Principal Investigator

First Name: Yang
Last Name: Li
Degree: Ph.D. in Statistics
Primary Affiliation: School of Statistics, Renmin University of China
E-mail: yang.li@ruc.edu.cn
State or Province: Beijing
Country: China

General Information

Key Personnel (other than PI):
First Name: Hao
Last name: Mei
Degree: Ph.D. in Biostatistics
Primary Affiliation: School of Statistics, Renmin University of China
SCOPUS ID:
Requires Data Access? No

First Name: Hang
Last name: Yang
Degree: Master of Medicine(Epidemiological and health statistics)
Primary Affiliation: School of Statistics, Renmin University of China
SCOPUS ID:
Requires Data Access? Yes

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/2024/12/YangLi.pdf
https://yoda.yale.edu/wp-content/uploads/2024/12/HaoMei.pdf
https://yoda.yale.edu/wp-content/uploads/2024/12/HangYang.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. 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)
2. NCT02236637 - 212082PCR4001 - A Prospective Registry of Patients With a Confirmed Diagnosis of Adenocarcinoma of the Prostate Presenting With Metastatic Castrate-Resistant

Prostate Cancer

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

Research Proposal

Project Title

Response-adaptive design leveraging real-world data with interval-censored survival outcome

Narrative Summary:

Incorporating real-world data (RWD) into clinical trials can effectively reduce sample size, costs, and duration of the trial. Furthermore, to assign more patients to better treatment groups and address the common issue of interval-censored outcomes in oncology trials, such as Progression-Free Survival (PFS), we are introducing a novel Response adaptive randomization (RAR) method for interval-censored survival outcomes. This method dynamically borrows information from participants receiving the same standard treatment in RWD as those in the control group of the trial, and allows for the simultaneous accumulation of both RWD and trial data.

Scientific Abstract:

1. Background
Response-adaptive randomization (RAR) is a dynamic method that adjusts the allocation probabilities of subjects, assigning more participants to better treatments based on accumulating data. Constructing RAR that can borrow real-world data (RWD) from patients receiving standard care can effectively mitigate the power loss caused by allocation imbalances, while reducing sample size, trial costs, and duration.
2. Objective
To propose a new RAR design leveraging real-world data with interval-censored survival outcome
3. Study Design
A RAR design leveraging real-world data with interval-censored survival outcome
4. Participants
Men with metastatic castration-resistant prostate cancer.
5. Primary/Secondary Outcome Measure(s)
Radiographic Progression-free Survival and overall survival.
6. Statistical Analysis
We will use the trial data (NCT02257736) and RWD (NCT02236637) as real data analysis part of our methods, to evaluate our method's performance. Using the trial data, we will estimate the treatment and covariate effects by applying a method for interval-censored data. The estimated model we obtain will be used to simulate potential outcomes, which will then be used in the real-data analysis. As patients are enrolled in the trial, we will employ the proposed RAR procedure to update the allocation probabilities.
Finally, we will evaluate the performance of the proposed method from several perspectives, including the allocation proportion of patients across treatment and control groups, the bias and the mean squared error of the efficacy estimator.

Brief Project Background and Statement of Project Significance:

Response adaptive randomization (RAR) is a dynamic method that sequentially adjusts the allocation probabilities of subjects, assigning more participants to better treatment based on accumulating data. Therefore, RAR is more ethical than fixed designs, such as completely randomized design.

However, similar to fixed designs, RAR requires substantial time, money, and participants. Additionally, the imbalance in patient allocation between the experimental and control groups in RAR may lead to a loss of statistical power. However, real-world data (RWD) are abundant, and incorporating RWD into the control arm can address many of the concerns inherent in RAR. Proper borrowing of RWD can accelerate the convergence of the sample fraction toward the targeted allocation proportion in RAR, enhancing patient benefit. It can also reduce the overall sample size while maintaining statistical power, leading to lower trial costs. In cases where the control group shows higher treatment effect than the experimental group, RWD can also facilitate early stopping of the trial, thus reducing trial duration (Wei et al. 2024).

Our first contribution lies in the use of real-world data (RWD) in Randomized Adaptive Randomization (RAR) trials for time-to-event outcomes. Currently, the majority of RWD borrowing is based on fixed designs, where the information from RWD does not influence the trial design, but instead supplements the trial data after completion. However, utilizing RWD at the beginning of the trial is meaningful, especially in adaptive designs. Regarding RAR, to our knowledge, only Kim et al. (2018) have discussed borrowing historical control data. Kim et al. (2018) focused on binary outcomes, yet many clinical trials involve time-to-event outcomes.

Second, our project explores the application of adaptive treatment allocation and leveraging RWD for interval-censored survival data. RAR has been successfully implemented in oncology trials, such as the BATTLE trials (Kim et al., 2011) and the I-SPY 2 trial (Barker et al., 2009). In oncology trials, many outcomes commonly encountered, such as Progression-Free Survival (PFS), are interval-censored because the event typically occurs between two follow-up visits. However, RAR procedures have been developed for time-to-event outcomes with right censoring (Mukherjee et al, 2023; Su and Cheung, 2018) but not for data with interval censoring. Therefore, developing an RAR methodology for survival data with interval censoring is meaningful

Third, our paper will focus on the practical issue of information borrowing from RWD and trial data as they accumulate simultaneously. Over the course of a long-term trial, patient data from RWD may be accumulating, allowing us to continually update and incorporate new RWD data into the ongoing study. However, most existing studies primarily discuss offline information borrowing, rather than online borrowing based on accumulating data.

Specific Aims of the Project:

The project will introduce a response-adaptive randomization (RAR) method that leverages real-world data with interval-censored survival outcomes. This approach includes handling interval censoring in both accumulated RWD and trial data for survival outcomes, dynamic borrowing of information from RWD, and updating the allocation probabilities.

Study Design:

Methodological research

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:

NCT02257736 (the trial data), and NCT02236637 (the real-world data) are requested. The trial data will be used in its entirety, while only the real-world data from participants treated with Abiraterone

acetate plus prednisone or prednisolone will be included.
There are no exclusion criteria defined.

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

The primary outcome measure will be Radiographic Progression-Free Survival (rPFS), with the definition consistent with that used in the clinical trial (NCT02257736).

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

The main predictor is the treatment that patients received.
Experimental Group: apalutamide (240 mg once daily) and abiraterone acetate (1000 mg once daily) plus prednisone (5 mg twice daily)
Placebo Comparator: placebo and abiraterone acetate plus prednisone in clinical trial (NCT02257736), or abiraterone acetate plus prednisone in RWD (NCT02236637).

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

ECOG performance status (0-5), Gleason score
Continuous covariates: Age, PSA level, Alkaline phosphatase, LDH (and ULN for LDH), Hemoglobin.
Categorical covariates: Ethnicity, Race, Geographic region (North America, Europe, and Rest of world), Metastasis stage at diagnosis (M0, M1, all others), presence of metastases (number and/or location), Opiate use (yes vs. no), Previous prostate cancer therapy.

Statistical Analysis Plan:

We use the clinical study data (NCT02257736) as part of the real-world data analysis to evaluate the performance of our method. As a novel clinical design approach, we are unable to recruit a large number of volunteers for a clinical study to directly assess the performance of our design. Therefore, we rely on clinical study data to complete the real-world data analysis component.
The real-world data analysis requires a two-arm randomized controlled trial (RCT) and real-world data (RWD) from participants receiving the same treatment as the RCT control group. Using trial data, we will estimate the treatment and covariate effects by applying method for interval-censored data. The estimated model we obtain will be used to simulate potential outcomes, which will then be used in the real-data analysis. We do not need to apply the same procedure to the RWD, as our method does not require participants in the RWD to have received the experimental drug.
Before implementing the RAR stage of the trial, equal randomization will be implemented for a certain period to mitigate instability of the estimators at the beginning of a trial due to sparse information. Once the RAR stage begins, we will apply the proposed method after each patient is enrolled, with the following steps:
1. Balance the distribution of important covariates between the RWD and trial data through nearest neighbor matching.
2. Implement dynamic borrowing of information from the RWD in the RAR process using commensurate priors, while handling interval censoring using the method proposed by Lin et al. (2015).
3. Update the allocation probabilities for patients using doubly adaptive biased coin design.
The RAR stage will end once all patients in the trial data have been allocated. Finally, we will assess the performance of the proposed method from several perspectives, including the allocation proportion of patients across the treatment and control groups, the bias and the mean squared error of the efficacy estimator.

Software Used:

RStudio

Project Timeline:

The project has already begun. Manuscript writing aside from the real-data component will be completed by October 2025, and real-data analysis as well as the finalization of the manuscript will be completed by December 2025. the manuscript will be submitted for publication by December 2025.

Dissemination Plan:

Project results will be disseminated via a journal of Statistics or Biostatistics or Medical Statistics, like Statistics in Medicine.

Bibliography:

Wei W, Zhang Y, Roychoudhury S, et al. Propensity score weighted multi-source exchangeability models for incorporating external control data in randomized clinical trials[J]. Statistics in Medicine, 2024, 43(20): 3815-3829.

Lin X, Cai B, Wang L, et al. A Bayesian proportional hazards model for general interval-censored data[J]. Lifetime data analysis, 2015, 21: 470-490.

Kim E S, Herbst R S, Wistuba I I, et al. The BATTLE trial: personalizing therapy for lung cancer[J]. Cancer discovery, 2011, 1(1): 44-53

Mukherjee A, Coad D S, Jana S. Covariate-adjusted response-adaptive designs for censored survival responses[J]. Journal of Statistical Planning and Inference, 2023, 225: 219-242.

Su P F, Cheung S H. Response-adaptive treatment allocation for survival trials with clustered right-censored data[J]. Statistics in Medicine, 2018, 37(16): 2427-2439.

Barker A D, Sigman C C, Kelloff G J, et al. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy[J]. Clinical Pharmacology & Therapeutics, 2009, 86(1): 97-100.

Robertson D S, Lee K M, López-Kolkovska B C, et al. Response-adaptive randomization in clinical trials: from myths to practical considerations[J]. Statistical science, 2023, 38(2): 185-208.

Kim M O, Harun N, Liu C, et al. Bayesian selective response-adaptive design using the historical control[J]. Statistics in medicine, 2018, 37(26): 3709-3722.

Pan W. A multiple imputation approach to Cox regression with interval-censored data[J]. Biometrics, 2000, 56(1): 199-203.