PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Outcomes reported in randomized controlled trials of major depressive disorder treatments in adolescents: a systematic scoping review protocol
AUTHORS	Monsour, Andrea; Mew, Emma J; Szatmari, Peter; Patel, Sagar; Saeed, Leena; Offringa, Martin; Butcher, Nancy

VERSION 1 – REVIEW

REVIEWER	Brett Thombs McGill University and Jewish General Hospital Canada
REVIEW RETURNED	28-May-2018

GENERAL COMMENTS	The protocol describes the methods that will be used to conduct a scoping review on outcomes used in treatment trials for adolescent depression. This is an important topic and there is a high likelihood that the proposed research will generate valuable results that lead to an increased rigor in trials research in the field. The protocol is clearly written and well-justified. Comments address areas where clarification would be useful. (1) The authors indicate that eligible trial reports are trials to treat major depressive disorder (MDD) defined based on the DSM. They should also include treatment for major depression as assessed using ICD. Additionally, they should explicitly define requirements for this to be a valid diagnosis. Will they require a validated diagnosis interview? Only clinician diagnosis? This should be clarified. (2) The authors indicate that they will include pilot and feasibility studies. Outcomes for these are often process-related (e.g., resource requirements, acceptability of interventions). Are they planning on including these outcomes? Or do they need to specify that they are including only outcomes related to health status? This should be clarified. (3) Ideally the database search strategy would be peer-reviewed, and PRESS is an option for this. If this is not done, it should be noted as a limitation. (4) The authors should indicate where they are in the process of conducting the review and provide dates (either past if started or anticipated if not).

	(5) In the PICOT, the "T" is intended for the timing of outcome assessments in the course of an included trial. It is not intended for when trials were published as used in the protocol. The authors should clarify the timing of outcomes in each trial that they will include. The publication dates of eligible trials should be listed separately in the inclusion/exclusion section. (6) It is common in title/abstract review that if either reviewer deems a citation potentially eligible for inclusion, the citation moves to full-text review without arbitration at the title and abstract stage. The authors are encouraged to consider using this model as reviewers at the title/abstract level don't have full information and if either reviewer believes the citation might be eligible, there is good reason to review the full text.

REVIEWER	Peng Xie Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
REVIEW RETURNED	15-Jul-2018

GENERAL COMMENTS	This is a scoping review protocol that focused on outcome reporting heterogeneity in randomized controlled trials of MDD treatments in adolescents. This is an interesting and meaningful topic. However the current form of this paper is so brief and vague that I do not understand why it needs to be published. Major Comments: 1. Why the authors only included studies for MDD in adolescents? In my previous studies, I found that many RCTs concurrently included children (6-12y) and adolescents (13-18y). 2. I think the author should generally review the current trial outcomes measurement, including the number, range, and reliability.ect. 3. The rational of core outcomes sets (COS), and how to complete and develop it, should be fully described. 4. A large numbers of studies used K-SADS or ICD as diagnostic criteria for adolescents MDD. How the authors deal with these studies? 5. I think embase and web of science are also important databases that should be considered to search. In addition, it is better to search some trial registers websites, such as clinicaltrials.gov and the International Clinical Trials Registry Platform (ICTRP) in the WHO.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Brett Thombs
Institution and Country: McGill University and Jewish General Hospital Canada
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
The protocol describes the methods that will be used to conduct a scoping review on outcomes used in treatment trials for adolescent depression. This is an important topic and there is a high likelihood

that the proposed research will generate valuable results that lead to an increased rigor in trials research in the field. The protocol is clearly written and well-justified. Comments address areas where clarification would be useful.

(1) The authors indicate that eligible trial reports are trials to treat major depressive disorder (MDD) defined based on the DSM. They should also include treatment for major depression as assessed using ICD. Additionally, they should explicitly define requirements for this to be a valid diagnosis. Will they require a validated diagnosis interview? Only clinician diagnosis? This should be clarified.

We have now specified that trial eligibility includes those where diagnoses were made using ICD criteria, as well as DSM criteria, using a validated diagnostic interview and/or a clinical diagnosis based on these criteria (see "Population" under "Eligibility criteria" in the Methods and Analysis section).

(2) The authors indicate that they will include pilot and feasibility studies. Outcomes for these are often process-related (e.g., resource requirements, acceptability of interventions). Are they planning on including these outcomes? Or do they need to specify that they are including only outcomes related to health status? This should be clarified.

We have now provided a more detailed explanation of the types of outcomes to be included in this review, which includes planned health status outcomes as well as resource use (e.g., number of outpatient appointments, impact on family finances) and delivery of care outcomes (e.g., acceptability of intervention, treatment adherence); these are recommended for consideration for inclusion in COS and a citation that elaborates on these types of outcomes with respect to COS has been provided (see "Outcomes" under "Eligibility criteria" in the Methods and Analysis section).

(3) Ideally the database search strategy would be peer-reviewed, and PRESS is an option for this. If this is not done, it should be noted as a limitation.

We have now provided additional information on the development process of the database search strategy, including review of the search using PRESS (see "Information sources and search strategy" in the Methods and Analysis section).

(4) The authors should indicate where they are in the process of conducting the review and provide dates (either past if started or anticipated if not).

The review dates and the review progress to date have been added (see "Protocol" in the Methods and Analysis section).

(5) In the PICOT, the "T" is intended for the timing of outcome assessments in the course of an included trial. It is not intended for when trials were published as used in the protocol. The authors should clarify the timing of outcomes in each trial that they will include. The publication dates of eligible trials should be listed separately in the inclusion/exclusion section.

For simplicity, the "T" in the PICOT has been removed as there are no relevant timing restrictions to be described. We have clarified in the text that there will be no restrictions on when the outcomes were measured or duration of follow-up after initiation of the intervention as are interested in the diversity of timing of outcomes in RCTs (see last paragraph under "Eligibility criteria" in the Methods and Analysis section). As suggested, the publication dates of eligible trials are now described elsewhere (see last paragraph under "Eligibility criteria" in the Methods and Analysis section).

(6) It is common in title/abstract review that if either reviewer deems a citation potentially eligible for inclusion, the citation moves to full-text review without arbitration at the title and abstract stage. The authors are encouraged to consider using this model as reviewers at the title/abstract level don't have full information and if either reviewer believes the citation might be eligible, there is good reason to review the full text.

We have clarified our approach for title/abstract screening; all discrepancies identified will be reviewed by a third reviewer, so that clarifications with respect to study eligibility can be made as needed and any obviously irrelevant reports can be removed. Studies included by both reviewers and those with unresolved discrepant decisions will move to full-text screening (see "Initial Screening" under "Source selection" in the Methods and Analysis section). In our experience this helps optimize the quality of title/abstract screening by providing ongoing feedback/clarification with respect to study eligibility while minimizing the number of false positives moving forward to full-text screening.

Reviewer: 2

Reviewer Name: Peng Xie
Institution and Country: Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
This is a scoping review protocol that focused on outcome reporting heterogeneity in randomized controlled trials of MDD treatments in adolescents. This is an interesting and meaningful topic. However the current form of this paper is so brief and vague that I do not understand why it needs to be published.

Thank you. The a priori preparation and dissemination of a scoping review protocol fosters research transparency, accountability, limits the occurrence of reporting bias, and helps reduce research waste. There is general agreement on this and it follows best-practices from the Joanna Briggs Institute for scoping review methodology (Joanna Briggs Institute Reviewers' Manual: 2015 edition).

Additional rationale and methodological details on why this work needs to be published have been included in the revised protocol. With respect to length and depth, we note that this protocol contains all details recommended for reporting by the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Protocols) reporting guideline (see online supplementary appendix A) and is similar in these respects to other scoping review protocols recently published in BMJ Open (e.g., Tricco AC, Zarin W, Lillie E, et al., BMJ Open 2017;7:e013474; Glonti K, Cauchi D, Cobo E, et al. BMJ Open 2017;7:e017468).

Major Comments:
1. Why the authors only included studies for MDD in adolescents? In my previous studies, I found that many RCTs concurrently included children (6-12y) and adolescents (13-18y).

This is a vast field of research. As you know, childhood depression as compared with adolescent depression (and adult depression) may present with different signs and symptoms, require different interventions, and have different short and long-term outcomes. The adolescent group has specific and unique challenges, and there is general agreement that measurement of outcomes and the tools chosen should be developmentally sensitive. Thus it would not be surprising to find wide divergence between the outcomes measured, and the tools used to measure them, between the two age groups. We have limited the scope of the COS, and therefore this review, to adolescents for these reasons. In the Discussion, we now highlight the need for work in the area of developing a COS for childhood depression and cite ongoing work to develop an adult depression COS (see second paragraph under "Implications").

As mentioned, many published RCTs nevertheless concurrently include children and adolescents. We have now described how we handle this with respect to study eligibility (see "Eligibility criteria" in the Methods and Analysis section).

2. I think the author should generally review the current trial outcomes measurement, including the number, range, and reliability.ect.

We agree. As described in the second paragraph of "Data charting" as well as under "Synthesis of results" in the Methods and Analyses section, data on the outcome measurement instruments will be collected and reported. Reliability, validity etc. are important concepts that will require systematic assessment in future studies; this is part of recommended separate methods when selecting the outcome measurement instruments to be used to measure each outcome that ends up in the final core outcome set, once the list of outcomes in the COS is identified (see Introduction, second paragraph for revised text and references addressing the later evaluation of outcome measurement instruments).

3. The rational of core outcomes sets (COS), and how to complete and develop it, should be fully described.

Additional text on the rationale and key references pertaining to COS has been added to the Introduction. As described in the first paragraph of the Discussion, specific methods outlining the development of our COS for adolescent MDD will be published separately.

4. A large numbers of studies used K-SADS or ICD as diagnostic criteria for adolescents MDD. How the authors deal with these studies?

Indeed, studies using these diagnostic criteria will be included. This is now clarified (see "Population (P) under "Eligibility criteria" in the Methods and Analysis section).

5. I think embase and web of science are also important databases that should be considered to search. In addition, it is better to search some trial registers websites, such as clinicaltrials.gov and the International Clinical Trials Registry Platform (ICTRP) in the WHO.
We agree that these are useful sources that have the potential to yield eligible studies. We worked closely with experienced research librarians and a MDD content expert to ensure that the selected databases would encompass the necessary eligible studies to reach saturation of reported outcomes in completed RCTs, as is appropriate for a scoping review design. As the focus is on outcomes measured in completed RCTs, trial registries were not searched. We have now provided additional details with respect to how the information sources and search strategy were developed (see "Information source and search strategy" in the Methods and Analysis section). To help reduce the risk of omitting any eligible trials, a disease expert will review the final list of included studies and any additional RCTs identified by the disease expert meeting study eligibility criteria will also be included (see "Full-text screening" under "Source selection" in the Methods and Analysis section).

Related to the point that not all trials, and therefore not all outcomes, may be identified in this review, we have provided new text to describe that additional outcomes for consideration for inclusion in the subsequent COS may also be identified during later stages of the COS development process during the stakeholder engagement process (see "Implications", first paragraph, in the Discussion section).

VERSION 2 – REVIEW

REVIEWER	Brett Thombs McGill University
REVIEW RETURNED	21-Sep-2018

GENERAL COMMENTS	The authors have addressed my previous comments.

REVIEWER	Peng Xie Chongqing Medical University, Chongqing, China
REVIEW RETURNED	28-Sep-2018

GENERAL COMMENTS	Largely Improved. I have no further comments.