PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Psychological interventions for positive symptoms in schizophrenia: protocol for a network meta-analysis of randomized evidence
AUTHORS	Bighelli, Irene Salanti, Georgia Reitmeir, Cornelia Wallis, Sofia Barbui, Corrado Furukawa, Toshi Leucht, Stefan

VERSION 1 – REVIEW

REVIEWER	Sameer Jauhar King's College, London, UK
REVIEW RETURNED	12-Sep-2017

GENERAL COMMENTS	I am gratified to see this group, which has a sterling reputation in the field of meta-analyses of pharmacological studies in schizophrenia, tackling psychosocial interventions, and their effects on positive psychotic symptoms (and other outcomes). The field badly needs thorough evaluation of the various interventions, and network meta-analysis offers this. I have the following suggestions 1. Methodology; An issue the authors may wish to tackle is the definition of CBT- Van Der Gaag included Avatar therapy as CBT, which significantly impacted on their findings, and clear definitions of what constitutes CBT will be needed for this review to have an impact on clinical care. 2. It is valid that first episode patients are excluded from the analyses, as they will usually respond better to pharmacological and probably psychological intervention. I am not quite sure if it is relevant to look at psychopathology in people receiving cognitive remediation, as this is not a primary goal of the therapy, and the cited meta-analysis looks at negative symptoms. I see that the authors will also look at other outcomes, such as total symptoms, nehtive symptoms, depression, and relapse. These are all necessary and warranted. I do look forward to the results of this meta-analysis, which will have significant effects on the clinical treatment of schizophrenia. Our colleagues at NICE may well benefit from reading this review, when it is completed.

	Sameer Jauhar Institute of Psychiatry, Psychology and Neuroscience, London.

REVIEWER	Danyael Lutgens, PhD Canada, Douglas Mental Health University Institute
REVIEW RETURNED	12-Oct-2017

GENERAL COMMENTS	October 7th, 2017-10-06 "Psychological interventions for positive symptoms of schizophrenia: protocol for a network meta- analysis of randomized evidence." (Manuscript ID: bmjopen-2017-019280) I am very glad for the opportunity to review this protocol. It is a very ambitious project and also very timely. There has been much thought and expertize applied to every aspect of the preparation for this undertaking, as is reflected through the details provided within the protocol. There are several considerations: 1. It is agreed that researcher bias is a critical risk factor that deserves evaluation within in a meta-analysis. However, it is not clear how this might be reliably measured. This warrants some explanation. For example, Leichsenring and Steinert (Jama, 2017) suggest that researcher bias may be reflected through the quality of the control comparison. That these controls are designed as "intent-to-fail" by extracting the very elements of the comparator treatment that would facilitate an effect (from Wampold, 2015). Such designs may not always be clear from manuscript descriptions and may not always be indicated by a possibly subjective determination of risk of researcher bias. As this is an important aspect of the study, some clarification as to how this will be assessed would be beneficial. 2. It is agreed that negative symptoms are an important treatment outcome in psychosis. However, it is not clear what this adds to the overall aim of this review and analysis. If treatments are not geared towards negative symptoms, this may be an uninformative comparison. On the other hand, all outcomes being equal, if a treatment works well for positive symptoms, is acceptable and also targets negative symptoms, this might tip the balance in favour of a particular intervention. Some clarification as to how this outcome variable is situated in the overall aims of the study and how it may be applied clinically would be helpful to the reader. 3. Study inclusion criteria of all Adults with schizophrenia should likely also include some populations of First Episode Psychosis. While it is agreed that FEP patients make up a particular sub-population, they are likely to reflect increased sensitivity to treatment. By excluding such sample groups, much information on treatment effectiveness may be missing, thus limiting the scope of this analysis and review. If this same argument that the authors make is carried the other way around, why include comparison of ACT with other treatments, as the former is meant for the most

	severely ill patients who are either treatment resistant or for various reasons cannot manage in the community. Please address this concern. 4. In the abstract authors lump FEP and 'prodromal' in the same basket. They are very different and the latter does not even exist as a category. The authors suggest a biased view of schizophrenia as a chronic debilitating disease as indicated by their first sentence. Selection of certain populations for exclusion suggests such bias a priori. 5. Non-active controls have been suggested to be NOCEBO --- but other studies have found that they may work similarly (ex. Supportive counseling) as other active controls – hence this part is confusing – It may be that wait list only needs to be considered as NOCEBO? Please clarify. 6. Many of the sub-outcomes including quality of life and functioning are agreed to be very important but given that there will be only a small subset of studies that report this, findings will be inherently biased. It may be that some outcomes are so rarely reported that they warrant exclusion? At what point might this be a consideration? 7. Finally, while it is important to identify which treatments are efficacious, at the end of the day in real clinical practice it is effectiveness that matters and not efficacy. Effectiveness may be enhanced by combining treatments the effect of which may be greater than the sum of their parts (individual treatments). Please address how you might incorporate this into your analyses.

REVIEWER	Ashok Malla & Franz Veru (Ph.D. student) McGill Uinversity, Canada
REVIEW RETURNED	26-Oct-2017

GENERAL COMMENTS	This protocol is well organized and follows a detailed methodology including a straightforward electronic search strategy, customary data extraction, standard measurement of treatment effects and implements an authoritative risk of bias assessment tool. Their analysis plan anticipates the evaluation of heterogeneity within same treatment comparisons, controlling for other covariates to assess for transitivity, and evaluate inconsistency within the included studies. By conducting a network meta-analysis, it aims to provide a comprehensive overview of all the available psychological based treatments for the positive symptoms of psychosis, intending to provide a hierarchy based on effectiveness. However, there are some issues that might have been overlooked. Comments It is important to clarify what the authors mean by “active phase” and check for some language inconsistencies. While it seems that they refer to an acute exacerbation of positive symptoms in chronic patients, this is not explicitly stated, leaving some room for doubt. This is further complicated by the fact that in the abstract, the authors indicate that they had excluded studies including patients with a first episode of psychosis or in the prodromal phase (p2, L20), which is truly the acute phase of psychotic disorders. However, they later indicate in the introduction that they focus on the “acute phase”

	(not active) of the illness (p3, L52). This can also be seen in the methods section where it is also indicated that some included studies have patients in the “acute phase of the illness” (p6, L42). I am not sure why they are excluding studies with first episode psychosis, when in fact it is in this population that psychological treatment is likely to be most beneficial. Further, lumping together FEP and so called 'prodromal' phase shows some lack of understanding about the large difference between these groups, if the latter can even be said to exist. What they are most likely referring to are patients who meet criteria for being at Clinical High Risk for psychosis. The latter can be justified to be left out of a systematic and meta-analytic review such as the one proposed but i do not accept why FEP patients would be excluded. I don’t understand the decision to systematically exclude studies from mainland China. The authors indicate that many do not use appropriate randomization procedures. This does not necessarily mean that all studies will be biased. Since the authors have already put a method to determine risk of bias, and are selecting studies from all over the world, why instead of assuming that all mainland China studies are biased, just assess them with the Cochrane’s risk of bias tool like any other study. Please comment on the reason why positive symptoms and related terms (e.g. delusions, hallucinations, disorganization) were excluded from the search strategy. What is the advantage of not including these search terms in the main query? Patients with a diagnosis of schizophrenia or psychosis have heterogeneous clinical outlines, and their profile of positive symptoms will reflect this. For example, while some patients will have a more delusional or paranoid component others might exhibit more disorganization. Thus, these different types of patients will probably be allocated to different types of therapy. This is not addressed in the methodology or in the evaluation of heterogeneity. If they are planning to do a sensitivity analysis by excluding open RCTs, I believe the authors could also conduct another sensitivity analysis based on diagnosis, including criteria-based diagnoses (ICD-10, DMS-V), and excluding non-guideline based diagnoses. While the bias section is clearly delineated point by point following the Cochrane risk of bias tool, it is important to explain how studies including patients with predominant negative symptoms are going to be excluded. Since most patients are treated with antipsychotic medication, and antipsychotics primarily target positive symptoms, it is expected that negative symptoms would be the most prominent problem for chronic patients. This means that the study could be biased towards patients that have a poorer response to pharmacological treatment, are more likely to present with acute exacerbations of positive symptoms, have lower adherence to pharmacological treatment, or are not treated with depot compounds. Perhaps the most prominent critique is that the role of pharmacological treatment seems to be placed in a secondary position. It is mentioned that only descriptive statistics will include co-medication (p11, L6). This implies that some trials might have been conducted with concomitant pharmacological treatment while others not. Given this, why co-medication is not included in the

	assessment of heterogeneity? What is the rationale for including the difference between low, middle, and high income countries in the heterogeneity analysis? Is there any evidence that psychological therapies are differently implemented in low-income countries? while this is likely the authors need to address this and provide some evidence. In the event that only wealthy people in low-income countries might have a better access to psychological therapies, thus biasing the studied cohort, this may need to be mentioned. In that sense, wouldn't be more reasonable to compare countries with universal access to healthcare versus those without? Since the authors indicate that there will be no language restriction, it is not indicated in the methodology who will translate or analyze and select studies not written in languages in which the authors are not fluent.

VERSION 1 – AUTHOR RESPONSE

Dear Editors,
please find below detailed answers to Reviewers' comments.
A new version of the manuscript with track-changes will also be attached.

Editorial Comment:

We suggest amending the title slightly to specify the type of studies considered in this meta-analysis i.e. "Psychological interventions for positive symptoms in schizophrenia: protocol for a network meta-analysis of randomized controlled trials."
ANSWER: the title was changed as suggested.

Reviewer 1

1. Methodology; An issue the authors may wish to tackle is the definition of CBT- Van Der Gaag included Avatar therapy as CBT, which significantly impacted on their findings, and clear definitions of what constitutes CBT will be needed for this review to have an impact on clinical care.
ANSWER: We decided not to have a priori definition for treatments, since we expect a broad variety of different treatments, and we plan to classify them after identifying eligible studies.
We will include all psychological treatments with the exclusion of those explicitly aimed at treating an outcome that is not positive symptoms, as stated in the paragraph "Types of interventions". We also do not apply restrictions depending on how the treatment is provided, therefore virtual reality CBT would be also included, if it is aimed at treating positive symptoms.
A sentence has been added as follows: "The identified treatments will be classified after identification of eligible studies."

2. It is valid that first episode patients are excluded from the analyses, as they will usually respond better to pharmacological and probably psychological intervention.
I am not quite sure if it is relevant to look at psychopathology in people receiving cognitive remediation, as this is not a primary goal of the therapy, and the cited meta-analysis looks at negative symptoms.

ANSWER: Cognitive remediation does not fall among the included interventions, because – as suggested – it is not aimed at treating positive symptoms.
The table provided just aims at giving a general overview of the existing evidence, in the form of systematic reviews, on psychological interventions for schizophrenia. The treatments mentioned do not coincide with the ones that will be included in our NMA.

Reviewer 2

1. It is agreed that researcher bias is a critical risk factor that deserves evaluation within in a meta-analysis. However, it is not clear how this might be reliably measured. This warrants some explanation. For example, Leichsenring and Steinert (Jama, 2017) suggest that researcher bias may be reflected through the quality of the control comparison. That these controls are designed as "intent-to-fail" by extracting the very elements of the comparator treatment that could facilitate an effect (from Wampold, 2015). Such designs may not always be clear from manuscript descriptions and may not always be indicated by a possibly subjective determination of risk of researcher bias. As this is an important aspect of the study, some clarification as to how this will be assessed would be beneficial.
ANSWER: We are aware that there might be other aspects connected to researchers' bias; but, since there is no agreed upon method on this, we decided for this review to base our judgement on the one aspect of researcher allegiance that can be reliably assessed based on the publication, that is whether the authors are founders of the therapy or have written a manual for that therapy.
A sentence for clarification has been added as follows: "An evaluation of high risk of bias will be given, for example, when the authors are founders of the therapy or have written a manual for that therapy".

2. It is agreed that negative symptoms are an important treatment outcome in psychosis. However, it is not clear what this adds to the overall aim of this review and analysis. If treatments are not geared towards negative symptoms, this may be an uninformative comparison. On the other hand, all outcomes being equal, if a treatment works well for positive symptoms, is acceptable and also targets negative symptoms, this might tip the balance in favour of a particular intervention. Some clarification as to how this outcome variable is situated in the overall aims of the study and how it may be applied clinically would be helpful to the reader.
ANSWER: As a first attempt to perform such a NMA we decided to focus on treatments aimed at positive symptoms, so that treatment with the same aim can be compared. Treatment specifically aimed at negative symptoms were therefore excluded. Nevertheless, we evaluate negative symptoms as a secondary outcome.
This sentence has been added in the paragraph "Secondary outcomes":
"Given the focus on treatments for positive symptoms, the results of this review will be informative for the treatment of positive symptoms. They will also describe how these interventions can have an effect on a number of other outcomes. With this aim, the following secondary outcomes will be assessed:".

3. Study inclusion criteria of all Adults with schizophrenia should likely also include some populations of First Episode Psychosis. While it is agreed that FEP patients make up a particular sub-population, they are likely to reflect increased sensitivity to treatment. By excluding such sample groups, much information on treatment effectiveness may be missing, thus limiting the scope of this analysis and review. If this same argument that the authors make is carried the other way around, why include comparison of ACT with other treatments, as the former is meant for the most severely ill patients who are either treatment resistant or for various reasons cannot manage in the community. Please address this concern.
ANSWER: The inclusion of First episode patients is discussed also in reply of Drs Malla and Jauhar's comments. We would keep these patients out of this review, because they represent a different population, and their inclusion would very likely create significant heterogeneity, preventig the

application of a Network meta Analysis. For the sake of conducting a NMA we need an homogeneous population, and we believe it would not make sense to compare interventions specifically addressed to the early phase of schizophrenia to other psychological treatments.
Regarding treatment resistant patients, we are aware that this population might be represented in the studies and that it is a peculiar population; therefore we planned a sensitivity analysis to check this difference.

4. In the abstract authors lump FEP and 'prodromal' in the same basket. They are very different and the latter does not even exist as a category. The authors suggest a biased view of schizophrenia as a chronic debilitating disease as indicated by their first sentence. Selection of certain populations for exclusion suggests such bias a priori.
ANSWER: Please see also the reply to the same comment by Dr Malla. The sentence in the abstract "prodromal or first episode" was not intended to say that these two groups are the same, but aimed to give examples of the excluded subgroups of patients. We agree that it could sound misleading, and we changed the sentence to "We will include studies on adult patients with schizophrenia, excluding specific subpopulations (e.g. first episode patients, or patients with psychiatric comorbidities). ".

5. Non-active controls have been suggested to be NOCEBO – but other studies have found that they may work similarly (ex. Supportive counseling) as other active controls – hence this part is confusing – It may be that wait list only needs to be considered as NOCEBO? Please clarify.
ANSWER: Thank you for pointing this out; the sentence has been changed to:
"The effect of “non-active” comparators will be analysed in a sensitivity analysis."

6. Many of the sub-outcomes including quality of life and functioning are agreed to be very important but given that there will be only a small subset of studies that report this, findings will be inherently biased. It may be that some outcomes are so rarely reported that they warrant exclusion? At what point might this be a consideration?
ANSWER: This is a relevant issue, since it might be true that some outcomes are not often reported. The interpretation of such results will take into account the number of studies and patients that provided information for that specific outcome. Moreover, the evaluation of the quality of evidence with GRADE (see "Evaluating the quality of the evidence" paragraph) will include this point.

7. Finally, while it is important to identify which treatments are efficacious, at the end of the day in real clinical practice it is effectiveness that matters and not efficacy. Effectiveness may be enhanced by combining treatments the effect of which may be greater than the sum of their parts (individual treatments). Please address how you might incorporate this into your analyses.
ANSWER: We agree with this comment: effectiveness is of primary importance in the choice of treatments in the practice. However, these complex consideration cannot be incorporated directly in data analyses; in the studies the interventions are mostly used alone, and rarely in combination.
This point concerns the interpretation of our results: based on the results on efficacy, it will be possible to reason on the effectiveness of the treatments. Dropout rates may also be considered a proxy measure of effectiveness, as patients may leave the treatment early for problems related to efficacy and tolerability of the treatment. We will address these reflections in the discussion.

Reviewer 3

1. It is important to clarify what the authors mean by “active phase” and check for some language inconsistencies. While it seems that they refer to an acute exacerbation of positive symptoms in chronic patients, this is not explicitly stated, leaving some room for doubt. This is further complicated by the fact that in the abstract, the authors indicate that they had excluded studies including patients with a first episode of psychosis or in the prodromal phase (p2, L20), which is truly the acute phase of psychotic disorders. However, they later indicate in the introduction that they focus on the “acute

phase" (not active) of the illness (p3, L52). This can also be seen in the methods section where it is also indicated that some included studies have patients in the "acute phase of the illness" (p6, L42). I am not sure why they are excluding studies with first episode psychosis, when in fact it is in this population that psychological treatment is likely to be most beneficial. Further, lumping together FEP and so called 'prodromal' phase shows some lack of understanding about the large difference between these groups, if the latter can even be said to exist. What they are most likely referring to are patients who meet criteria for being at Clinical High Risk for psychosis. The latter can be justified to be left out of a systematic and meta-analytic review such as the one proposed but i do not accept why FEP patients would be excluded.
ANSWER: We always talk about "acute" phase, never "active" (the term "active" has been used only referring to "active treatments"). With this we aim to select patients currently experiencing positive symptoms, consistently with our aim of investigating the efficacy of treatments for this outcome.
We agree that this population could be better identified with the description "acute exacerbation of positive symptoms", so we changed the text as follows: "We will include studies recruiting patients with positive symptoms, either delusions, hallucinations or both, or in the phase of acute exacerbation of positive symptoms, however defined by inclusion criteria of the trial."
First episode and prodromal patients are not lumped – the same comment was made by Dr Lutgens. The sentence in the abstract aims to say that they will be both excluded. The reason for excluding first episode patients is that they are a different population, in which the treatments might have a greater effect (as the reviewer suggests, and as it was pointed out by Dr Jauhar); this will create a considerable heterogeneity and prevent the possibility of doing a NMA.
We acknowledge that the sentence in the abstract might create confusion; therefore it has been changed to "We will include studies on adult patients with schizophrenia, excluding specific subpopulations (e.g. first episode patients, or patients with psychiatric comorbidities)."

2. I don't understand the decision to systematically exclude studies from mainland China. The authors indicate that many do not use appropriate randomization procedures. This does not necessarily mean that all studies will be biased. Since the authors have already put a method to determine risk of bias, and are selecting studies from all over the world, why instead of assuming that all mainland China studies are biased, just assess them with the Cochrane's risk of bias tool like any other study.
ANSWER:
Thank you for making this point; if the problem was about randomization, then we would agree with this comment. However, the decision to exclude these studies was not made because they use inappropriate randomization procedures, but because they were found to have broader methodological flaws, and even to be fraudulent in their reporting (see Woodhead 2016); for this reason their evaluation with the risk of bias would not be helpful in detecting methodological weaknesses. However, we acknowledge that we might have been too extreme, since the main problem is about Chinese studies found in Chinese databases.
The text was therefore changed as follows: "As an exception, we will not search Chinese databases, since serious concerns have been raised on the trustworthiness of Chinese trials found in these databases (35, 36) Chinese studies found in Western databases will be considered for inclusion."

3. Please comment on the reason why positive symptoms and related terms (e.g. delusions, hallucinations, disorganization) were excluded from the search strategy. What is the advantage of not including these search terms in the main query?
ANSWER: The results of the search were in this way broader, providing more potentially relevant studies that had to be manually screened. This involved a considerable amount of work, but allowed us to be more precise and check in each study's inclusion criteria whether patients with positive symptoms were enrolled.

4. Patients with a diagnosis of schizophrenia or psychosis have heterogeneous clinical outlines, and their profile of positive symptoms will reflect this. For example, while some patients will have a more

delusional or paranoid component others might exhibit more disorganization. Thus, these different types of patients will probably be allocated to different types of therapy. This is not addressed in the methodology or in the evaluation of heterogeneity.
ANSWER: We agree that it may be worth to investigate this point with a subgroup analysis.
A sentence was added as follows:"different types of patients, with a different clinical outline concerning symptoms (if identified)".

5. If they are planning to do a sensitivity analysis by excluding open RCTs, I believe the authors could also conduct another sensitivity analysis based on diagnosis, including criteria-based diagnoses (ICD-10, DMS-V), and excluding non-guideline based diagnoses.
ANSWER: Thank you for this suggestion. We reasoned about such a sensitivity analysis, but then opted for a pragmatic analysis, that reflects what happens in the real world, since in clinical practice explicit diagnoses are lumped together with implicit diagnoses.

6. While the bias section is clearly delineated point by point following the Cochrane risk of bias tool, it is important to explain how studies including patients with predominant negative symptoms are going to be excluded. Since most patients are treated with antipsychotic medication, and antipsychotics primarily target positive symptoms, it is expected that negative symptoms would be the most prominent problem for chronic patients. This means that the study could be biased towards patients that have a poorer response to pharmacological treatment, are more likely to present with acute exacerbations of positive symptoms, have lower adherence to pharmacological treatment, or are not treated with depot compounds.
ANSWER: We will consider the inclusion criteria of the studies regarding patients, and the definitions given in the studies. Studies will be included if they explicitly mention that their patients must have positive symptoms, unless they state that negative symptoms are predominant. A sentence has been added in the section "Types of participants": "studies recruiting patients in which negative symptoms are predominant, according to authors' definition".
The effect of studies whose patients are also defined as treatment resistant will be separately considered in a sensitivity analysis.
Information about the concurrent medication received by the patients will also be collected, as well as scales measuring adherence.

7. Perhaps the most prominent critique is that the role of pharmacological treatment seems to be placed in a secondary position. It is mentioned that only descriptive statistics will include co-medication (p11, L6). This implies that some trials might have been conducted with concomitant pharmacological treatment while others not. Given this, why co-medication is not included in the assessment of heterogeneity?
ANSWER: We are aware of only one trial that enrolled participants without concomitant medication (Morrison 2014), and even here patients started to take medication during the study. We will collect all the available information about concomitant medication; however we expect that this information will be rarely reported in detail. Therefore to conduct sensitivity analysis according to this variable is not feasible. However, given the focus on patients with current positive symptoms, we reasonably assume that medication is offered to all of them, and therefore from this point of view the studies will be homogeneous.

8. What is the rationale for including the difference between low, middle, and high income countries in the heterogeneity analysis? Is there any evidence that psychological therapies are differently implemented in low-income countries? while this is likely the authors need to address this and provide some evidence. In the event that only wealthy people in low-income countries might have a better access to psychological therapies, thus biasing the studied cohort, this may need to be mentioned. In that sense, wouldn't be more reasonable to compare countries with universal access to healthcare versus those without?

ANSWER: Our aim was to explore possible differences in low-income countries, but this is not the primary focus of this work and we decided to drop this analysis.

9. Since the authors indicate that there will be no language restriction, it is not indicated in the methodology who will translate or analyze and select studies not written in languages in which the authors are not fluent.
ANSWER: We will at first rely on our scientific contacts (the authors group involves scientists in many countries, including Germany, Italy and Japan). In case we retrieve studies in languages that we cannot manage, we will contact study authors (to ask further information that allow us to select the study for inclusion, and to ask relevant data for our analyses).
This sentence has been added to the protocol:
"In case we retrieve references in languages in which we are not fluent, study authors will be contacted to check inclusion criteria and eventually ask for study data".

VERSION 2 – REVIEW

REVIEWER	Danyael Lutgens McGill University, Canada
REVIEW RETURNED	15-Nov-2017

GENERAL COMMENTS	October 7th, 2017-10-06 "Psychological interventions for positive symptoms of schizophrenia: protocol for a network metaanalysis of randomized evidence." (Manuscript ID: bmjopen-2017-019280) I am very glad for the opportunity to review this protocol. It is a very ambitious project and also very timely. There has been much thought and expertise applied to every aspect of the preparation for this undertaking, as is reflected through the details provided within the protocol. There are several considerations: 1. It is agreed that researcher bias is a critical risk factor that deserves evaluation within in a metaanalysis. However, it is not clear how this might be reliably measured. This warrants some explanation. For example, Leichsenring and Steinert (Jama, 2017) suggest that researcher bias may be reflected through the quality of the control comparison. That these controls are designed as "intent-to-fail" by extracting the very elements of the comparator treatment that would facilitate an effect (from Wampold, 2015). Such designs may not always be clear from manuscript descriptions and may not always be indicated by a possibly subjective determination of risk of researcher bias. As this is an important aspect of the study, some clarification as to how this will be assessed would be beneficial. 2. It is agreed that negative symptoms are an important treatment outcome in psychosis. However, it is not clear what this adds to the overall aim of this review and analysis. If treatments are not geared towards negative symptoms, this may be an uninformative comparison. On the other hand, all outcomes being equal, if a treatment works well for positive symptoms, is acceptable and also targets negative symptoms, this might tip the balance in favour of a particular intervention. Some clarification as to how this outcome variable is situated in the overall aims of the study and how it may

	be applied clinically would be helpful to the reader. 3. Study inclusion criteria of all Adults with schizophrenia should likely also include some populations of First Episode Psychosis. While it is agreed that FEP patients make up a particular sub-population, they are likely to reflect increased sensitivity to treatment. By excluding such sample groups, much information on treatment effectiveness may be missing, thus limiting the scope of this analysis and review. If this same argument that the authors make is carried the other way around, why include comparison of ACT with other treatments, as the former is meant for the most severely ill patients who are either treatment resistant or for various reasons cannot manage in the community. Please address this concern. 4. In the abstract authors lump FEP and 'prodromal' in the same basket. They are very different and the latter does not even exist as a category. The authors suggest a biased view of schizophrenia as a chronic debilitating disease as indicated by their first sentence. Selection of certain populations for exclusion suggests such bias a priori.

REVIEWER	Ashok Malla and Franz Veru (under supervision) McGill University, Canada
REVIEW RETURNED	29-Nov-2017

GENERAL COMMENTS	The authors have addressed all the comments. The additions and changes to the manuscript clarify the issues raised in the first revision. It was clarified that the studies included in the protocol had recruited chronic patients with an acute exacerbation in the methods and by eliminating the word “prodromal” from the abstract. However, I am still not clear on the reasons nor convinced about the wisdom of excluding patients with a first episode psychosis if they meet criteria for schizophrenia spectrum disorders, unless they mean they will exclude studies on FEP who do not meet the criteria for schizophrenia spectrum. They should include that as a limitation. The rewording on the exclusion of studies from mainland China clarifies this issue and links it more appropriately with their references. The authors also dropped the “high versus low and middle income countries” item from the exploration of heterogeneity, and other comments clarify other concerns. Although a purely stylistic issue, the language is still a bit vague, and the reader has to make an extra effort to understand the authors’ assumptions.

REVIEWER	Sameer Jauhar King's College, London, UK.
REVIEW RETURNED	09-Dec-2017

GENERAL COMMENTS	They have addressed my comments clearly.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Reviewer Name: Danyael Lutgens

1. It is agreed that researcher bias is a critical risk factor that deserves evaluation within in a metaanalysis. However, it is not clear how this might be reliably measured. This warrants some explanation. For example, Leichsenring and Steinert (Jama, 2017) suggest that researcher bias may be reflected through the quality of the control comparison. That these controls are designed as "intent-to-fail" by extracting the very elements of the comparator treatment that would facilitate an effect (from Wampold, 2015). Such designs may not always be clear from manuscript descriptions and may not always be indicated by a possibly subjective determination of risk of researcher bias. As this is an important aspect of the study, some clarification as to how this will be assessed would be beneficial.

ANSWER: We are aware that there might be other aspects connected to researchers' bias; but, since there is no agreed upon method on this, we decided for this review to base our judgement on the one aspect of researcher allegiance that can be reliably assessed based on the publication, that is whether the authors are founders of the therapy or have written a manual for that therapy.
A sentence for clarification on how this will be evaluated with the Risk of Bias tool has been added as follows: "An evaluation of high risk of bias will be given, for example, when the authors are founders of the therapy or have written a manual for that therapy".

2. It is agreed that negative symptoms are an important treatment outcome in psychosis. However, it is not clear what this adds to the overall aim of this review and analysis. If treatments are not geared towards negative symptoms, this may be an uninformative comparison. On the other hand, all outcomes being equal, if a treatment works well for positive symptoms, is acceptable and also targets negative symptoms, this might tip the balance in favour of a particular intervention. Some clarification as to how this outcome variable is situated in the overall aims of the study and how it may be applied clinically would be helpful to the reader.

ANSWER: As a first attempt to perform such a NMA we decided to focus on treatments aimed at positive symptoms, so that treatment with the same aim can be compared. Moreover, the effect of psychological treatments on negative symptoms has already been evaluated in a work by Lutgens and colleagues, which we cite in our introduction. Treatments specifically aimed at negative symptoms were therefore excluded. Nevertheless, we evaluate negative symptoms as a secondary outcome, among others; if we didn't, that could be also criticized.
In order to clarify the role of evaluating this outcome, a sentence has been added in the paragraph "Secondary outcomes":
"Given the focus on treatments for positive symptoms, the results of this review will be informative for the treatment of positive symptoms. They will also describe how these interventions can have an effect on a number of other outcomes. With this aim, the following secondary outcomes will be assessed:".
In addition, we are aware that if a positive effect will be found on negative symptoms, this might be secondary to the effect of the treatment on positive symptoms. We will highlight this in the discussion and interpretation of results.

3. Study inclusion criteria of all Adults with schizophrenia should likely also include some populations of First Episode Psychosis. While it is agreed that FEP patients make up a particular sub-population, they are likely to reflect increased sensitivity to treatment. By excluding such sample groups, much information on treatment effectiveness may be missing, thus limiting the scope of this analysis and review. If this same argument that the authors make is carried the other way around, why include comparison of ACT with other treatments, as the former is meant for the most severely ill patients who are either treatment resistant or for various reasons cannot manage in the community. Please address this concern.

ANSWER: Please see extensive explanation about the inclusion of First Episode patients in answer to Dr Malla's comment below.

Regarding treatment resistant patients, we are aware that this population might be represented in the studies and that it is a peculiar population; therefore we already planned a sensitivity analysis to check this difference.

4. In the abstract authors lump FEP and 'prodromal' in the same basket. They are very different and the latter does not even exist as a category. The authors suggest a biased view of schizophrenia as a chronic debilitating disease as indicated by their first sentence. Selection of certain populations for exclusion suggests such bias a priori.

ANSWER: The sentence in the abstract "prodromal or first episode" was not intended to say that these two groups are the same, but aimed to give examples of the excluded subgroups of patients (since, due to the words limit, we cannot give here the full list of exclusion criteria).
We acknowledge that that sentence, so formulated, might create confusion; therefore it has been changed to "We will include studies on adult patients with schizophrenia, excluding specific subpopulations (e.g. first episode patients, or patients with psychiatric comorbidities)."
The exclusion of some specific sub-populations is necessary in order to have a homogeneous population, that is a methodological requirement for performing the Network meta-Analysis.

Reviewer: 3
Reviewer Name: Ashok Malla and Franz Veru (under supervision)

The authors have addressed all the comments. The additions and changes to the manuscript clarify the issues raised in the first revision. It was clarified that the studies included in the protocol had recruited chronic patients with an acute exacerbation in the methods and by eliminating the word "prodromal" from the abstract.
However, I am still not clear on the reasons nor convinced about the wisdom of excluding patients with a first episode psychosis if they meet criteria for schizophrenia spectrum disorders, unless they mean they will exclude studies on FEP who do not meet the criteria for schizophrenia spectrum. They should include that as a limitation.
The rewording on the exclusion of studies from mainland China clarifies this issue and links it more appropriately with their references. The authors also dropped the "high versus low and middle income countries" item from the exploration of heterogeneity, and other comments clarify other concerns.
Although a purely stylistic issue, the language is still a bit vague, and the reader has to make an extra effort to understand the authors' assumptions.

ANSWER:
We are pleased to see that the changes to the protocol clarified some of the issues previously raised. Here below we provide extensive explanation regarding our reasoning in excluding patients with a first episode psychosis.
For conducting the network meta-analysis that we plan, we must ensure some underlying assumptions; one of these is the transitivity assumption (Salanti 2012). This assumption implies that studies comparing different sets of interventions are sufficiently similar to provide valid indirect inferences. In other words, it should be theoretically possible that patients could be randomized to any of the arms in the included studies.
This assumption will be assessed at the data analysis stage, but must be ensured at the stage of study selection applying narrow inclusion criteria, so that populations within and across treatment comparisons are similar. For this reason we were really careful and strict in our inclusion criteria.
Including specific populations, such as first episode patients, would introduce heterogeneity in our analyses, most likely preventing the possibility of conducting a network meta-analysis, that is the original contribution that we want to bring in the field, since it has never been done.
First episode patients would represent a specific population for many reasons.

First, as it was already mentioned by reviewers at the first stage comments, they have a higher response to treatments compared to chronic patients. This was confirmed for antipsychotic medication in a recent meta-analysis (Zhu et al., 2017). Response rates for first episode patients were found to be 81.3% (compared to 53% in chronic patients (Leucht et al. 2017)), when considering at least 20% Positive and Negative Syndrome Scale (PANSS) total score or Brief Psychiatric Rating Scale (BPRS) total score reduction from baseline, and 51.9 % compared to 23% of chronic patients when considering a cutoff of at least 50% reduction from baseline. We added a sentence to clarify this: "Among other reasons, we exclude first episode patients because they were found to have significantly higher response rates to treatments compared to chronic patients (39, 40)."
Secondly, even if we decided to include first episode patients that already have a diagnosis of schizophrenia, a certain degree of diagnostic uncertainty would still persist; for example, when using ICD criteria, one month of symptoms would be enough to diagnose schizophrenia.
Finally, when evaluating the role of psychological treatments, we have to bear in mind that patients are usually also receiving concomitant medication; this is the case in the majority of studies that we reviewed so far. First episode patients would be a very heterogeneous population from this point of view, since the pharmacological treatment might not have been already established or even started in some cases. This would represent a significant source of confounding that would be extremely difficult to control, since details on pharmacological treatments are not always reported.
As a first attempt of this kind of analysis on this topic, we want to be cautious in our selection criteria. We are aware that excluding specific populations, like first episode patients, the generalizability of our findings will be limited, and the results will be applicable only for patients with acute exacerbation of positive symptoms, our target population. In the final publication this will be highlighted in the discussion and in the interpretation of results. On the other side, we aim with these strict selection criteria at having a high internal validity. Future works might expand the focus of investigating the efficacy of psychological treatments for broader populations of schizophrenic patients.

VERSION 3 – REVIEW

REVIEWER	Danyael Lutgens Douglas Hospital, Montreal, Quebec, Canada
REVIEW RETURNED	10-Jan-2018

GENERAL COMMENTS	October 7th, 2017-10-06 "Psychological interventions for positive symptoms of schizophrenia: protocol for a network meta- analysis of randomized evidence." (Manuscript ID: bmjopen-2017-019280) I am very glad for the opportunity to review this protocol. It is a very ambitious project and also very timely. There has been much thought and expertize applied to every aspect of the preparation for this undertaking, as is reflected through the details provided within the protocol. There are several considerations: 1. It is agreed that researcher bias is a critical risk factor that deserves evaluation within in a meta-analysis. However, it is not clear how this might be reliably measured. This warrants some explanation. For example, Leichsenring and Steinert (Jama, 2017)

	suggest that researcher bias may be reflected through the quality of the control comparison. That these controls are designed as "intent-to-fail" by extracting the very elements of the comparator treatment that would facilitate an effect (from Wampold, 2015). Such designs may not always be clear from manuscript descriptions and may not always be indicated by a possibly subjective determination of risk of researcher bias. As this is an important aspect of the study, some clarification as to how this will be assessed would be beneficial. 2. It is agreed that negative symptoms are an important treatment outcome in psychosis. However, it is not clear what this adds to the overall aim of this review and analysis. If treatments are not geared towards negative symptoms, this may be an uninformative comparison. On the other hand, all outcomes being equal, if a treatment works well for positive symptoms, is acceptable and also targets negative symptoms, this might tip the balance in favour of a particular intervention. Some clarification as to how this outcome variable is situated in the overall aims of the study and how it may be applied clinically would be helpful to the reader. 3. Study inclusion criteria of all Adults with schizophrenia should likely also include some populations of First Episode Psychosis. While it is agreed that FEP patients make up a particular sub-population, they are likely to reflect increased sensitivity to treatment. By excluding such sample groups, much information on treatment effectiveness may be missing, thus limiting the scope of this analysis and review. If this same argument that the authors make is carried the other way around, why include comparison of ACT with other treatments, as the former is meant for the most severely ill patients who are either treatment resistant or for various reasons cannot manage in the community. Please address this concern. 4. In the abstract authors lump FEP and 'prodromal' in the same basket. They are very different and the latter does not even exist as a category. The authors suggest a biased view of schizophrenia as a chronic debilitating disease as indicated by their first sentence. Selection of certain populations for exclusion suggests such bias a priori. 5. Non-active controls have been suggested to be NOCEBO --- but other studies have found that they may work similarly (ex. Supportive counseling) as other active controls – hence this part is confusing – It may be that wait list only needs to be considered as NOCEBO? Please clarify. 6. Many of the sub-outcomes including quality of life and functioning are agreed to be very important but given that there will be only a small subset of studies that report this, findings will be inherently biased. It may be that some outcomes are so rarely reported that they warrant exclusion? At what point might this be a consideration? 7. Finally, while it is important to identify which treatments are efficacious, at the end of the day in real clinical practice it is effectiveness that matters and not efficacy. Effectiveness may be enhanced by combining treatments the effect of which may be greater than the sum of their parts (individual treatments). Please address how you might incorporate this into your analyses.