the YODA PROJECT | Forging a unified scientific community

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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: European Medicines Agency
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_-_gr.docx_0.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_-_nb.docx_0.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_-_hs.docx_0.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_ed_001.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

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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. 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

A statistical methodology study to evaluate External Comparator Arm study results versus Randomized Controlled Trials in cancer drug development

Narrative Summary:

The European Medicines Agency (EMA) contracted IQVIA to advance the knowledge around using single-arm trials (SATs) with external comparators for cancer drug development. Based on simulation studies using data from randomized controlled trials (RCTs) and real world data, the project will develop recommendations on how to incorporate external comparators in the analysis in the best way. This is important because single-arm trials have an increasing role in cancer drug development for (subtypes of) cancers that are rare or have a high unmet medical need.

Scientific Abstract:

Background: The Gold Standard design for drug approval studies is the RCT. However, there are cases where RCTs are either unethical or unfeasible. In these circumstances SATs might be conducted and submitted to regulatory authorities for drug approval. Since SATs lack results for control patients, information from external data sources can be compiled and utilized to provide context for better interpretability of study results.
Objective: In this project, we seek to evaluate current statistical methodologies in the specific context of external comparator arm (ECA) studies to provide evidence-based methodological recommendations. Ultimately, this will also lead to recommendations on when ECA studies would provide sufficient scientific evidence to support regulatory decision-making.
Study Design: The experimental arm of the RCT is taken as a hypothetical SAT. The requested 4 prostate cancer RCTs are carefully selected using multiple criteria, e.g. significant overall survival benefit, availability of endpoints, and sufficient sample size. External data collected in the real world for patients with the same indication will be organized in parallel to serve as an ECA. This set-up enables a comparison of RCT treatment effect estimates versus RW treatment effects estimates.
Participants: Prostate cancer patients in selected RCTs and external real-world data collected in parallel.
Main Outcome Measure: Overall survival.
Statistical Analysis: Different analytical methods (e.g. propensity score methods) will be used to assess best approaches to estimate treatment effects.

Brief Project Background and Statement of Project Significance:

Oncology drug development has evolved in the past 10 years with an increased focus on personalized therapies, sometimes sub-setting a larger oncology indication into a grouping of essentially rare diseases, created by biomarkers or genetic testing. There has also been an active movement in the development of treatments for advanced and specialty cancers. Competition for oncology patients in the research setting has become a barrier to

traditional study enrolment and traditional study design. Cancer clinical trials design and methodology has had no choice but to change to meet the progress in clinical sciences and the unmet medical need. One of these evolutions has been the growth of use and acceptance of external comparators in this active research space.

A number of new clinical trial designs have been introduced in oncology based on clinical scientific insights (e.g. biomarkers) and there has been interest in exploring ways to augment clinical trial data with existing data from other clinical trials or RW databases. One specific use of such data is to contextualise results of clinical trials by providing external data. This is considered particularly useful in the case of trial designs without a parallel randomised control group, such as single-arm trials, with the generated evidence being used as pivotal evidence of efficacy in the context of a marketing authorisation application. A number of analysis methods have been proposed to address some of the shortcomings of using external comparators in clinical trials for comparison of efficacy in a specific indication, including methods that require individual data, see the given references. These analysis methods aim to incorporate external comparators in the analysis with minimum bias.

Eichler et al. in a paper from 2016 presented a framework for situations in which RCTs are not feasible to establish the treatment effect in a proposed indication. Simulations studies, including different sensitivity analyses, were put forward as a way to further define available methodologies that can provide insight in different sources of bias. For these simulation studies, validation would consist of use of conventional RCTs to concurrently analyse results as single-arm trials with historical comparators and then compare results from the randomized and nonrandomized analyses. These validation exercises would provide insight in where new methodologies are adequate and where not. Over the recent years as a result of efforts to increase transparency, access to data from completed clinical trials has increased and this makes it feasible to start working on these type of simulation studies.

To facilitate regulatory decision making this study aims to explore the impact of using external comparator data by means of a simulation study. Results of this simulation study will contribute to developing recommendations regarding methodologies to be applied and characteristics of situations where data from a single arm study with historical controls can form a basis for drug approval.

Specific Aims of the Project:

The general objective of this research project is to assess various statistical approaches in the specific context of ECA studies and to provide evidence-based recommendations when analysing ECA studies.
Objectives
1. To simulate SATs on the basis of completed randomised-controlled clinical trials, and to compare External Comparator Arm study results with the concurrent control results from the randomised controlled trials.
2. To assess the impact of non-randomised trials in a clinical development program. It is of interest to know how repeated single-arm trials (with a potential external comparator arm) would perform as compared to Randomised Controlled Trials with respect to bias, precision, variability of the treatment effect estimation, sample size and the probability to come to false positive conclusions.
3. To develop recommendations about methods and situations when it may be informative or not to use ECA RW data in various situations of data availability and the natural history of the disease.

What is the purpose of the analysis being proposed? Please select all that apply.
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:

All patients from the full analysis set from the selected RCTs will be used, therefore following the inclusion/exclusion criteria from the individual study protocols. The same inclusion/exclusion criteria are intended to be used (as available) to select external comparators from RW data sources.

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

Overall Survival, defined as time from randomization until death from any cause. Survival time of living patients will be censored on the last date a patient is known to be alive or lost to follow-up.

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

The main predictor is the treatment received. Other important baseline covariates will be included in statistical models to adjust for selection bias.

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

Other endpoints to be analysed may include overall response, duration of response, time to next treatment, progression free survival.
Demographic and other baseline covariates will be used for model building (e.g. propensity score modelling).

Statistical Analysis Plan:

A study protocol detailing the key methodological and operational aspects of the study, such as clinical trial selection, RW data source selection, needed sample size for a priori defined hypotheses, analysis methods, study timelines, analysis plan, study conduct is being created and will be further detailed when access to selected clinical trial data is confirmed. IQVIA will ensure that the study protocol complies with local Acts and Regulations within each country of the participating data partners. This includes obtaining ethics committee approval as appropriate and where necessary.
Specifically, the used RCT and RW data will be outlined, including how to develop recommendations for future ECA studies:
·Develop recommendations for statistical approaches: Assess operating characteristics (performance measures) of approaches: type I error, power (type II error), bias, mean-squared error, coverage of confidence intervals
·Develop design recommendations
·Develop recommendations for the level of sensitivity analysis to ensure robust conclusions
·Develop recommendations for regulatory requirements
The data from the RCT will be re-analysed following the analysis specified in the protocol. That is, distribution of time-to-event variables will be estimated using the Kaplan-Meier product limit method. Median event times with two-sided 95% confidence intervals will be estimated, together with event rate estimates, e.g. at 6 and 12 months. The Cox proportional hazards model or similar methodology will be used for the estimation of treatment effects and the associated 95% confidence interval.
The data from the treatment arm of the RCT will be used as if it was a single-arm trial where it will be analysed together with the External Comparator Arm. Analytical methods like propensity score (PS) methods will be used to compare different approaches to estimate the treatment effect.
Substantial additional sensitivity analyses will be performed, including applications of different estimands, different handling of missing values, subgroup analyses (e.g. by country, line of therapy, severity of disease, sex, age group) and sensitivity analyses for unmeasured confounding.
The RCT data will also be used as a basis to simulate artificial data that follows realistic assumptions. The simulated data will then be intentionally modified to measure the effect of different situations on the bias of the estimated treatment effect.
Descriptive analyses of the simulation results will be undertaken to assess the performance of the methods. Further analyses will investigate the distribution of the point estimates of the effect size across the repetitions of the simulation study in addition to the estimated bias to assist in spotting outliers and methods that, while being unbiased, have undesirable properties. Monte Carlo standard errors will be reported for all estimates to quantify the simulation uncertainties and visualizations of the simulation performance results will display 95% CIs. By presenting estimates of uncertainty, the presentation of results will acknowledge that the simulations are themselves an empirical experiment and therefore the performance measures (e.g. bias, mean squared error) are themselves estimated and subject to error. Careful consideration will be given to the number of repetitions needed in each simulation study for minimizing simulation errors.
Since contracting with RW database owners is currently work in progress, only data access on the YODA platform (but not outside YODA) is requested at the moment, deviating from the original request. When having finalized contracting with database owners, there might be the necessity to request data access outside of YODA, but it is hoped that the contracts to be developed will allow shifting RW data to YODA servers. If it will not be possible to shift the RW data to YODA servers, it might be asked at a later time point to move the RCT data to IQVIA's high-security servers
Software Used:
I am not analyzing participant-level data / plan to use another secure data sharing platform
Project Timeline:

• Preliminary Study Protocol/Outline: Apr 2021

• Study Start-up (incl. ethics approval, RW data owner contracting): Apr – Jun 2021
• Study Protocol: Apr – May 2021
• Data Collection / Preparation: Jun – Aug 2021
• Start of Data Analyses: Aug – Oct 2021
• Study Report: Oct – Nov 2021
• Manuscript: Nov – Dec 2021

Dissemination Plan:

Upon completion of the study, IQVIA will create a detailed study report including a description of the used methods, the generated results and their interpretation according to the agreed statistical analysis plan. Further, recommendations as per Section 7 will be derived. The final study report will serve as a basis for the main publication of the study.
IQVIA will draft one or more manuscripts ready to be submitted for publication in cooperation with the EMA.

Bibliography:

General references to External Comparator Arm studies (not specifically referenced in text).
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Supplementary Material:

https://yoda.yale.edu/sites/default/files/ema_letter_of_recommendations_0.pdf
https://yoda.yale.edu/sites/default/files/yoda_-_secure_server_for_analysis_2021-4649.docx