Author’s response to reviews

Title: Weight loss as a predictor of cancer and serious disease in primary care: an ISAC approved CPRD protocol for a retrospective cohort study using routinely collected primary care data.

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Author’s response to reviews:

Dear DAPR,

Many thanks for the opportunity to revise our protocol manuscript entitled “Weight loss as a predictor of cancer and serious disease in primary care: an ISAC approved CPRD protocol for a retrospective cohort study using routinely collected primary care data.”

We had originally submitted the ISAC approved protocol with the understanding that only editorial review would occur due to the internal ISAC peer review system. Reviewer 2 has clarified the expectation of DAPR for the recommendations from DAPR peer review to be addressed in the Discussion section of the manuscript.

We have consequently revised the manuscript in line with the reviewers’ second round of comments and responded to each below.
Yours sincerely,

Dr Brian D Nicholson

(on behalf of all authors)

We respond to reviewer #2 first as this review contains information from the journal editors about the expectations for an ISAC protocol related publication.

* Reviewer #2: In light of the author responses to my reviewer comments, and the fact that DAPR is a new journal, I sought advice from the journal editors regarding the expectations for this type of article. Specifically, while I completely understand that the methods of an approved ISAC protocol cannot be changed, I sought clarification about whether it is appropriate for reviewers to request more information/clarification about aspects of the protocol, or whether the published article should simply be verbatim publication of the approved protocol. I include the relevant portion of the editors' response below to provide context for my subsequent reviewer feedback:

"As the protocol has already received ethical approval and funding, the authors/investigators are unlikely to be able to make major changes to their protocol design so review should be focused on reporting, with a focus on clarification rather than changes to the intended research. However, even if changes cannot be made to methods it's sometimes useful for the authors to discuss some of the recommendations from reviewers in the Discussion section in relation to their study."

**Author Response: Thank you to Reviewer #2 for clarifying the position of DAPR and the areas of the manuscript that we should edit to allow us to address the reviewers’ comments. We have consequently addressed previous current review comments in the Discussion section and added detail throughout the protocol.

* Reviewer #2: Based on this I have reiterated a few of my previous points below in which I requested further information about aspects of the protocol, but did not suggest any alterations.

[1] It appears that they propose the development of an EHR algorithm for weight loss - what steps do the authors propose to take in order to validate the algorithm developed?
-- (Previous) Author Response - We will develop this algorithm using a small subset of clinical records, and then cross-validate it using the remaining dataset.

-- (Previous) Reviewer Response - It would be helpful to include this information in the article (e.g., under Aim 1 in the Data/Statistical Analysis section). It would also be helpful to have more information about the methods you plan to use in developing the algorithm. I may have completely missed it, but it wasn't clear to me whether you're proposing rule-based methods or some type of machine learning approach or something entirely different.

**Author Response: For the descriptive components of the study (Aims 1.1 & 1.2) we have developed rule-based methods (a widening search strategy) to classify each weight measurement and weight loss code in terms. As recommended, we have included additional detail under Aim 1 in the Data/Statistical Analysis section, and tracked changes, to clarify this and added to the Discussion.

* Reviewer #2: [2] If I have understood correctly, the authors also appear to be proposing the development of another algorithm for what they have termed "Serious Disease", but it was not clear what conditions might be included in the endpoint, or how this algorithm might be validated.

-- (Previous) Author Response - This serious disease codelists are being developed by literature review to identify likely candidate conditions that are known to cause weight loss.

-- (Previous) Reviewer Response - As in my query above, are you able to provide more information on the methods that will be used to create the algorithm once codelists are defined, and how it will be validated?

**Author Response: We have added detail to describe the development of the codelist of candidate serious diseases that have been reported as being linked with weight loss, based on literature review. This is further informed by the descriptive component, in particular Aim 1.2, which searches for and ranks new diagnostic codes related to weight loss codes. We have added detail about methods used to generate this codelist in the manuscript (in the Outcome – Serious Disease section), and tracked changes.

* Reviewer #2: [3] The cohort definition was somewhat unclear given that different time windows are proposed for different variables. I appreciate that extracting relevant information from EHR is complex and there will be rationales for the authors decisions, but these are currently hard to follow. A clear statement of inclusion/exclusion, cohort entry, outcome/exit definitions is needed, as well as the time windows used for each set of variables - a diagram may be helpful here?
-- (Previous) Author Response - This is wording used in the approved ISAC protocol.

-- (Previous) Reviewer Response - I appreciate that you cannot change these definitions, but I think further explanation of this would be helpful for the reader. If you do not feel that it is appropriate to expand on this in the text, then a diagram may be the best way forward in terms of explaining the sample definitions for the descriptive and cohort analyses without actually having to alter the original text.

**Author Response: Many thanks for this suggestion. As recommended, we have included a box to show the inclusion and exclusion criteria for the descriptive and cohort analyses.

* Reviewer #1: Thank you to the authors for answering many of the reviewers' questions. However, I believe many of their answers can and should be included in an updated manuscript before publication.

I understand that the protocol has been accepted by ISAC and the content of the study, and wording of the protocol, cannot be changed. And I have no doubt that the study will be sound when carried out. However, I believe that what the reviewers are asking for is more explanation of the thought processes and choices in developing the protocol, so that the readers of the journal are not just reading an ISAC protocol, but rather a fully discussed article. I would suggest that many of the questions asked by the reviewers, and answered in the authors' responses, should be included in the discussion of the article.

**Author Response: We agree that an manuscript allowing greater detail would be of added value. We were initially informed that ISAC protocols would only undergo editorial review by DAPR given the internal peer review process conducted by ISAC. This explains our initial persistence with that approach. We have now followed the advice from the editor (detailed by Reviewer #2 above) when revising the manuscript, and so have expanded the discussion section to cover many of the points raised during both stages of the DAPR peer review.

* Reviewer #1: I suggest that the ISAC protocol itself should be an appendix, while the article itself would give a full introduction/background to the development of the protocol (much of which would come from the protocol, but could go further), brief methods planned (also from the protocol, with some choices explained), and a full discussion of the choices made for the protocol, with strengths and potential limitations, and compromises needed, all discussed - referring where appropriate to the protocol.

**Author Response – It is now clear that an expanded protocol is expected. We have edited the manuscript to add more detail in line with the advice from both Reviewers and the Editor. If
DAPR wish to additionally append the original ISAC, the authors would be happy with this editorial decision.

The authors would like to thank each reviewer for their recommendations and clarifications regarding the format and structure of ISAC protocol for submission to DAPR.