Author's response to reviews

Title: Psychosocial interventions for children exposed to traumatic events in low and middle income countries: study protocol of an individual patient data meta-analysis

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Author's response to reviews: see over
Dear Sir,

Many thanks for providing us with feedback on Ms. 2073874055114845. “Psychosocial interventions in children exposed to traumatic events in low and middle income countries: an individual patient data meta-analysis”.

We have taken the Reviewer’s comments into careful consideration, and the paper has been revised accordingly. Please find below our response to each item raised by the Reviewer.

We hope that the revised version of our work may now be suitable for publication in the Systematic Reviews journal.

Looking forward to hearing from you,

Best regards,

Marianna Purgato
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Reviewer comments:

Registration of the protocol
• The authors are requested to register this protocol with PROSPERO (i.e., international register of systematic review protocols).

Authors response: The protocol is registered in PROSPERO. We added this information together with the registration number at the end of the abstract (as requested by the editor).

Background
Page 4
• What do you mean by ‘complex’ results/findings? Does it mean ‘inconsistent’?

Authors response: Complex is intended as inconsistent and heterogeneous.

Study objective - hypothesis
Pages 6-7
• The authors state the following and provide two hypotheses: “In order to examine whether clinical and socio-demographic characteristics, trauma exposure related variables, environmental conditions and social support may act as moderators and mediators of intervention effect, an IPD-MA will be carried out.”

Hypothesis 1. Psychosocial preventive interventions will be moderated by individual variables (for example gender, age, displacement status, exposure to traumatic events).
Hypothesis 2. Psychosocial preventive interventions will be mediated by social support (for example household size, family connectedness) and coping methods.
In order to test these hypotheses, there must be a clear understanding and prior evidence (or causal models) as to which variable/covariate is moderator, mediator, and confounder (i.e., these factors should be distinguished). This will bear on data analysis because addressing effect moderators, mediators, and confounders requires different statistical approaches. Here I list them with my definitions: Moderator = effect modifier/interaction the level of which modifies the effect size (or direction) Mediator = extraneous variable which explains (partially, totally?) the association between exposure and outcome; lies in a causal pathway between exposure and outcome Confounder = extraneous variable which distorts the association between exposure and outcome; does not lie in a causal pathway between exposure and outcome.

Authors response: thanks for this comment and for providing us with the definitions. In order to guarantee a clear understanding of these crucial concepts, we added the definitions of moderators and mediators next to the hypotheses in the “Objective” paragraph. Moreover, we provided details on the statistical approaches we will use to manage these aspects in “Data analysis” paragraph (please, see our response to the penultimate point below).

Methods – types of studies
Page 7
• PRISMA is a reporting guideline for systematic reviews/meta-analyses, it does not guide as how to identify studies; please revise the sentence accordingly.

Authors response: OK, we revised the sentence as follows: “The study selection process will be reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines”.

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Methods – search methods for identification of studies
Page 9
• Please, provide the search strategy used by Tol and colleagues updated according to your needs in the appendix of this protocol.

Authors response: This is a good point, but we have not updated the search strategy yet as the review process is at a very early stage. We will provide the readers with details on the search strategy in the next publications of this work.

• I disagree that searches in Medline, Embase, PsycInfo and PILOTS be supplementary, instead these databases along with CENTRAL need to be main electronic sources to be searched, supplemented by other searches.

Authors response: OK, we slightly modified this sentence in order to make clear that these sources (Medline, Embase, PsycInfo, PILOTS and CENTRAL) will be searched as well as the Cochrane registers.

• Will the authors seek additional info via relevant specialist websites and references of potentially relevant papers?

Authors response: Yes, we made clear that we will search these sources as well.

Methods – study selection
Page 9
• Will the authors screen studies in two stages: abstract/title first and then full text levels?

Authors response: Yes. We better explained this two stages-approach in the “Study selection” paragraph, as follows: “Material downloaded from electronic sources will include details of author, institution or journal of publication. As initial step, on the basis of titles and abstracts two reviewers (MP and WT) working independently will select potentially relevant studies. Studies rated as possible candidates by either of the two review authors will be added to a preliminary list and their full texts will be retrieved”.

Methods – Data collection, transfer, and management
Page 10
• Please, add this section (‘Data collection, transfer, and management’) following the ‘study selection’ section.

Authors response: OK, thanks, we added this section.

• The following sentence found in ‘study selection’ section (“Principal investigators will be asked to contribute to the IPD-MA with the original datasets”) belongs in ‘Data collection, transfer, and management’ section.

Authors response: We moved this sentence in the “Data collection, transfer, and management” paragraph.

• Describe briefly the IPD data which will be requested (e.g., study info, study level info, individual level info), its acquisition process as well as its storage, and management (software, security, data accuracy and validation). Some of this info is already in ‘data management’ section; please, move this info here in this Section.
Authors response: OK. We moved the contents of 'Data management' paragraph in this section and added more details on the IPD data which will be requested, the acquisition process, the storage and the management.

Authors response: Authors response: Yes, we will. We've added this information in the paragraph "Data collection, transfer, and management".

Methods

- Change the title to 'assessment of risk of bias' Authors response: OK, done.
- Replace 'quality' with 'risk of bias' Authors response: OK, done.

Methods – Study materials, study level information, individual level information

Pages 10-11
- The info in these three sections should be moved to 'data extraction' section (needs to be created) which should precede 'assessment of risk of bias' section.

Methods – Data analysis

- This section should include and integrate info from these sections: statistical analysis, 'strategies for data analysis', and subgroup analysis.
- Authors response: OK, we created a paragraph entitled "Data analysis" integrating the previous three paragraphs.
- Authors response: Yes, we will explore the presence of selective outcome reporting for each included study using the Cochrane risk of bias tool. We mentioned the "selective reporting" bias in the "Assessment of risk of bias" paragraph.
- Authors response: Yes. We added in the "data analysis" paragraph the following sentence: "Data from included studies will be entered into a funnel plot. Funnel plot will be visually inspected in order to detect the presence of publication bias (Higgins 2011)."

Authors response: Yes, we will assess impact of publication bias on their meta-analytic estimates. We mentioned the "funnel plot" in the "Assessment of risk of bias" paragraph.

• Will the authors plan to determine the presence of selective outcome reporting given the IPD of included RCTs? Authors response: Yes.

• Will the authors report for how many of the included studies there are missing IPD (i.e., what proportion of requested trials give their IPD)? Info on what are the reasons? Authors response: Yes. We added the "assessment of risk of bias" paragraph the following sentence: "Data from included studies will be entered into a funnel plot. Funnel plot will be visually inspected in order to detect the presence of publication bias (Higgins 2011)."
We will describe the analysis of included studies, the number of studies contributing with data to the IPD meta-analysis, and the types of outcomes provided by each study. The number of excluded studies together with the reasons for exclusion will be also reported (following the PRISMA statement).

- Will the impact of studies lacking IPD be investigated through sensitivity analysis?

Authors response: yes, we specified this at the end of the “Data analysis” paragraph (before listing subgroup analyses).

- Will the authors conduct meta-regression techniques to account for clustering effects in their IPD meta-analysis?

Authors response: This has not been planned as we expect that only cluster trials will be included.

The authors do not mention what analytic approaches they will use to test their hypotheses on moderators and mediators. Will they define and distinguish their moderators, mediators, and confounders a priori as well as during their analyses (e.g., meta-regression techniques)? As it is known, addressing effect moderators, mediators, and confounders through a meta-regression technique requires different statistical approaches. For example, moderators need to be accounted using interaction terms (with exposure), adjustment for confounders (their inclusion as covariates), and mediators since they lie on causal pathway (unlike confounders), they should not be included in the regression equation.

Authors response: thanks for this comment. We added a description of the analytic approaches we will use in the “Data analysis” paragraph (page 14), as follows: “We will adjust for confounding variables in regression models of outcomes on predictors. We will select potentially confounding variables using a priori assumptions and exploratory data analysis. We will analyze mediation using structural equations modeling to implement a one-step procedure that simultaneously models relationships between exposure and mediator, mediator and outcome, and exposure and outcome (MacKinnon et al, 2008). The test of mediation will be based on a test of the distribution of the product of z-scores for the associations between the exposure and mediator and the mediator and outcome (MacKinnon et al., 1998); this approach has been demonstrated in simulation studies to have superior power than other approaches for our particular case (MacKinnon et al., 2002). Potential effect modification will be examined by including terms for exposure, suspected moderator, and the interaction between the two and testing the significance of the interaction”.

Discussion

- Please add this section where you would describe main findings, limitations and strengths (of evidence and your IPD meta-analysis), consistency of your findings with those of other systematic reviews/meta-analyses, research and policy implications, future recommendations.

Authors response: OK, we agree with your request. We added the “Discussion” section at the end of the protocol, as follows: “This systematic review and IPD meta-analysis will focus on the effects of preventive psychosocial interventions for children exposed to traumatic events in LMIC. Some variables, like socio-demographic characteristics, trauma-related variables, environmental conditions and social support have been suggested to act as moderators/mediators of intervention effect, but no formal evaluation has been conducted on this topic so far. Likely, the results of this study may shed light in the field of preventive psychosocial interventions, helping generate a better understanding of this complex field.”

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understanding of the reasons why some children benefit from some interventions more than others. This will in turn facilitate a better matching of interventions with individual and contextual factors in this field". 