

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.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Psychosocial treatments for relapse prevention in schizophrenia: study protocol for a systematic review and network meta-analysis of randomized evidence
AUTHORS	Bighelli, Irene; Rodolico, Alessandro; Pitschel-Walz, Gabi; Hansen, Wulf-Peter; Barbui, Corrado; Furukawa, Toshi; Salanti, Georgia; Leucht, Stefan

VERSION 1 - REVIEW

REVIEWER	Jac Dinnes University of Birmingham, UK
REVIEW RETURNED	08-Nov-2019

GENERAL COMMENTS	<p>Thank you for you the opportunity to review this protocol which comprehensively outlines the planned methods for a systematic review and network meta-analysis to compare psychosocial interventions for prevention of relapse in people with schizophrenia. The methods are sound and well set out, as is the planned analytic approach. The inclusion only of RCTs with similar inclusion criteria should provide a strong network on which to base results and the authors clearly outline the approaches that will be taken to check the transitivity assumption and consistency of results. The protocol adheres to PRISMA-P and also covers items in the PRISMA NMA checklist. My only small suggestion is to include the time period to be covered by the search. There are one or two places where the written English could be improved but it is perfectly readable as it is.</p> <p>I am not a topic expert but I would imagine that, once published, the review will provide a valuable contribution to the field.</p>
-------------------------	---

REVIEWER	Pere Castellvi Department of Medicine, Universitat Internacional de Catalunya (UIC). Spain
REVIEW RETURNED	22-Nov-2019

GENERAL COMMENTS	<p>Comments to the author</p> <p>This manuscript describes a protocol about which psychosocial treatments are more effective for relapse prevention in schizophrenia using a network meta-analysis. This paper tries to answer a big issue for preventing schizophrenia relapse. It is well</p>
-------------------------	---

	<p>written, methodologically rigorous, and of interest to the field. Only few comments have been raised after reading:</p> <ol style="list-style-type: none"> 1. I would add other efficacy measures in Objectives. For assessing clinical severity, I would add “days of hospitalization” using means and standard deviation 2. In Criteria for considering studies for this review subsection, a rationale in which studies that randomized by date of birth or day of the week are excluded is needed. 3. This manuscript will not only include participants with a diagnosis of schizophrenia, but also schizophreniform and schizoaffective disorders. However, these disorders are not included as search terms. 4. There is no estimate of when the review begins 5. I would consider other variables to include in the sensitivity analyses: a) the length of the therapy, b) brief vs standard versions of psychosocial treatments; c) Single psychosocial therapy vs. multicomponent therapies, and d) time of follow-up as authors reported at page 6, paragraph 5
--	--

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Jac Dinnes

Institution and Country: University of Birmingham, UK Please state any competing interests or state ‘None declared’: None declared

Thank you for you the opportunity to review this protocol which comprehensively outlines the planned methods for a systematic review and network meta-analysis to compare psychosocial interventions for prevention of relapse in people with schizophrenia. The methods are sound and well set out, as is the planned analytic approach. The inclusion only of RCTs with similar inclusion criteria should provide a strong network on which to base results and the authors clearly outline the approaches that will be taken to check the transitivity assumption and consistency of results. The protocol adheres to PRISMA-P and also covers items in the PRISMA NMA checklist. My only small suggestion is to include the time period to be covered by the search. There are one or two places where the written English could be improved but it is perfectly readable as it is.

I am not a topic expert but I would imagine that, once published, the review will provide a valuable contribution to the field.

ANSWER: We thank the reviewer for these positive comments.

The search has no restrictions for publication period, as reported under “Electronic searches”. In the final work we will report the date in which the search was latest updated.

The corresponding text has been amended as follows:

“The following sources will be searched without restrictions for language or publication period: EMBASE, MEDLINE, PsycINFO, PubMed, BIOSIS, and the clinical trials registers Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov and WHO International Clinical Trials

Registry Platform (ICTRP). A draft search strategy for PsycINFO is presented in Table 1. The date of the last search update will be provided in the final publication.”

Reviewer: 2

Reviewer Name: Pere Castellvi

Institution and Country: Department of Medicine, Universitat Internacional de Catalunya (UIC), Spain
Please state any competing interests or state 'None declared': None declared

Comments to the author

This manuscript describes a protocol about which psychosocial treatments are more effective for relapse prevention in schizophrenia using a network meta-analysis. This paper tries to answer a big issue for preventing schizophrenia relapse. It is well written, methodologically rigorous, and of interest to the field.

ANSWER: We thank the reviewer for the positive opinion.

Only few comments have been raised after reading:

1. I would add other efficacy measures in Objectives. For assessing clinical severity, I would add “days of hospitalization” using means and standard deviation

ANSWER: All the outcomes of the review are currently listed under Objectives. We modified this section, so that the naming of the outcomes better reflects what is reported under Outcome measures.

It reads now:

“To estimate relative treatment effects and obtain a hierarchy for the psychosocial treatments for relapse prevention in patients with schizophrenia, in terms of:

1. relapse and hospitalisations
2. other efficacy measures: overall symptoms, positive symptoms, negative symptoms, depressive symptoms, quality of life, adherence, overall functioning
3. acceptability (dropout) and tolerability (adverse events).”

ANSWER: We carefully considered the best way to measure the outcome relapse, and we would not add “days of hospitalization” as a measure of clinical severity. This is a measure that is usually connected with the costs related to the hospitalization, while our work focuses on the outcome of the patients.

2. In Criteria for considering studies for this review subsection, a rationale in which studies that randomized by date of birth or day of the week are excluded is needed.

ANSWER: Thank you for giving us the opportunity of better clarifying this point.

The sentence was still referring to the previous version of Risk of Bias, that we used as a reference at the very beginning of this project. We decided then to use the revised version of the tool, RoB 2.0. In this tool, the consideration about the randomisation sequence falls within the domain "Risk of bias arising from the randomization process". Therefore, we decided to exclude studies with a bad judgement (high risk of bias) in this domain.

The rationale for this is that, since randomization is a necessary condition for inclusion of studies in this review, when doubts arise about it the study is not considered for inclusion.

The text was accordingly changed as follows:

Studies described as randomized, but in which a closer evaluation with the RoB 2.0 leads to a "high risk of bias" judgement in the domain "Risk of bias arising from the randomization process" will be excluded.

We deleted the same sentence that was reported under Risk of bias assessment to avoid redundancy.

3. This manuscript will not only include participants with a diagnosis of schizophrenia, but also schizophreniform and schizoaffective disorders. However, these disorders are not included as search terms.

ANSWER: In the search presented as example (for PsycINFO) the first three lines refer to the diagnosis, and are "exp Schizophrenia/", "exp psychosis/" and "schizo\$.mp.". The first two are "expanded", so they work as umbrella term and include other more detailed terms like schizophreniform and schizoaffective. Moreover, the term "schizo\$.mp." is truncated, including all the words that begin with "schizo".

Similarly, the search strategies for the other databases include Mesh terms like "Schizophrenia"[Mesh] for Pubmed.

So conditions like schizophreniform and schizoaffective disorders should be well covered with the search.

4. There is no estimate of when the review begins

ANSWER: The funding of this review started on 01.02.2019, as reported in the Prospero record. The first phase of planning and organisation was followed by the drafting of the protocol. It was submitted

to Prospero at the 20.08.2019, and the registration took almost three months (the platform is currently receiving a high number of records). At that stage, the Formal screening of search results against eligibility criteria had begun, as reported in the Prospero record.

5. I would consider other variables to include in the sensitivity analyses: a) the length of the therapy, b) brief vs standard versions of psychosocial treatments; c) Single psychosocial therapy vs. multicomponent therapies, and d) time of follow-up as authors reported at page 6, paragraph 5

ANSWER: We agree that it would be interesting to assess many other variables, but we have been warned by our expert statistician about the risk of multiple testing. With 6 subgroup and 7 sensitivity analyses we are already investigating many potential effect modifiers.

With subgroup analysis “e) Number of sessions” we are somehow covering the length of the therapy as well.

Brief versions of psychosocial treatments might not be so relevant for the maintenance treatment, which should cover longer periods of time. We have indeed set a minimum duration of 3 months for study inclusion. So this aspect might be not of primary importance in the context of this review.

The aspect of single or multicomponent therapies is indeed challenging; however, it could be better addressed with the structure of nodes and comparison that will form the network, instead of a sensitivity analysis.

As reported at page 6, the primary outcome will be analysed considering different time points separately. This will be done, and the different time points will be provided as different outcomes, and not as a sensitivity analysis. This is why it was not mentioned under sensitivity analyses.

VERSION 2 – REVIEW

REVIEWER	Pere Castellvi Universitat Internacional de Catalunya (UIC), Spain
REVIEW RETURNED	04-Dec-2019

GENERAL COMMENTS	The authors have been responsive to the comments of the reviewers, and hence the protocol is improved. In my opinion, the manuscript can be considered for publication.
-------------------------	---