The YODA Project
Research Proposal Review

The following page contains the final YODA Project review approving this proposal.

The Yale University Open Data Access (YODA) Project
Yale University Center for Outcomes Research and Evaluation (CORE)
195 Church Street, 5th Floor, New Haven, CT 06510

The YODA Project
Research Proposal Review - Final
(Protocol #: 2022-4974)

Reviewers:

- ☐ Nihar Desai
- ☐ Cary Gross
- ☐ Harlan Krumholz
- ☒ Richard Lehman
- ☒ Joseph Ross
- ☒ Joshua Wallach

Review Questions:	**Decision:**
1. Is the scientific purpose of the research proposal clearly described?	Yes
2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health?	Yes
3. Can the proposed research be reasonably addressed using the requested data?	Yes, or it's highly likely
4. Recommendation for this data request:	Approve

Comments:

No additional comments

The YODA Project
Research Proposal Review

Revisions were requested during review of this proposal.
The following pages contain the original YODA Project review and the original submitted proposal.

The Yale University Open Data Access (YODA) Project
Yale University Center for Outcomes Research and Evaluation (CORE)
195 Church Street, 5th Floor, New Haven, CT 06510

The YODA Project
Research Proposal Review - Revisions Requested
(Protocol #: 2022-4974)

Reviewers:

- ☐ Nihar Desai
- ☐ Cary Gross
- ☐ Harlan Krumholz
- ☒ Richard Lehman
- ☒ Joseph Ross
- ☒ Joshua Wallach

Review Questions:	**Decision:**
1. Is the scientific purpose of the research proposal clearly described?	No
2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health?	Yes
3. Can the proposed research be reasonably addressed using the requested data?	Yes, or it's highly likely
4. Recommendation for this data request:	Not Approve

Comments:

1. Main outcome measure: Which outcome and time period is the 'primary endpoint'? It is important to distinguish between primary, secondary, and exploratory analyses.
2. Main Predictor/Independent Variable: Currently, 'Change in QOL score' is listed as the independent variable, but the presence of an AE during treatment should really be listed since the proposed purpose of the study is to determine if QOL (outcome) changes in the context of a treatment AE (predictor/independent variable). Please provide more detail on which AEs are being studied and how 'maximum grade AE' is defined.
3. Statistical Analysis: The analysis proposed seems to merge detail into wide cross-condition and cross-treatment general associations which could not be used in patient/HCP communication. Please explain how this analysis will lead to a more detailed understanding of how patients experience an adverse event that will help to improve communication between patients and health care providers.
4. Please confirm to the best of your ability that all of the requested trials have QOL data (according to their ClinicalTrials.gov pages, or publicly available sources.)

Principal Investigator

First Name: Amanda
Last Name: Hird
Degree: MD MSc FRCSC
Primary Affiliation: University of Toronto
E-mail: amanda.e.hird@gmail.com
Phone number: 6473821717
Address: Univerity of Toronto

City: Toronto
State or Province: Ontario
Zip or Postal Code: M4N 3M5
Country: Canada

General Information

Key Personnel (in addition to PI):
First Name: Christopher
Last name: Wallis
Degree: MD PhD FRCSC
Primary Affiliation: University of Toronto
SCOPUS ID: 27267957700

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/coiform-cwallis.pdf
https://yoda.yale.edu/system/files/coiform-ahird2.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. NCT00653952 - 30-57 - A Phase 3, Randomized, Open-Label, Comparative Study of CAELYX® versus Paclitaxel HCl in Patients with Epithelial Ovarian Carcinoma Following Failure of First-Line, Platinum-Based Chemotherapy
3. 30-49 - A Phase 3, Randomized, Open-Label, Comparative Study of DOXIL/CAELYX® versus Topotecan HCl in Patients with Epithelial Ovarian Carcinoma Following Failure of First-Line, Platinum-Based Chemotherapy
4. 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
5. NCT01343277 - ET743-SAR-3007 - A Study of Trabectedin or Dacarbazine for the Treatment of Patients With Advanced Liposarcoma or Leiomyosarcoma
6. NCT02136134 - 54767414MMY3004 - Phase 3 Study Comparing Daratumumab, Bortezomib and Dexamethasone (DVd) vs Bortezomib and Dexamethasone (Vd) in Subjects With Relapsed or Refractory Multiple Myeloma
7. NCT00796120 - ET-C-002-07 - An Efficacy and Safety Study of Trabectedin Versus Doxorubicin-Based Chemotherapy in Participants With Translocation-Related Sarcomas (TRS)
8. NCT01985126 - 54767414MMY2002 - An Open-label, Multicenter, Phase 2 Trial Investigating the Efficacy and Safety of Daratumumab in Subjects With Multiple Myeloma Who Have Received at Least 3 Prior Lines of Therapy (Including a Proteasome Inhibitor and IMiD) or Are Double Refractory to a Proteasome Inhibitor and an IMiD
9. 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
10. NCT01088529 - COU-AA-203 - A Randomized, Open-Label, Neoadjuvant Prostate Cancer Trial of Abiraterone Acetate Plus LHRHa Versus LHRHa Alone
11. NCT01722487 - PCYC-1115-CA - Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Versus Chlorambucil in Patients 65 Years or Older With Treatment-naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma
12. 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
13. 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)
14. NCT02252172 - 54767414MMY3008 - A Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd) in Subjects With Previously Untreated Multiple Myeloma Who Are Ineligible for High Dose Therapy
15. NCT01381874 - 212082BCA2001 - Randomized, Open-Label Study of Abiraterone Acetate (JNJ-212082) Plus Prednisone With or Without Exemestane in Postmenopausal Women With ER+ Metastatic Breast Cancer Progressing After Letrozole or Anastrozole Therapy
16. 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
17. 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

Association between adverse events and change in quality-of-life scores in phase II-III cancer clinical trials

Narrative Summary:

Safety and quality of life are important outcomes to measure in studies of new cancer treatments. The goal of this study is to determine how an adverse event (a negative side effect from a study drug) impacts quality of life among cancer patients on a clinical trial. We will determine if there are differences in the quality of life impact of an adverse event based on primary cancer site, gender, and other important patient characteristics and study features. We will also explore how an adverse event impacts overall survival. A more detailed understanding of how patients experience an adverse event will help to improve communication between patients and health care providers.

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Scientific Abstract:

Background: Clinical trials are a critical part of the development of novel cancer treatments and patient reported quality-of-life (QOL) is an important outcome to assess. QOL can be used as a surrogate indicator for the tolerability of therapy. However, QOL is a complex construct that is related not only to treatment-related adverse events (AEs) and physical symptoms but can also be impacted by other factors. No large-scale studies have correlated AE severity and change in QOL scores.

Objectives: Among patients with cancer receiving hormonal therapy, immunotherapy, or chemotherapy as part of a phase II-III randomized clinical trial captured in the YODA collaborative, our objectives are to correlate change in overall QOL score with the occurrence of a treatment-related AE, assess which QOL domains are most significantly affected by treatment-related AEs, and to explore how the relationship between QOL and AEs is affected by disease site, gender, treatment stage, performance status, treatment response, and treatment blinding. We will also correlate AE and QOL with overall survival.

Methods: This will be a meta-analysis of individual patient data from phase II-III randomized controlled trials. Overall QOL scores will be compared by maximum grade AE. Change in QOL score will be compared based on AE grade groups using the Wilcoxon rank-sum test. Correlation between QOL score and AE will be assessed using Spearman correlational coefficient and the Bland-Altman approach. Subgroup and sensitivity analyses will be completed by primary cancer site, gender, performance status, and treatment response.

Significance: Understanding impact of AEs on overall QOL scores and specific QOL domains will allow us to better manage the effect of treatment-related AEs as well as improve patient-physician communication and the quality of patient care.

Brief Project Background and Statement of Project Significance:

Clinical trials are a critical part of the development of novel cancer treatments. In addition to efficacy and survival, patient reported quality-of-life (QOL) is an important outcome. It may seem intuitive that QOL scores should be affected by adverse events (AEs) and, indeed, QOL scores can sometimes be used as a surrogate indicator for the tolerability of therapy. However, QOL is a complex construct that is related not only to treatment-related AEs and physical symptoms but can also be impacted by other factors including patient expectation, performance status, gender, as well as psychosocial determinants1-4.

During the conduct of clinical trials, collection and classification of AEs is traditionally done as part of a standardized toxicity assessment tool and presented on an ordinal scale5. The amount of distressed caused by the AE is not specifically collected. QOL score can be a potential method to gauge the impact of an AE during cancer treatment; however, the impact of an AE on QOL has been poorly characterized. No large-scale studies have correlated AE severity and change in QOL scores.

It has been shown that regular assessment of patient QOL can independently improve survival6. Understanding impact of AEs on overall QOL scores and specific QOL domains will allow us to better manage the effect of treatment-related AEs as well as improve patient-physician communication and the quality of patient care. In the setting of advanced cancer, the attribution of the AE to anti-cancer treatment, as opposed to the disease itself, can also be a challenge. Thus, exploring the relationship between AE and QOL based on assigned treatment group is also of interest.

Patient reported QOL and treatment related AEs are rigorously monitored during the conduct of any clinical trial. Therefore, meta-analysis of individualized patient data from well-conducted cancer clinical trials in the YODA project will enable us to explore the relationship between AE and QOL.

Understanding impact of AEs on overall QOL scores and specific QOL domains will allow us to better manage the effect of treatment-related AEs as well as improve patient-physician communication and the quality of patient care.

Specific Aims of the Project:

Among patients with cancer receiving hormonal therapy or immunotherapy as part of a phase II-III comparative

clinical trial captured in the YODA collaborative, our objectives are to:

1. To correlate change in overall QOL score (from baseline) with the occurrence of a treatment-related AE at 3- (primary outcome), 6-, and 12- months (secondary outcomes).
2. To assess which QOL domains are most significantly affected by treatment-related AEs (secondary outcome).
3. To explore how the relationship between QOL and AEs is affected by disease site, gender, treatment stage, performance status, treatment response, and treatment blinding (subgroup analysis).
4. To explore the relationship between AEs and overall survival (OS) (exploratory analysis).
5. To explore the relationship between QOL and OS (exploratory analysis).

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

Explore the relationship between patient-reported change in QOL, adverse events, and overall survival

Research Methods

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

We will include all phase II-III randomized cancer-based clinical trials using hormonal therapy, immunotherapy, or chemotherapy. Patients with who have available and complete QOL and adverse event data on at least one follow-up assessment will be included. Patients who do not have any captured QOL data will be excluded. Incomplete QOL assessments (where calculating an overall QOL score is not possible) will be excluded.

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

Overall QOL scores will be compared by maximum grade AE at 3- (primary outcome), 6-, and 12-months (secondary outcomes). Given that the most common AEs may vary depending on the disease site and treatment agent, all types of AEs will be considered, but the AE with the highest grade (using the Clavien Dindo scoring system) will be used as the primary predictor in the model. Change in QOL score will be compared based on maximal AE grade group using the Wilcoxon rank-sum test. Correlation between QOL score and AE will be assessed using Spearman correlational coefficient where low correlation, 0.10 to 0.29; moderate correlation, 0.30 to 0.49; and high correlation, > 0.50 and the Bland-Altman approach. Subgroup analysis will be completed as stated above based on disease site, gender, treatment stage, performance status, treatment response, and treatment blinding. We will assess which QOL domains are most significantly affected by AEs. We will explore the impact of experiencing any grade III-IV AE (at any time) and the impact of multiple grade III-IV AEs on OS. We will explore the impact of change in QOL score on OS.

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

Most severe AE at each time period (graded according to the Clavien Dindo system)

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

Due to potential variability of the type of AE based on patient and disease characteristics, subgroup analysis will be completed by:
- Primary disease site
- Type of agent received
- Localized or metastatic disease
- Gender
- Age
- Baseline comorbidities
- Baseline performance status score (ECOG 0 vs 1 vs 2)
- Treatment response (i.e. responders vs non-responders)
- Open label versus blinded

Statistical Analysis Plan:

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Summary statistics will be presented to describe the baseline characteristics of included patients. Demographic variables that are continuous and normally distributed will be reported as mean with standard deviation. Demographic variables that are continuous and not normally distributed will be reported as median with interquartile range. Categorical variables will be presented as numbers with percentages. Overall QOL scores will be compared by maximum grade AE at each time interval as categorized using the Clavien Dindo system. Change in QOL score will be compared based on AE grade groups using the Wilcoxon rank-sum test. Correlation between QOL score and AE will be assessed using Spearman correlational coefficient to assess the strength of linear associations and agreement where low correlation, 0.10 to 0.29; moderate correlation, 0.30 to 0.49; and high correlation, > 0.50 and the Bland-Altman approach.
Software Used:
R

Project Timeline:

Date Objective
March – October 2022 Project submission
November 2022 – January 2023 Data cleaning
February – April 2023 Data analysis
May 2023 Manuscript drafting
June 2023 Submission for publication

Dissemination Plan:

Our results will be presented at local, national, and international cancer meetings. The results of this project will be published in a high-impact oncology journal.

Bibliography:

1. Rodríguez AM, Mayo NE, Gagnon B. Independent contributors to overall quality of life in people with advanced cancer. Br J Cancer. May 14 2013;108(9):1790-800. doi:10.1038/bjc.2013.146
2. Huschka MM, Mandrekar SJ, Schaefer PL, Jett JR, Sloan JA. A pooled analysis of quality of life measures and adverse events data in north central cancer treatment group lung cancer clinical trials. Cancer. Feb 15 2007;109(4):787-95. doi:10.1002/cncr.22444
3. Atherton PJ, Watkins-Bruner DW, Gotay C, et al. The Complementary Nature of Patient-Reported Outcomes and Adverse Event Reporting in Cooperative Group Oncology Clinical Trials: A Pooled Analysis (NCCTG N0591). J Pain Symptom Manage. Oct 2015;50(4):470-9.e9. doi:10.1016/j.jpainsymman.2015.04.016
4. Niska JR, Thorpe CS, Halyard MY, et al. Patient-reported quality-of-life outcomes in relation to provider-assessed adverse events during head and neck radiotherapy. J Patient Rep Outcomes. Jul 16 2020;4(1):60. doi:10.1186/s41687-020-00227-4
5. Institute NC. Common Terminology Criteria for Adverse Events. Accessed January 4, 2022.
6. Basch E, Deal AM, Dueck AC, et al. Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. JAMA. 07 11 2017;318(2):197-198. doi:10.1001/jama.2017.7156

Supplementary Material:

https://yoda.yale.edu/sites/default/files/table_1.pdf