Author’s response to reviews

Title: Physical activity and the prevention, reduction, and treatment of alcohol and/or substance use across the lifespan (The PHASE review): protocol for a systematic review.

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Author’s response to reviews:

*Responses are also provided in the covering letter for easier reading.*

Reviewer #1: This is a protocol for a potentially very interesting review. The proposed review is very broad and I could see it be potentially being challenging to manage. It appropriately will include quantitative and qualitative studies, as well as economic evaluations. The background for the review highlights the need for a review in this area and gaps in the literature. The methods generally appear comprehensive and robust. The inclusion of a stakeholder group is interesting and will also hopefully help with transforming the results into feasible recommendations for practice.
Comment: Response:

I think there are a just a few minor issues that need attention:

Objectives

In the abstract it is stated as "The objectives of this mixed methods systematic review are to describe and evaluate the quantitative and qualitative research obtained by a diverse search strategy on the impact of physical activity and its potential to…". However, the objective stated on line 204 is "to assess the impact of physical activity on the prevention, reduction, and treatment of alcohol and substance use across the lifespan". This seems to suggest a focus on outcomes as measured by trials. This section does go on to state that the authors will describe and evaluate the available quantitative and qualitative research, although this phrasing makes it seem more like a scoping review. Mention is also made of an economic evaluation. Some clarification around specific research questions and what forms of data will be used to answer them would be helpful here.

Text has been edited to address this discrepancy, and subsequent description of analyses including the economic evaluation have been clarified.

Methods

* Line 239. Frequency analysis on a sub-sample of relevant literature. Some more description around this is needed. Does this mean no relevant studies were published before this date?

Up updated frequency analysis has been conducted on the most recent search strategy, which is much more sensitive than the initial strategy. The updated analysis demonstrates that there is a negligible amount of research (a few studies per year) published prior to 1975. Therefore, we have updated our search strategy cut-off date to studies published between 1975 and the present. Any studies published before that date are unlikely to be relevant to the current social and health services environment.

* Lines 267-272. It is stated that these studies will be assessed on a case-by-case basis. It is not clear against what criteria will these assessments be made (i.e. what will determine whether or not the study should be included).

More information has been added describing potential secondary data that may match our primary outcomes for the review. If viable data can be extracted and causality demonstrated it will be considered for inclusion.
* Lines 275-278. It is not described how multi-component interventions are to be handled.

Studies will be addressed on a case by case basis to assess whether there is any viable data which can demonstrate causality and the text has been amended to reflect this.

* Outcomes. Will the final agreed upon outcomes be reported a-priori to enable measurement of selective outcome reporting bias?

We mapped the primary outcomes against our domains of PA. We kept the definition of outcomes broad due to the broadness of our research question and our intend to look at direct and indirect effect of the intervention.

Regarding assessing reporting outcome bias, we are using the risk of bias tool of Cochrane collaboration for RCTs that incorporate this element. We will consider all published protocols that comes up in our searches for this assessment, however, we do not intend to contact authors or research/ethics committees to identify original unpublished clinical trials to assess this outcome as due to the workload of this review, it is unmanageable.

* Suggest searching the WHO's International Clinical Trials Registry Platform and clinicaltrials.gov

Excellent suggestion. Our information specialist has suggested searching OpenTrials, which collates clinical trials information from many different sources, including WHO and clinicaltrials.gov.

* Although measures of assessment for statistical heterogeneity are described, it is not described if/how it will be addressed.

We will conduct random-effects meta-analyses to incorporate heterogeneity among studies. In addition, we will explore the potential causes of (statistical) heterogeneity by using subgroup analyses or meta-regression where possible, as described in lines 501-504. For clarity, we have now added this description under “Assessment of statistical heterogeneity”.

* Detail on the approach to be used for integration of the quantitative and qualitative data would be helpful (e.g. is this the approach developed by the EPPI centre)?

The approach is described in lines 421-423 where we intend to follow the Cochrane Handbook of systematic reviews using a multi-level approach resulting in a detailed narrative synthesis. The approach has been amended to incorporate any economic data more explicitly as per reviewers’ comments.
Reviewer #2: This review will be interesting to see what evidence is available and whether PA has an effect on the alcohol and/or substance use. A major concern is the huge scope of the review. The review will cover PA in all its forms for prevention, reduction and treatment of alcohol and/or substance use. It will include a large number of quantitative research designs and qualitative data for synthesis. I am concerned that the protocol does not sufficiently cover the complexities of this review. Wouldn't this review benefit from being a number of specific reviews both, qualitative and quantitative, that could then be synthesised into a final paper?

Comment: Response:

The paper would also benefit from clearly defined aims and objectives. Aims and objectives are not clearly provided upfront and are mentioned throughout the protocol making it difficult to read and determine whether the methods match the objectives of the review. For instance there are no mention of qualitative aims until line 444 and there are no aims for economic analysis even though it is described as an important part of the paper.

The objectives have been redefined throughout.

1. I was unsure reading the paper why both alcohol and drug use are being addressed in the same review. Most of the justification provided is for either drugs or alcohol. Some of the justification is in the discussion (lines 575-587). The introduction would be better if this was made clearer in the introduction.

   Thank you for this feedback. Additional text has been added to the introduction.

2. It is not clear whether this is a protocol for three different papers or one paper with three different sections. This needs to be made clearer both in the abstract and the methods section.

   After restructuring the aims and objectives, we feel it is clearer now that this is for one paper with 3 different sections.

3. The review frequently mentions alcohol and substance use. Are you looking at both or one or the other? Should it be alcohol and/or substance use?

   Changed to and/or throughout.

4. You have mentioned that this is a mixed-methods review. It is not clearly written in your objectives section what the aim for the quantitative or qualitative reviews are other than to describe and evaluate. More succinct aims would strengthen the justification for a mixed-methods review eg barriers and facilitators of individuals participating in PA for the prevention, reduction and treatment of drug and/or alcohol use. In addition economics is mentioned quite a bit but is not part of the objectives. This should be an objective as well.
5. In the types of studies section you have mentioned a number of quantitative study designs. What designs will be used in your meta-analysis? How will local service evaluations be incorporated into the review? This hasn't been discussed.

Thank you for the feedback. The protocol has been redrafted throughout to reflect this feedback and present more consistent and clearly defined aims.

Additional information has been included to describe how service evaluations and grey literature will be incorporated in the review.

6. For the interventions section (line 274) what about multidisciplinary programs eg a program for diabetes that includes PA, nutrition and pharmaceutical advice that may implicitly reduce alcohol use will these programs be included? They have PA but how will you assess whether PA was the result of reduced intake of alcohol if nutrition advice was also provided.

Interventions of this nature will be discussed on a case by case basis to identify if there is any viable data which can be included within the defined primary outcomes. If there is too much uncertainty over attributing causality studies will not be included in any analyses, but may be discussed as part of the narrative synthesis.

7. Line 2277-278 - I don't understand what this line means in regards to the intervention. Clarification is needed - This could be through either prevention, reduction or treatment as a standalone or adjunct treatment.

This line has been adjusted.

8. Outcomes section: The primary outcomes for prevention, harm reduction and treatment includes variable that would seem to be secondary outcomes based on the primary aim of preventing/reducing/stopping alcohol and drug use. For example mental health and wellbeing, biomedical outcomes, service users' experience and perceived utility (I'm not sure how you would measure this or what it is) of PA, physical levels/fitness should be secondary outcomes. Then some of the primary outcomes are repeated in the secondary outcomes. This section needs to be much clearer.

This section has been reworked in light of this comment to more clearly reflect distinct primary outcomes relating to the three domains.

9. Line 317 'We will select an appropriate representative measure for each domain where possible.' - What does this mean?
10. Why are you searching MEDLINE ovid and pubmed? This seems excessive.


11. It is not clear whether two review authors will be reviewing full texts (line 397-399). This needs to be clarified. If two review authors aren't reviewing full text articles this needs to justified as it is completed to reduce individual screening bias. How will you account for this bias?

12. Will you be using the ROBINS-I for all non-RCT studies including ecological cross-sectional studies? This needs to be made clearer.

Two review authors will be reviewing each full-text. The text was slightly confusing, and we have amended to now read: “Full texts will be obtained for studies appearing to meet the criteria above, and screened by two reviewers (each paper reviewed by one member of the team and checked by another).”

Cross sectional studies have been removed from the review.

13. Are you planning on doing a meta-analysis for all research designs? The protocol implies that you will be. Further information needs to be provided for all the research designs and how you will be completing the meta-analysis using these designs.

We will not combine studies which used different designs. As stated in line 494-496 and lines 505-508, we will conduct meta-analysis for studies which have the similar design, and we will not combine data from RCT and non-randomised studies, and do not combine non-randomised studies which used different designs.

14. What qualitative method will you be using eg thematic analysis, content analysis?

A thematic analysis approach will be used. Additional information has been added.
15. Section narrative synthesis (analysis 3): What is the aim of the narrative synthesis? What will this achieve? Aims for the narrative synthesis have been more clearly defined throughout.

16. Line 464: Would the economic evaluation also be an analysis Eg (analysis 4)?

Thank you for this observation, the aims and subsequent analysis have been redrafted throughout to reflect this more consistently. Information has been added describing this approach.

17. Measures of intervention - what happens when there is more than one intervention group? How will you deal with this?

Studies which report outcomes separately for groups which meet the criteria for physical activity will be included. Studies where data are not available for meta-analysis will be used to inform the narrative synthesis.

18. Advisory groups - this reads that it will happen but the protocol is being published now. For instance the 'The service user group will offer input into what outcomes we should be searching for'. Have they already? If they haven't this needs to be revised as will as other parts in the section e.g methods and scope for the academic group. This section needs to reflect what has been done and what will be done.

Sections have been revised accordingly.

Minor issues:

Line 219-221: this would be better placed in the population section - The broad scope of the proposed work covers inclusion of patients, service users, and those who may be neither, so the term 'people' or 'individuals' is used to represent the broad range of participants who may be included in studies forming part of the review.

Line 223-225 - this would be better placed in the intervention section - The scope of this review is to include research on alcohol and substance use in its broadest sense. We plan to include data on alcohol and substance use which may not be considered a 'disorder' which reflects levels and prevalence of use, as well as including research on AUD and SUD as classified in the DSM-V[43].
Line 77: Revise sentence: 'We aim to assess how what we know can be translated into policy and practice with the input of key stakeholders throughout.'

Line 109 - 113: The Cochrane Drug and Alcohol Group has published 11 and 30 reviews of pharmacological interventions for alcohol and substance use, respectively, whilst psychosocial interventions (e.g. brief interventions and motivational interviewing) are less well reported, with six and eight published reviews, respectively. Preventive interventions only have five reviews for alcohol use, and three reviews for substance use.

The two sentences above need to be referenced.

Line 127-128: In 2001 (with updates in 2005 and 2008), AT (with co-researchers), reviewed and reported the effects of exercise on smoking from eight randomised controlled trials (RCTs) as part of a Cochrane Review. Needs referencing

This line has been removed.

These lines have been moved to the intervention section.

This sentence has been revised.

Reference added.
Reviewer #3: Authors have well prepared the review protocol, however, the clarity on the following points would add more value to this review:

Comment: Response:

1. It is not clear about the selection of the report from health surveys conducted at regional/national level by any country related to the alcohol & addiction for a given time-period.

   Unsure of the meaning of this comment, apologies.

2. Authors need to specify their strategy about the estimation & re-estimation cross-sectional studies.

   Cross sectional studies have been removed from the protocol.

3. I suppose authors missed to report PROSPERO registration in the methodology section. Please add at appropriate place.

   PROSPERO registration will be completed following successful peer review.

4. Kindly also mention that how many times reviewer would contact to the author to seek specific information if required in a study.

   Added.

5. Please also add that what proportion of the literature will be used to check the inter-rater agreement and what will be the minimum cut-off for that agreement.

   Inter rater agreement will not be checked. An iterative approach is being implemented to ensure consistent screening rather than end up with poor inter-rater agreement.

6. It is also possible that some of the studies report standard error or 95% CI for mean instead of standard deviation. So, it is not clear that it'd be considered as missing data or it'd imputed by some appropriate methodology.

   If standard errors are reported instead of standard deviation, we will convert the standard errors into standard deviations. Similarly, we will calculate effect measure and its standard deviation if they are not reported but the 95% CI is reported.
7. Please add reference(s) to the 'Assessment of statistical heterogeneity' section and also define the levels of heterogeneity considerations. We have now added the references to this section. We have now also defined the level of heterogeneity as suggested.

Reviewer #4: This paper appropriately fits the scope of Systematic Reviews as the authors describe a systematic review of physical activity interventions targeting the prevention, reduction and treatment of alcohol and substance use incorporating both quantitative and qualitative studies. In review the protocol, this appears to be an extremely large undertaking; akin to a best evidence synthesis of the literature. Overall, the authors provide sound rationale for this study, which will be an important contribution to the field.

Areas in need of clarification:

Comment: Response:

Line 187 - Impact of stakeholder Engagement: Involving stakeholders in this systematic review process is of importance. However, it would be useful to readers if the mechanism by which this will happen is further explained in more detail in this section. Having read the entire protocol, the authors should consider moving pertinent sections of the discussion section that further describe the specifics of such engagement - back to this section when 'stakeholder engagement' is first introduced. The level of detailed provided in the current discussion section on specific organization and names of those involved as stakeholders may be better suited in an appendix, with a summary description of the process and types of agencies/key stakeholder positions mentioned in the article.

Thank you for this feedback, changes have been made in line with your suggestions.

Line 354 - Search strategy: has consideration been given to having the main search strategies peer reviewed (PRESSED)?

Thank you for this suggestion. This has now been completed by a qualified information specialist.

Line 382 - Data management: given the potential screening and extraction volume, has the study team given consideration to the use of an online collaborative systematic review software system (beyond EndNote and bespoke extraction forms)? This would be a potential time saver in terms of project management in real time, and creating efficiency in screening (one could do liberal accelerated screening at titles and abstracts - 1 to include but 2 to exclude) in terms of collating conflicts automatically. It would facilitate data extractions, data mining and report generation;
filtering studies by type and whether AUD and/or SUD related. DistillerSR and Eppi Reviewer are two main products that come to mind but there are others available.

Thank you for this suggestion. We have implemented the use of the Rayyan software (QCRI) to support the screening process. Protocol updated to include this information.

Line 400-401: RK will be consulted in relation to economic evaluations - does this mean that economic papers will be reviewed by two persons or just one?

Two reviewers will screen for economic evaluations, and RK will be consulted over any uncertainty. This line has been amended to more clearly reflect this.

Line 574 - DISCUSSION - Stakeholder Involvement and Public and Patient Involvement (PPI) - the suggestion to the authors is to move much of the specifics provided below (Lines 575-596; and Lines 601-615) to the previous section "Impact of Stakeholder Engagement" - see above comment. This will then address 'how' the engagement will take place, and with which types of organizations.

The discussion section has been rewritten, and the existing sections edited and moved into other sections of the protocol. Authors thank you for this suggestion.

One suggestion is for the authors to take Lines 596-598 and make this the first sentence under this discussion section, and from there describe how service provider and user perspectives have influenced the application (providing a high-level overview of what has already been described in the protocol). This should be referenced as a general strength of the protocol. In the discussion section authors should also point out other strengths, and challenges of this review, and emphasize intended impact/implications of this work to round out this section.

Similar to the previous comment, this section has been rewritten.