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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:** Food and Drug Administration
**How did you learn about the YODA Project?:** Internet Search

## Conflict of Interest

https://yoda.yale.edu/system/files/coi_form_dc.pdf
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## 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. NCT01867710 - 212082PCR2023 - A Randomized Phase 2 Study Evaluating Abiraterone Acetate With Different Steroid Regimens for Preventing Symptoms Associated With Mineralocorticoid Excess in Asymptomatic, Chemotherapy-naïve and Metastatic Castration-resistant Prostate Cancer (mCRPC) Patients

**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 a single global item for side effect bother

**Narrative Summary:**

Patient-reported side effects are of increasing importance and regulatory interest in oncology. Drug tolerability is an important consideration for patients and regulators, particularly in a setting where therapies can extend survival but impose significant toxicities. A single global item for patient-reported side effect bother may be potentially useful as a tolerability endpoint in cancer clinical trials. This project will evaluate the measurement characteristics of this item, specifically its association with patient-reported outcomes of interest in cancer trials. This research can help inform patient-centered drug development.

**Scientific Abstract:**

Background: Patient experience, including the patient's perspective on the tolerability of treatment, is an important consideration in cancer drug development. A single global item (FACT GP5) measuring side effect bother has potential usefulness as a trial endpoint, but further evaluation is required.
Objective: We aim to evaluate the association of a single global item measuring side effect bother with 1) physical and role function; 2) symptoms (e.g., pain, nausea); 3) clinical outcomes (e.g., treatment modification/discontinuation, death), and 4) to evaluate the between-group differences in item scores between subgroups with differences in symptomatic side effects. Our supplementary objectives are to evaluate 1) the completion rate of and distribution of scores for this item at baseline and the end of treatment visit; and 2) if feasible, participant trajectories for clinical outcomes based on baseline item scores.
Study Design: Retrospective cohort design.
Participants: We will use participant data from NCT01867710, a randomized phase II trial of abiraterone acetate (AA) in combination with different steroid regimens for prostate cancer. Participants who complete questionnaires and receive treatment will be included in the analysis.
Main Outcome Measures: The main outcome measure is the GP5 item, from the Functional Assessment of Cancer Therapy-Prostate (FACT-P). Other outcome measures include function (EQ-5D) and symptoms (FACT-P, Brief Pain Inventory-Short Form [BPI-SF]), and clinical outcomes.
Statistical Analyses: We will use descriptive, correlation and regression analyses. Unstratified analyses and analyses stratified by treatment arms will be conducted.

**Brief Project Background and Statement of Project Significance:**

Background: Patient-reported outcomes (PROs) play an increasingly important role in oncology, from drug development1 to clinical care.2 Treatments for cancer often have substantial toxicities, making side effects a key consideration. Although clinician reporting of adverse events will remain essential for the evaluation of safety, PROs can provide information on tolerability3 to understand the extent of an adverse event (AE) burden therapies impose on patients. There is interest in a summary measure that can help communicate how patients might feel and function on treatment,4 which is highly relevant for communication and decision making about cancer therapy. One such item is the Functional Assessment of Chronic Illness Therapy (FACIT) item 5, "I am bothered by the side effects of treatment." Response options are on a five point scale and range from "not at all" to "very much." GP5 is included in many FACIT instruments. There is published evidence that GP5 is significantly associated with clinician-reported AEs5 and early discontinuation of therapy.6 However, more work is needed to understand its potential suitability as a trial endpoint, including further understanding of the GP5's measurement characteristics.
Significance: This work can contribute to the evidence base for the use of patient reporting of tolerability in cancer trials. If our work demonstrates the usefulness of this single global item, it can lead to the use of such an item as a "tolerability endpoint" which could complement primary efficacy endpoints in future oncology trials. For this project, we are using datasets from different cancer and treatment types to understand the usefulness of this item in multiple contexts. Data from this Phase II study can contribute helpful information about the usefulness of this item

in an early phase setting.

**Specific Aims of the Project:**

The specific aims of this project are to:
1) Assess the association between the GP5 and patient-reported items relevant to physical and role function;
Hypothesis: Higher scores (higher bother) will be associated with worse/lower function.
2) Evaluate the association between the GP5 and patient-reported symptoms, such as pain, nausea and fatigue;
Hypothesis: Higher scores will be associated with worse/higher scores for symptoms.
3) Evaluate the association between the GP5 and clinical outcomes such as treatment modification, discontinuation, hospitalization and death;
Hypothesis: Higher scores will be associated with clinical outcomes.
4) Evaluate the between-group difference in GP5 scores between subgroups with differences in symptomatic AEs;
Hypothesis: Scores will be higher in the subgroup with more/higher symptomatic AEs.
5) Examine the completion rate and distribution of scores for GP5 at baseline and the end of treatment visit, to ascertain the usefulness and feasibility of this item at those timepoints;
6) Examine participant trajectories for clinical outcomes such as treatment modification and hospitalization as well as subsequent GP5 scores for participants grouped by baseline GP5 scores, to examine the usefulness and feasibility of this item at baseline

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

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Other

## Research Methods

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

Data Source: Data will be drawn from NCT01866710, a randomized phase II trial of abiraterone acetate (AA) in combination with different steroid regimens for men with metastatic castration-resistant prostate cancer. The trial collected PRO data at screening (BPI) and baseline (FACT-P, EQ-5D) and again at cycles 6, 18 and the end of treatment. Given anticipated attrition after 6 months due to progression and/or death, our primary timepoint of interest will be on cycle 6 unless otherwise specified.
Inclusion/Exclusion Criteria: All patients who receive ?1 dose of treatment and complete the GP5 item will be included. Patients who do not complete the questionnaire will be excluded, but their clinical and sociodemographic characteristics will be compared to included patients in a supplementary analysis.

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

The main outcome measure is the GP5 item on the FACT-P, which asks patients to respond to the statement “I am bothered by the side effects of treatment” (Not at all – Very much/0 – 4). This will be operationalized in two ways. Initially, it will be kept in its native format as shown above. We will then conduct secondary analyses, with the GP5 dichotomized into high (scores of 3 – 4) vs low (scores <3) bother.5 The BPI-SF7 has subscales that measure pain intensity and interference, both of which range from 0 – 10 (higher=worse). This will be operationalized as a continuous outcome. The EQ-5D items of interest can take on one of five levels, ranging from “no problems” (level 1) to “unable” (level 5). For this study, given our focus on specific items and interest in association, we will not transform the EQ-5D into its index score, and focus on specific domains of mobility and usual activities. This approach is consistent with that used in another study that focused on specific EQ-5D domains.8 The FACT-P symptom items, like the GP5, are on a 0 – 4 scale. Clinical outcomes will be categorized as binary variables (0/1), or count variables if relevant and indicated in data.

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

Aim 1: For the correlation analyses in aim 1, the primary independent variables are the EQ-5D items relating to mobility and usual activities. These will be defined as above. For the regression models, the GP5 item will be the primary independent variable.
Aim 2: For the correlation analyses, the primary independent variables are 1) the FACT-P symptom items, defined as above. For the regression models, the GP5 item will be the primary independent variable.
Aim 3: The primary independent variable will be the GP5 item. Depending on data availability (e.g., date of death), survival (Cox) models will be used, otherwise logistic regression models will be used. If count data are available/relevant, Poisson regression models will be used.
Aim 4: The primary independent variable will be GP5, categorized both in its 0-4 format and dichotomized.
Aims 5 and 6: The primary independent variable will be GP5, categorized in its 0-4 format.

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

For the regression models, we will adjust for relevant clinical and demographic variables (e.g., age). Covariates will be chosen based on variables available in the CSR upon review of the CSR with clinical co-investigators. As noted above, both unstratified analyses and analyses stratified by treatment arm will be conducted.

**Statistical Analysis Plan:**

Aim 1: Using its ordinal scale, we will estimate correlations between GP5 and the function items using Spearman's rho. We will also evaluate the correlation between the GP5 item at the relevant post-treatment time point(s) and the change from baseline in the function items. We will consider correlations of >0.40 to evidence an important association.9
The second analysis will dichotomize GP5 consistent with previous research.5 Response scores of 3 or 4 on a 0 – 4 point scale ("Not at all" – "Very much") will indicate high bother 5. We will follow this approach by dichotomising the GP5 into scores of 0-2/3-4 and then comparing mean physical and role function item scores at the relevant time point(s) using two sample t-tests or a non-parametric equivalent (e.g., Wilcoxon rank sum). We will also repeat this analysis using the change from baseline in the function item scores. As a supplementary analysis, we will also evaluate point biserial correlations between the item scores and the GP5.
Because the question of interest pertains to an association in general, rather than between-arm discrimination, all analyses described above will be conducted in each trial without stratification for trial treatment arms. Additionally, we will also conduct an analysis of the function items stratified by treatment arms. If there is a between-arm difference in the function items, we expect that we will see between-arm differences in GP5 scores of at least one response category.
Finally, to adjust for potential confounders, we will fit multiple linear regression models with the function items as the outcome and GP5 as the covariate of central focus. Each item will be analyzed separately. Potential confounders will be determined through discussion with the clinical and patient investigators on the team. However, we anticipate some initial covariates for adjustment as described above.
Aim 2: The correlation and t-test/Wilcoxon analyses, this time using the symptom scales/items, will be conducted as described for Aim 1. As in Aim 1, we will consider correlations of ?0.40 as important. To adjust for potential confounders, we will fit multiple linear regression models with the symptom item(s) as the outcome(s) and GP5 as the covariate of central focus. Each item/scale will be analyzed separately. The decision-making on covariates for adjustment will be as described for Aim 1.
Aim 3: Subgroups of patients with different experiences of clinician-reported symptomatic AEs will be compared in terms of their GP5 score, using t-test/Wilcoxon analyses. These subgroups will be identified a priori based on review of available/published trial information (e.g., clinicaltrials.gov).
Aim 4: We will use logistic regression and survival (Cox) models to evaluate the association between the occurrence of the events of interest and the time to the events of interest. For those outcomes where recurrence is possible (e.g., hospitalization), Poisson regression models will be used as required.
Aims 5 and 6: Descriptive statistics and graphical visualization of data will be the focus for these aims. For completion rates, we will calculate rates for both the GP5 and neighboring items to provide context for baseline completion rates.
Missing Data Handling – Aims 1 to 4: The extent of missing outcome and covariate data will be evaluated using descriptive analysis. Missingness patterns will be examined. Initially, all analyses will use available case analysis. If required, multiple imputation (MI) will be used to address missing data, with analyses conducted within each imputed dataset, and then pooled at the end using standard combining rules.10 Sensitivity analyses for the assumption underlying MI will be undertaken as required.
Supplementary Analysis: T-tests or chi-square tests, as appropriate for the different variables, will be used to

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compare the clinical and sociodemographic characteristics of the included and excluded patient populations.
Software Used:
RStudio
**Project Timeline:**

The project can start when the data are available. Estimated start: June 2022.
Data Cleaning/Preparation: 6 months (June 2022 – December 2022)
Data Analysis: 6 months (December 2022 – May 2023)
Manuscript Writing and Revisions: 8 months (May 2023 – January 2024) (this includes anticipated journal submission and revision time)
Project Closeout: February 2024

**Dissemination Plan:**

Initially, we aim to produce four manuscripts: one for each aim for aims 1 – 3 and one that addresses aims 4 – 5. As we are also using datasets from other sources, the findings from all evaluated datasets will be presented together. We will aim for methodological journals (Journal of Patient-Reported Outcomes, Quality of Life Research, Value in Health) and more clinically focused journals (Cancer, Cancer Clinical Research, Journal of Clinical Oncology).
In addition, we will disseminate the findings through presentations at conferences. This will include clinically focused conferences such as the American Society of Clinical Oncology and methodological conferences such as the International Society for Quality of Life Research.

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