Principal Investigator

First Name: Lysbeth (Libby)
Last Name: Floden
Degree: PhD, MPH
Primary Affiliation: Clinical Outcomes Solutions
E-mail: libby.floden@clinoutsolutions.com
Phone number: 520-360-3962
Address:

City: Chicago
State or Province: IL
Zip or Postal Code: 60604
Country: USA
SCOPUS ID: 36096708100

General Information

Key Personnel (in addition to PI):

First Name: Jessica
Last name: Roydhouse
Degree: PhD
Primary Affiliation: Menzies Institute for Medical Research
SCOPUS ID: 25724591400

First Name: Jennifer
Last name: Beaumont
Degree: MS
Primary Affiliation: Clinical Outcomes Solutions
SCOPUS ID: 7102153197

First Name: Stacie
Last name: Hudgens
Degree: MS
Primary Affiliation: Clinical Outcomes Solutions
SCOPUS ID: 6603830659

First Name: Michael
Last name: DeRosa
Degree: MA
Primary Affiliation: Clinical Outcomes Solutions

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/floden_coi.pdf
https://yoda.yale.edu/system/files/coi_hudgens.pdf
https://yoda.yale.edu/system/files/yoda_coi_beaumont.pdf
https://yoda.yale.edu/system/files/yoda_coi_tte_jr.pdf
https://yoda.yale.edu/system/files/yale_yoda_mderosa.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)

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

Research Proposal

Project Title

Analytical Approaches of Time to Event of Patient-reported Outcomes: A Case Study in Patients with Metastatic Castration-resistant Prostate Cancer

Narrative Summary:

Summarizing cancer trials with time-to-event results is a helpful tool for understanding the treatment benefit. In addition to understanding, say, the median survival time on treatment A versus treatment B, patients may also be interested in knowing the median time until disease symptoms get worse on each treatment. While this information may be useful for making treatment decisions, there are challenges on how to best conduct the statistical analysis. This paper explores the impact on the results when variations of the worsening event are used and when different (censoring) rules are used.

Scientific Abstract:

Background: In oncology trials, patient-reported outcomes (PROs) including health-related quality of life (HRQoL), specifically symptom burden and functional status, can enhance the interpretation of progression-free survival estimates. Recent regulatory guidance on the incorporation of symptoms, function and tolerability in anti-cancer clinical trials elevates the patient experience in the endpoint strategy but recent work has highlighted the challenges with applying time-to-deterioration endpoints to PRO data. (Fiero 2022) Patient-focused time-to-event endpoints align directly to survival endpoints, which makes them easier to interpret for clinical and other stakeholders, but special consideration to the definition of events, censoring rules, handling of intercurrent events (ICEs), and estimation approach is necessary. Understanding the impact of the ICEs of treatment discontinuation or switching is critical to clearly evaluate time-to-event endpoints in oncology, as they are often related to treatment tolerability or efficacy. Endpoint definitions and other analytic decisions must also consider cancer type (e.g., metastatic) and treatment modality (e.g., chemotherapy vs immuno-therapy). Statistically, how does one best estimate a time-to-HRQoL endpoint in the presence of ICEs that alter the patient journey? Further, sensitivity analyses to assess the robustness of the primary results are recommended but can be challenging to identify. Decisions points considered include endpoint definition and handling ICEs. Basic approaches to handle ICEs, depending on the strategy, include censoring or including post-ICE assessments if collected. An alternative approach to censoring is to analytically consider those who experienced an ICE as still at risk for the event by assuming that post-ICE observations come from the distribution of people who have not experienced that ICE, i.e. multiply imputing the event under a MAR assumption. Further extensions using a pattern mixture model framework under an MNAR assumption may be appropriate sensitivity analyses.
Objective: In this work, we introduce TTE analyses of PRO endpoints and how, with a worked example, to define estimands and apply appropriate sensitivity analyses.

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }

Study Design: A post-hoc analytic demonstration comparing treatment arms under different statistical and theoretical assumptions.
Participants: Men with chemotherapy-naive metastatic castration-resistant prostate cancer.
Primary and Secondary Outcome Measures: The patient-reported outcome from Functional Assessment of Cancer Therapy – Prostate (FACT-P) Physical Well-Being Subscale item, “I am bothered by side effects of treatment”. A second outcome for demonstration will be the Brief Pain Inventory – Short Form (BPI -SF) score.
Statistical Analysis: Demographic variables and stratification factors will be described. Time to deterioration will be compared between treatment groups using Kaplan-Meier (K-M) method and described using median with 95% confidence interval. Proportional hazards regression models will be used to estimate the hazard ratio (HR), 95% confidence interval, and p-value for time to deterioration in treatment versus placebo. Models will include baseline stratification factors.

Brief Project Background and Statement of Project Significance:

Time-to-event (TTE) methods have been increasingly used to analyze HRQoL and other PRO data from clinical trials. In oncology trials, these endpoints are intended to enhance the interpretation of traditional time-to-event endpoints such as progression-free survival and overall survival and provide the patient and other stakeholders with relevant information for decision making. In conjunction with this, the estimand framework, specified in an addendum to the ICH E9 guideline E9(R1), presents a systematic approach to ensure alignment among objectives, trial execution, statistical analyses, and interpretation of results from clinical trials. Included in the addendum is the need for sensitivity analyses to assess the robustness of the primary analysis.
Ambiguity arises when applying the estimand framework to TTE analysis of PROs. These endpoints, often ordinal in structure without an inherently meaningful measurement unit, need to be categorized in accordance to the event definition (e.g., deterioration vs stable/improvement). Other factors related to clinical trial design, such as infrequent assessment scheduling, can render the event definition imprecise. Further, other relevant events along the patient journey, termed intercurrent events (ICEs) in the estimand framework, can cloud the interpretation of the results. These issues and others raise methodological questions when defining estimands and sensitivity analyses for TTE of PRO endpoints.
To date, there is no known work that has outlined the various decision points necessary or applied them to an example dataset and compared results when PROs are used in a TTE analysis in an oncology trial with ICEs.

Specific Aims of the Project:

The objective of this work is to provide context to the decision points needed to develop an estimand and related sensitivity analyses when analyzing PRO data using TTE methods, and to illustrate this with a concrete example from a trial of chemotherapy-naive metastatic castration-resistant prostate cancer (JNJ-56021927).

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:

The patient population for analysis will include all randomized participants with chemotherapy-naive metastatic castration-resistant prostate cancer (mCRPC) from study JNJ-56021927. The sample size is expected to be N = 982.

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

Main outcome measures will be: The Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index (FAPSI) and the item, “I am bothered by side effects of treatment” from the Functional Assessment of Cancer Therapy – Prostate (FACT-P) Physical Well-Being Subscale . We may also consider other outcomes such as the Brief Pain Inventory – Short Form (BPI -SF) score as appropriate for this demonstration.
Outcomes will be categorized into responder status. Since all participants are metastatic, they are likely to experience deterioration. The likely favorable treatment-related outcome is extended time to deterioration. Status will be defined using meaningful change thresholds (MCTs) according to the following:

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }

- If a change score is negative and greater in magnitude than the MCT, or death has occurred, the patient will be categorized at this cycle as “declined.”
- If a change score is positive or smaller in magnitude than the MCT, the subject will be categorized at the specified cycle as “stable/improved.”
The MCTs will be 3 points for the FAPSI, 1 point change for the item, “I am bothered by side effects of treatment”, and 2 points change for any items from the BPI-SF.

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

The predictor will be the treatment arm classification.

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

Variables of interest include demographic characteristics such as age and ethnicity. The following study stratification factors will also be included:
- Gleason score at diagnosis (?7 vs. >7),
- Geographic regions (categorized as NA/EU vs. Other Countries, or similar) and
- Prior docetaxel use (yes vs. no).
Variables that correspond to ICEs or clinical events will also be incorporated into the sensitivity analyses via modification of the censoring/event definition or analytic model:
- Treatment discontinuation
- Death
- Disease progression
- Concomitant medications
These variables will be described and may be included in the model.

Statistical Analysis Plan:

Demographic variables and stratification factors will be described using mean and standard deviation or median with interquartile and range.
Time to deterioration on the outcomes of interest will be compared between treatment groups using Kaplan-Meier (K-M) method and described using median with 95% confidence interval. Proportional hazards regression models will be used to estimate the hazard ratio (HR), 95% confidence interval, and p-value for time to deterioration in treatment versus placebo. Models will include baseline stratification factors.
In this demonstration, various event definitions and censoring rules will be applied to each outcome. Time to first deterioration will be defined as the time interval from the date of randomization to the date of the first deterioration, according to the MCT classification rules, as compared to the baseline score. Time to confirmed HRQoL deterioration will be defined as the time interval from the date of randomization to the date of the first two consecutive deterioration scores, according to the MCT classification rules, as compared to the baseline score. Time to definitive HRQoL deterioration will be defined as the time interval from the date of randomization to the date of the first deterioration, according to the MCT classification rules, as compared to the baseline score, with no further improvement (Anota 2015).
Censoring rules may include:
- time of the last available HRQoL assessment,
- disease progression,
- treatment discontinuation, and/or
- death.
All analyses will be performed with SAS version 9.4 or higher (SAS Institute, Inc., Cary NC, USA)
All tests will be two-sided and performed at the statistical significance level of 0.05.
Software Used:
R
Project Timeline:

Anticipated project start date: September 2022
Analysis completion: October 1 2022
Results reported back to the YODA project: October 15 2022
Presentation of results at the Special Interest Group Symposium at the International Society for Quality of Life Research Annual Meeting: October 19 2022

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }

Manuscript submitted to the Biopharmaceutical Statistics Special Issue for review: December 1 2022

Dissemination Plan:

The dissemination plan includes a presentation of results at an annual conference targeting researchers, pharmaceutical industry and biotechnology representatives, clinicians, and patient research partners from around the world. In addition, an abstract (without results) has been provided to the guest editors at the Journal of Biopharmaceutical Statistics for consideration of publication.
Presentation of results at the Special Interest Group Symposium at the International Society for Quality of Life Research Annual Meeting: October 19 2022
Manuscript submitted to the Biopharmaceutical Statistics Special Issue for review: December 1 2022

Bibliography:

Anota A, Hamidou Z, Paget-Bailly S, Chibaudel B, Bascoul-Mollevi C, Auquier P, Westeel V, Fiteni F, Borg C, Bonnetain F. Time to health-related quality of life score deterioration as a modality of longitudinal analysis for health-related quality of life studies in oncology: do we need RECIST for quality of life to achieve standardization? Qual Life Res. 2015 Jan;24(1):5-18.
Bell, M. L., Floden, L., Rabe, B. A., Hudgens, S., Dhillon, H. M., Bray, V. J., & Vardy, J. L. (2019). Analytical approaches and estimands to take account of missing patient-reported data in longitudinal studies. Patient related outcome measures, 10, 129
Bonnetain F, Dahan L, Maillard E, Ychou M, Mitry E, Hammel P, Legoux JL, Rougier P, Bedenne L, Seitz JF. Time until definitive quality of life score deterioration as a means of longitudinal analysis for treatment trials in patients with metastatic pancreatic adenocarcinoma. Eur J Cancer. 2010 Oct;46(15):2753-62.
Charton E, Bachet JB, Hammel P, Desramé J, Chibaudel B, Cohen R, Debourdeau P, Dauba J, Lecomte T, Seitz JF, Tournigand C, Aparicio T, Guerin-Meyer V, Taieb J, Volet J, Louvet C, Anota A, Bonnetain F. Impact on health-related quality of life deterioration-free survival of a first-line therapy combining nab-paclitaxel plus either gemcitabine or simplified leucovorin and fluorouracil for patients with metastatic pancreatic cancer: Results of the randomized phase II AFUGEM GERCOR clinical trial. Cancer Med. 2019 Sep;8(11):5079-5088.
Charton, E., Cuer, B., Cottone, F., Efficace, F., Touraine, C., Hamidou, Z., ... & Anota, A. (2020). Time to deterioration in cancer randomized clinical trials for patient-reported outcomes data: a systematic review. Quality of Life Research, 29(4), 867-878.
Coens, C., Pe, M., Dueck, A. C., Sloan, J., Basch, E., Calvert, M., ... & Bottomley, A. (2020). International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium. The Lancet Oncology, 21(2), e83-e96.
Fiero, M. H., Roydhouse, J. K., Vallejo, J., King-Kallimanis, B. L., Kluetz, P. G., & Sridhara, R. (2019). US Food and Drug Administration review of statistical analysis of patient-reported outcomes in lung cancer clinical trials approved between January, 2008, and December, 2017. The Lancet Oncology, 20(10), e582-e589.
Floden, et al. Estimand Considerations for Time-to-Event Analysis of Patient-Reported-Outcomes. ISOQOL Annual Meeting, 2021.
Hamidou, Z., Dabakuyo, T. S., Mercier, M., Fraisse, J., Causeret, S., Tixier, H., et al. (2011). Time to deterioration in quality of life score as a modality of longitudinal analysis in patients with breast cancer. Oncologist, 16(10), 1458–1468.
Lawrance, R., Degtyarev, E., Griffiths, P., Trask, P., Lau, H., D'Alessio, D., ... & Rufibach, K. (2020). What is an estimand & how does it relate to quantifying the effect of treatment on patient-reported quality of life outcomes in clinical trials? Journal of Patient-Reported Outcomes, 4(1), 1-8