conformal prediction to estimate the range of plausible change in SLD and PSA level, the following approach will be used.

Given one trial A, we will consider all the patients under Abiraterone acetate + prednisolone in the pool of clinical trials PA, excluding the one considered, and restrict to the set of patients that share similar background therapy and inclusion/exclusion criteria in order to comply with the positivity assumption required for causal inference. All the patients in PA will be used to derive a model to predict the change in SLD (or in PSA level) from baseline. Conformal prediction will then be used to produce intervals for the predictions that are guaranteed to contain the ground truth with 95% probability. The model will then be applied on the Abiraterone acetate + prednisolone arm of the trial A to assess that the coverage of the methodology is as expected. On top of the coverage, we will also assess the MSE (mean squared difference between predicted and observed changes in SLD or PSA), MAE and the width of the confidence interval. Finally, we will apply the model to the other arm of the trial A and assess the number of times the predicted plausible SLD/PSA changes under Abiraterone acetate + prednisolone overlap with the observed outcome under the other treatment. We expect to observe a clear separation when the trial is successful.
To evaluate the relevance of external control arm methodologies applied on SLD/PSA changes, and more particularly G-computation, the following approach will be used. Given one trial A, we will consider all the patients under Abiraterone acetate + prednisolone in the pool of clinical trial PA, excluding the one considered, and restrict to the set of patients that share similar background therapy and inclusion/exclusion criteria in order to comply with the positivity assumption required for causal inference. We will then perform the following experience:
Experiment 1: Assessing a treatment effect of zero between the Abiraterone acetate + prednisolone arm of A and the patients under Abiraterone acetate + prednisolone in PA;
Experiment 2: If A contains a comparator arm, we compare this comparator arm with patients under Abiraterone acetate + prednisolone in PA. The confidence intervals obtained using G-computation on difference SLD/PSA changes are then compared to the confidence interval originally obtained using OLS and the two arms of the trials. Additionally the ability to recover the results on OS using the conclusion from the G-computation analysis.
To assess the relevance of the analysis relying on conformal prediction, we will compute the coverage (how many time the observed change in SLD/PSA falls into the predicted range of plausible values), we will also assess the MSE (mean squared difference between predicted and observed changes in SLD or PSA), MAE and the width of the confidence interval.
To compare the different estimators of treatment effect on the change from baseline in SLD and change from baseline in PSA level and assess the potential added value of G-computation, we will compute the MSE, the MAE and the confidence interval width. Additionally, when replacing the Abiraterone acetate + prednisolone arm of one trial by the set of patients that share similar background therapy and inclusion/exclusion criteria in other trials, we will assess the ability of the methodology to reproduce the results of the original trial on the hard endpoints (OS/PFS) using the regulatory agreement. The regulatory agreement is the percentage of time the cutoff $P-value

Project Timeline:

Project start date: May 1, 2023 or when data accessed
Analysis completion: December 1, 2023
Manuscript draft completion: May 1, 2023

Dissemination Plan:

We plan on submitting this research as a research article in one of the following journals: 'Statistics in Medicine? or ?Statistical Methods in Medical Research? or ?BMS methodological research?.

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