**EPIDEMIOLOGY: PREP METHODS REVIEW SUMMARY  
REVIEWER COMMENTS**

Instructions: Each PREP reviewer and protocol submitter will enter review and response comments into this document, respectively. Anything requiring discussion will be covered during the PREP review. This summary will be stored in Wrike and in ReCap Methods Review area if required. Final protocols including a version with tracked changes or where specific changes are noted (e.g., page number) based on PREP review should be submitted to PREP Chair and posted in an agreed respository.

| Section | Reviewer Comments/ Suggested changes (reviewer initials) | Submitter response, including any proposed changes | Is submitter explanation/ proposal(s) sufficient? (Reviewer: Yes/No and list what requires discussion) | Additional changes (e.g., add additional information if additional adjustments are proposed by PREP beyond those proposed in submitter’s response) |
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| **Study Background**  **/Rationale**  [e.g., Is the purpose of the study clear?] | RD: Consider adding more context about the pilot and if this research question is for cause vs. demonstration | We have revised Section 4 – Background and Rationale to further clarify the motivation for conducting this study. This research question arose from a pilot collaboration between GMS, Clinical Oncology, Epideimology, and OHDA. However, it is more than just a demonstrative study since it was motivated by a published abstract that indicated possible elevation of cardiovascular risk after patients initiate use of Zytiga (abiraterone). |  |  |
|  | LH: In particular, you may want to mention the AACR abstract that stimulated this study (as well as its poor study design). | We have added a reference to the abstract in the last paragraph of Section 4. |  |  |
| **Objectives**  [e.g., Have the objectives been defined?] | RD: no comments |  |  |  |
|  | LH: I didn’t see this in the outcome (specifically, the hospitalization for heart failure). Did I miss this?  LH: Can we make it clear in the description that these are all outcomes during hospitalizations or ER visits? | In section 5.1 of the paper, we have clarified that all of the outcomes are evaluated only when they occur during a hospitalization. |  |  |
|  | HQ: Would you consider severe ventricular arrythmia? | We did not consider including severe ventricular arrythmia since it is already included on the Zytiga label as an important safety event. |  |  |
| **Data Source**  [e.g., Have the data source(s) been described with respect to geographical coverage, type of data (e.g., claims data, SEER registry), population covered?] | RD: no comments |  |  |  |
| **Study Design**  [e.g., Has a study design been proposed and discussion included of any comparison groups?] | RD: Consider putting in 6.1 some background on what you have done already (cohort selection up to diagnostics) and what’s left to do. The past tense throws me off as a protocol is typically what you plan and you’ve done lots of diagnostics and such already. | We have added additional description in the 2nd paragraph of Section 6.1 We have also revised tense throughout the manuscript in order to reduce confusion. |  |  |
| **Study Population**  [e.g., Has the study population been defined and inclusion/exclusion criteria presented?] | RD: Section 6.3. The enzalutamide comparator is indicated with concurrent use of GnRH or have orchiectomy. Will you require that or ignore that? You might want to clarify as you mention concurrent prednisolone in the treatment arm. | For both the target and the comparator cohort, all patients have castration-resistant prostate cancer (CRPC) and thus have already received some form of androgen-deprivation therapy (most commonly in the form of GnRH treatment or orchiectomy). |  |  |
|  | LH: Normally, in a cancer study, we would require two malignancy codes and the codes would need to occur soon before the treatment (within a year). I’m guessing that you are being a little more lax in your cohort definition given that there are no other cancers approved for these drugs and that you want the largest cohort possible. | We used a single diagnosis code for a number of reasons. As the reviewer pointed out, doing so provides a larger study cohort, which is already prohibitively small for a number of analyses we sought to perform. Furthermore, these drugs have no alternate indications so it is unlikely that we are including people who are receiving these treatments to treat any condition besides prostate cancer. Finally, we anchored our cohort entry on patients having had prior androgen-deprivation therapy, which is the first-line therapy before use of abiraterone or enzalutamide. By requiring that ADT therapy precedes initiation of abiraterone or enzalutamide, we feel confident our study cohort only includes patients being treated for active prostate cancer. |  |  |
|  | LH: Is there a supplement with the concept sets for ADT and other concepts? | Annex Document #1: conceptSetExpressions - Exposures and Outcomes.xlsx |  |  |
|  | LH: I think this definition could also be called severe CVD. Without including drug/procedure adherence patterns into this definition, I don’t think we can technically call this “uncontrolled.” | In response to the reviewer’s comment, we have changed the description of our CVD-stratified analyses from “uncontrolled” and “controlled” to “more severe” and “less severe.” |  |  |
| **Variables**  [e.g., Did the Methods adequately describe the variables collected including a description of the exposures, outcomes and any potential confounding variables?] | RD: no comments |  |  |  |
|  | LH: Do you have validation information for any of these outcomes? | We do not. However, we added a citation to the publication which describes the development of these outcome phenotypes (Suchard 2019). |  |  |
|  | HQ: I understand the rationale of the 30-day rule. But it will not be able to evaluate the short-term safety. I’m wondering if there are RCT data to convince that the short-term safety has been well documented. On the other hand, how will you handle those patients have CV events happened during this 30-day, which would affect the assessed outcome? Those events could be effect modifiers in the analyses. | In the first paragraph in Section 6.4, we have added additional information and explanation for our for studying only patients who remain enrolled and event-free until Day 30. |  |  |
|  | LH: Due to lower availability of prednisone data, we may also be missing patients who would otherwise qualify for this study if the prednisone is not observed in the 30 day period before or after new abiraterone acetate use. This will be good to mention in limitations of a manuscript/report. | We have added a paragraph discussing this point to the limitations section (see second-to-last bullet in Section 10.2) |  |  |
| **Sample Size**  [e.g., Was sample size specified?] | RD: no comments |  |  |  |
| **Data Analysis**  [e.g., Was the proposed analysis plan in sufficient detail? (e.g. matching, modeling approach, modeling period)] | RD: 6.4 I start appreciating that there are multiple models in this section, and it is not as clear as it could be how many how to get the 600 possible individual models possible, which reduces to 9. A figure or table before Table 5 in Section 9 would be helpful to show the math that appears in the paragraph above it. | We have added a description in section 6.1 which clarifies that we evaluated multiple possible analyses for possible unblinding. The paragraph directs the reader to section 9.3, which includes more detailed explanation as well as the table recommended by the reviewer. Between the table and text, we explain that we assessed 600 possible analyses which include all possible combinations of 5 target/comparator comparisons, 6 outcomes, two databases, and 10 analysis variations. |  |  |
|  | LH [commenting on the list of selected negative controls]: You will also need clinical review of this list on top of these criteria. I’m going to go through and highlight some of these negative controls that I believe should be removed. Those that I am suggesting to be removed are direct adverse events of one of the treatments, linked to the urogenital area, potential diagnoses related to prostate cancer metastasis, or are related to the cardiovascular outcomes.  RD [commenting on the list of selected negative controls]: How was this selected? I am assuming this has been reviewed by medical co-authors to confirm that these are a reasonable list of negative controls? | We did have clinical collaborators complete the (guided) task of selecting appropriate negative controls. We appreciate the reviewer’s additional input and dropped all of the negative controls she identified as being potentially problematic. The revised/narrowed list has 124 negative control outcomes total. |  |  |
| **Strengths and Limitations of the Research Methods**  [e.g., Were the strengths and any potential limitations of the study described?] | RD: It is worth closing on a more positive note that you are hoping that this pilot helps you in some way – with evaluating ADR and otherwise. Consider listing what you hope to gain despite limitations of the data. | Excellent feedback. Please refer to the final bullet in the strengths and limitations section where we have summarize useful insights that the project has yielded / will yield as it progresses. |  |  |
| **Additional Sections/Tables/**  **Figures reviewed** [e.g., is the information clear and sufficient?] | RD: No comments. Annex show how thoroughly this has been thought through / interrogated. If you post the protocol, consider how/where/if you are posting Annex. | Thanks for the advice. We will consider posting without the annex if collaborators do not deem it necessary. |  |  |
| **General Comments** | RD: This is a very well written protocol. Thank you.  A priori - You might want to consider when you would consider the results medically important, since you are doing a head-to-head comparison with a Janssen medication and a comparator. And, what reporting and to whom might you do beyond publication and under which circumstances? | In response to this comment, we have added the following statement in Section 12 (Safety Data Collection and Reporting): “The study results will be assessed for medically important results and regardless of findings, will be shared with the safety management team (who is actively collaborating on this project) in order to inform next steps.” To be clear, the safety management team is an active collaborator as part of this project. Results will be shared with them no matter what the finding is. |  |  |

# PREP Decision (completed by Chair)

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|  | Approved |
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|  | Approved with the following minor changes: |
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|  | Conditionally approved with the following major changes: |
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|  | Approval denied due to the following: |
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**Review Information**

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| **PREP Chair:** |
| **PREP Reviewers:** |
| **Protocol Authors:** |