Author's response to reviews

Title: Predicting OptimaL cAncer Rehabllitation and Supportive care (POLARIS); Rationale and design for meta-analyses of individual patient data of randomized controlled trials evaluating the effect of physical activity and psychosocial interventions on health-related quality of life in cancer survivors.

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Author's response to reviews: see over
We would like to thank the editor and reviewer for thoroughly critiquing our manuscript and for the suggestions to improve our paper. Please find our point-to-point response to the reviewer’s comments below. We hope that we have successfully improved our manuscript according to the reviewer’s suggestions and that you will consider a publication in Systematic Reviews.

1. **The description of moderators and mediators may be confusing for readers (page 5).** As currently written, it is not entirely clear what the difference between moderators and mediators is. I think this can be easily remedied by modifying the language in these two paragraphs. For example, clarify that moderating factors are factors present at baseline that may impact responsiveness to an intervention, but are not changed by the intervention. On the other hand, mediating factors (as I understand it) are those factors that the intervention changes and, by changing these factors, impacts the outcome of interest. In your examples, then, physical activity might improve HRQoL by reducing fatigue (or by reducing psychological distress).

Treatment moderators identify for whom and under what circumstances treatments have their effects. They can help identify subgroups of patients that are most responsive to treatment and subgroups of patients that are not responsive to treatment, and need more appropriate treatments. Treatment mediators identify why and how a treatment might achieve its effects. These mechanisms are causal links between treatment and outcome. Identification of mediators can help identify critical intervention components. By subsequently targeting these critical intervention components, efficacy and efficiency of interventions may improve. In the revised version of the manuscript, we explained moderators and mediators more clearly by adding: “Moderators identify which (subgroups of) patients are most responsive to the intervention, and which are not responsive...”, and “Mediators are causal links between the intervention and the outcome and identify how an intervention might achieve its effects.”

2. **I’m not sure I understand the difference between physical activity and exercise interventions - please clarify.**

Physical activity has been defined as any bodily movement produced by skeletal muscles that results in energy expenditure. Exercise is a form of physical activity that is planned, structured and repetitive and aims to improve fitness, performance or health (Caspersen et al. 1985, Publ Health Rep 100; 126-131). Since physical activity also includes exercise, we used the term physical activity interventions in the revised version of the manuscript. In the method section, we have added the definition of exercise (page 7): “i.e. form of physical activity that is planned, structured and repetitive and aims to improve fitness, performance or health.”

3. **page 7 - inclusion criteria - how did you arrive at these exclusions? How is mindfulness different from a coping skill?**
Cunningham (Support Care Cancer 1995) described five broad types of psychosocial interventions for cancer survivors: providing information, support, coping skills training (e.g. cognitive behavioural therapy), psychotherapy, and spiritual/existential therapy (including also meditation). To reduce the heterogeneity among interventions to be included, we chose to focus on the first four categories in this wave of data collection. Therefore, we excluded interventions focusing on spiritual or existential therapy including meditation and mindfulness.

Cunningham defined coping skills training as structured psychoeducation groups including cognitive behavioural therapy. Spiritual/existential therapy is defined as a category of psychosocial intervention that includes the main features of the other four categories, but with a spiritual or existential component. We agree with the reviewer that there are similarities between a coping skill and mindfulness. However, mindfulness also contains a meditation component, and therefore it is categorized into the 5th category. We acknowledge the importance of mindfulness training among cancer survivors, and perhaps in the future, we will extend our database with additional types of interventions including spiritual/existential therapy, yoga, pain management, and multimodal lifestyle interventions in a second wave of data collection. We have explained this more clearly in the revised version of the manuscript: “Although we acknowledge the importance, we will initially exclude studies focusing on spiritual or existential therapy, including meditation and mindfulness, in order to reduce the heterogeneity among the interventions to be included. We also excluded studies focusing on yoga, pain management, diet or multimodal lifestyle interventions (e.g., physical activity and diet combined).” (page 7).

4. page 11 - statistical analysis - it seems that there might be important “clustering” effects from study to study - ie - there are similarities among patients within a given study based on site/treatment team characteristics. How do you account for these effects?

We agree with the reviewer that clustering effects from study to study are present and that they should be accounted for in the statistical analyses. We will conduct one-stage IPD meta-analyses to evaluate the effects of physical activity and psychosocial interventions on HRQoL compared with wait-list, usual care or attention control group. Clustering effects will be accounted for by the multilevel regression analysis, in which we will define patients within each trial as level 1 and the trial as level 2. In the revised manuscript, we have now explicitly mentioned that we take clustering effects into account by using multilevel regression analysis: “Clustering effects from study to study will be taken into account by using multilevel regression analyses with a two-level hierarchical structure: the patients within each trial as level 1 and the trial as level 2.” (page 11).

5. predictive model - will there be different models for each different intervention type? It seems that the type of model constructed would depend on the question being asked and the end user needs. For example, one might want to know given a patient with characteristic (metastatic cancer or elderly), what type of intervention might work best. Or, people designing and implementing interventions might want to understand the implementation characteristics that are associated with success. It
would be helpful to more clearly identify the potential uses of such models and whether or not you will be designing different models based on intervention type.

The reviewer correctly understood that the type of model depends on the research question being asked. First, we will conduct moderation analysis to identify which (subgroups of) patients are most likely to benefit from each type of intervention (as described under the heading moderators, page 11 and 12). Second, for each type of intervention, we aim to identify predictors of intervention success (improvement in HRQoL). Relevant moderators will be taken into account when building the prediction model. Third, important predictors of intervention success will be used to build one clinical prediction model. This model will able to select which type of intervention has the highest probability of success for specific (subgroups of) patients. The first two steps provide insight into for whom and which subgroups are most likely to benefit from a certain intervention. The third step will support with choosing the most successful intervention for an individual patient.

In the revised version of the manuscript, we have now made this more clearly by adding the following information: "For each type of intervention, we will build prediction models identifying predictors of intervention success (i.e. improvement in HRQoL), using multivariable backward logistic regression analyses on pooled data.” and: “In addition, we will build a clinical prediction model to select the most successful intervention to improve HRQoL for (subgroups of) patients.....” (page 12).

6. page 15 - you identify lack of willingness to participate as a potential issue. Even if the results are not biased by non-participation, high rates of non-participation will threaten the ability to carry out many of the analyses you propose simply from lack of power. It would also threaten the generalizability of results. Please describe any incentives you have in place to mitigate this issue, or any plans for repeated contact etc to help decrease non-response. As the methods are currently written, it sounds like there will simply be an e-mail sent out to PIs - as we all know, it is incredibly easy to ignore e-mails and I am concerned that non-response could be a very real issue without a clear plan in place to reduce this risk.

We agree with the reviewer that high rates of non-participation will threaten the power and generalizability of results. To minimize non-response, we will send reminders via e-mail, and will contact principle investigators by telephone. If necessary, another (principle) investigator involved in the project will be contacted. We have added this information to the revised version of the manuscript: “The POLARIS Steering Committee will send a letter of invitation to join the POLARIS consortium to the principal investigator of each study that is eligible for the POLARIS database. This (e)mail contains a short introduction to POLARIS, including the aim and inclusion criteria, and a short description of the POLARIS policy and procedures. Reminders will be send to principal investigators who do not respond to the first letter of invitation, and telephone contact will be sought. If necessary, another (principle) investigator involved in the project will be contacted.” (page 9).