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)	Protocol for a systematic review of psychological treatment for methamphetamine use: an analysis of methamphetamine use and mental health symptom outcomes.
AUTHORS	Stuart, Alexandra; Baker, Amanda; Bowman, Jenny; McCarter, Kristen; Denham, Alexandra; Lee, Nicole; Colyvas, Kim; Dunlop, Adrian

VERSION 1 - REVIEW

REVIEWER	Steven Shoptaw PhD David Geffen School of Medicine at UCLA Department of Family Medicine USA
REVIEW RETURNED	25-Dec-2016

GENERAL COMMENTS	Overall Opinion. This is a solid proposal for a systematic review and meta analysis for psychosocial and pharmacological treatments for methamphetamine addiction, with primary outcome variables being both methamphetamine use at end of treatment (abstinence and methamphetamine reductions) and mental health symptoms. This is an outstanding author team and there is ample experience in the team to be able to pull this off well. Data reflecting this assessment is the high level of precision in describing the protocol and the very well written text throughout. The paper is easy to read and concepts are presented plainly. I believe the authors need, however, an increased level of precision in measuring the two primary outcome variables. I think this might be facilitated by a more thoughtful and comprehensive rationale for why this review is necessary and how it will advance what is already known. One suggestion would be to include in the rationale sections clear descriptions of how this review will offer a meaningful advance beyond a simple update of what is already done in existing Cochrane reviews. It is a real strength that this team has extensive experience in doing this kind of work. Here are some options for how this review/meta-analysis could be improved. 1. Page 4. The epidemiology of meth use presented in terms of type of meth used and the changes in use patterns in Australia is provincial. Evidence from on global methamphetamine use trends would seem more appropriate for this journal. 2. Page 5. Top of page. The issue of psychiatric symptoms, psychiatric diagnoses and the link between these and methamphetamine addiction, withdrawal and protracted abstinence is not fully developed. This section reflects this struggle. In this

	paragraph, there is a struggle with the concept of psychiatric symptoms versus psychiatric diagnoses, a key concept that needs to be sorted out from the start. Depression, anxiety and other symptoms co-occur frequently with the experience of methamphetamine use and quitting meth, but are not interpreted as having diagnostic importance until these occur 6 months or more independent of meth use (see DSM IV-TR and DSM5; ICDM-9 and 10). Some effort to specify exactly what symptoms are being measured and how these are understood relative to methamphetamine addiction, withdrawal and protracted abstinence is vital. For example, in this paragraph is a sentence that conflates symptoms with diagnoses. There is no indication of how the data collected in the review will be sorted (or if it will). Will reviews be sorted such that there is one for meth outcomes, one for meth outcomes by psychiatric symptoms and one for meth outcomes by co-morbid psychiatric disorders? This is a key problem is never resolved and if not addressed, is in my mind a fatal flaw to this work. Here are the kinds of questions that come to mind: Within the psychiatric symptoms area, how would different symptoms be grouped? There are differences in scales used to measure symptoms. How would these be harmonized in the review? How would the team control for differential influence on outcomes for the review/meta-analysis from studies that have include extensive batteries for measuring psychiatric symptoms while others have less data? Would separate review/analyses be done for depression symptoms? Anxiety? Insomnia? Other symptoms? 3. Page 5, Line 33. This sentence that opens the rationale for the review is simplistic. It's hard to stay in meth treatment. Period. It is not due solely to psychiatric symptoms. This section does not serve the proposed work well and confuses rationale for reviewing outcomes from pharmacotherapy studies in the area. How are psychiatric outcomes measured in the meth trials distinguished? Line 52 in the paragraph would seem to present evidence for NOT including medication studies in the review. A better rationale is needed here. 4. Page 6, Line 33. This rationale for how this review is organized is not satisfying. My read is that what is being proposed is more of the same, an update of what is known, without guiding the reader to expect that some new information is going to come from this effort excepting more similar findings, though with a few more studies tucked in. If the team wants to go in this direction, then I see no useful purpose for this review. A more useful approach seems necessary. If this is the proposal for an update to a Cochrane review, I see no need to publish the protocol. 5. The dependent variables are not well described. There has been a host of literature over the past 15 years or so that highlight problems in measuring outcome for meth trials. Some clear definition of outcomes (even abstinence can vary how it's measured) seems essential to organize this review so that findings will provide new and useful information. For example, in analyzing abstinence vs harm reduction outcomes across both behavioral and medication trials, a rationale needs to be presented why this is an important distinction. In our field there is heated controversy over abstinence as the only desirable outcome compared to value in reductions in methamphetamine use (and corresponding harms). The outcomes collected would seem to go a long way in this proposed comprehensive systematic review/meta-analysis toward helping organize this area of science. 6. The concept of dose of treatment to outcomes in trials is not mentioned and is conspicuously absent. For behavioral studies, this

	could involve dose measured by session attendance (or missing data/drop outs), metrics assessing knowledge/skills learned, etc that could be analyzed relative to outcomes. But in medication studies, dose is essential and is to date poorly and inconsistently measured. Drop out and pill count data have been used to measure dose, but this metric remains woefully inadequate (see the Anderson bupropion trial for an embarrassingly low rate of confirmed medication taken. The authors pay only lip-service to the fact that a conclusion is made that bupropion is a failed drug when data show the majority of subjects took no study medication. This is bad science!). Highlighting biological confirmation of study medication doses taken in reviewing the pharmacological trials would offer a great advancement to the science. Dosing is THE single factor that presents significant risks for Type 2 errors simply because investigators didn't verify that meth users were taking their study meds. 7. Page 6, Line 38. Another example of conflating depression symptoms and co-occurring depression condition. These are not the same thing, though this paragraph again is confused on this issue.

REVIEWER	Dr Niall Galbraith University of Wolverhampton Black Country Partnership NHS Foundation Trust
REVIEW RETURNED	28-Apr-2017

GENERAL COMMENTS	1. The aims of the review are justified, there are no existing reviews which address the questions of this proposed paper. 2. The proposed methodology is rigorous and technically good. 3. My principal concern is the scope of the review - it is very broad. Firstly, the review will look at both psychological and pharmacological interventions. I understand the rationale for considering these two approaches together, but these two approaches could arguably be the subjects of two separate reviews. 4. Secondly, even a review of psychological interventions alone would be very complex. Psychological interventions are highly heterogeneous and there is a question about the validity of grouping this wide range of psychological approaches into one category. Again, one could conduct numerous separate reviews of the different psychological interventions listed within. 5. I would recommend that the authors acknowledge the complexity and heterogeneity of the concepts that they are combining and offer a justification for why this is acceptable in this case. The limitations of the might include a recognition of that the review risks homogenising psychological approaches, which, if subjected to a more fine-grained analysis, might yield different conclusions.

VERSION 1 – AUTHOR RESPONSE

Thank you for your email dated 2 May 2017 requesting recommended revisions to our manuscript entitled "Protocol for a systematic review of psychosocial and pharmacological treatment for methamphetamine use: an analysis of methamphetamine use and mental health symptom outcomes." We sincerely thank the editor and the reviewers for their valuable and insightful comments. Please find below a detailed list of revisions. We have attempted to address all comments, and where we believed changes were not required, we have provided a justification. Please note we have addressed Reviewer 2's comments first as these required a substantial change in focus.

Reviewer #2: Reviewer comments for Dr Niall Galbraith

Specific comments:
“My principal concern is the scope of the review - it is very broad. Firstly, the review will look at both psychological and pharmacological interventions. I understand the rationale for considering these two approaches together, but these two approaches could arguably be the subjects of two separate reviews. Secondly, even a review of psychological interventions alone would be very complex. Psychological interventions are highly heterogeneous and there is a question about the validity of grouping this wide range of psychological approaches into one category. Again, one could conduct numerous separate reviews of the different psychological interventions listed within.”

Based on the reviewer’s comments, this review will consider psychological intervention only studies. This review will now exclude pharmacological intervention only studies and psychological and pharmacological combined intervention studies.

“I would recommend that the authors acknowledge the complexity and heterogeneity of the concepts that they are combining and offer a justification for why this is acceptable in this case. The limitations of the might include a recognition of that the review risks homogenising psychological approaches, which, if subjected to a more fine-grained analysis, might yield different conclusions.”

Considering the reviewer’s comments, the review has been revised to address psychological interventions only. Interventions similar in length and approach will be comparable. Heterogeneous psychological interventions will not be included in a meta-analysis. Similar interventions will be grouped together and compared in a meta-analysis if appropriate. Upon further exploration there appear to be 9 studies incorporating psychological interventions for MA that use the BDI assessment to measure symptoms of depression. Therefore, data collected in the review will be sorted as follows: studies will be grouped by methamphetamine outcomes, methamphetamine outcomes by mental health symptoms and one for methamphetamine outcomes by co-morbid mental disorders. Separate analyses will be conducted for depression, anxiety, psychosis and hostility symptoms.

Different outcomes will not be combined in pooled synthesis (e.g. anxiety, depression, or hostility together). Only measures of the same outcome (e.g. measures of depression) will be pooled using a random effects model. Separate meta-analyses will be conducted for each outcome. Meta-analysis, will however, be contingent on the availability of appropriate data and following assessment and consideration of heterogeneity (described in the manuscript under ‘data synthesis and analysis’).

Reviewer #1:
Overall Opinion. “This is a solid proposal for a systematic review and meta-analysis for psychosocial and pharmacological treatments for methamphetamine addiction, with primary outcome variables being both methamphetamine use at end of treatment (abstinence and methamphetamine reductions) and mental health symptoms. This is an outstanding author team and there is ample experience in the team to be able to pull this off well. Data reflecting this assessment is the high level of precision in describing the protocol and the very well written text throughout. The paper is easy to read and concepts are presented plainly.”

“I believe the authors need, however, an increased level of precision in measuring the two primary outcome variables. I think this might be facilitated by a more thoughtful and comprehensive rationale for why this review is necessary and how it will advance what is already known. One suggestion would be to include in the rationale sections clear descriptions of how this review will offer a meaningful advance beyond a simple update of what is already done in existing Cochrane reviews.”

This has been addressed in the manuscript (page 7):
No review has focused solely on psychological treatment for methamphetamine use and co-occurring

mental health symptoms. Existing Cochrane reviews such as Minozzi, Saulle Crescenzo and Amato (2016), have focused on all psychological interventions for psychostimulants, including MDMA, amphetamine-type stimulants and cocaine. However, they did not focus on methamphetamine use and mental health outcomes, and only included two studies on depression and methamphetamine. Other reviews by Shoptaw (2009) have focused on treatment for amphetamine withdrawal, incorporating psychological and pharmacological treatment and primarily focusing on the withdrawal syndrome when using amphetamines. A review by Shoptaw, Kao and Ling (2009) focused on pharmacological treatment for amphetamines and psychosis. This indicates that Cochrane reviews conducted thus far have not focused on psychological treatment for methamphetamine and co-occurring mental health symptoms. This review will focus on methamphetamine use outcomes, methamphetamine use and psychiatric symptom outcomes, and methamphetamine use and co-morbid psychiatric disorders.

“The epidemiology of meth use presented in terms of type of meth used and the changes in use patterns in Australia is provincial. Evidence from on global methamphetamine use trends would seem more appropriate for this journal.”

The paper has been modified to include global methamphetamine use trends, yet will still include trends in Australia considering the origin and author affiliations.
This has been addressed in the manuscript (page 4):

Substance use accounts for an increasing proportion of the global burden of disease9. Amphetamine-type stimulants have become the most prevalent type of psychostimulants in the world, and it is estimated that there are 24 million users worldwide 10. In South Asia and the Middle East, MA is becoming increasingly popular, yet the current market is in the United States, China, Mexico and Thailand 11. Due to the drug’s psychosocial and medical impact, the detrimental effects can be seen in entire communities, whole populations and individual users 10. The disease burden attributable to amphetamines is of international relevance as Australia has reputable data for mortality rates, and the rates of illicit drug use are similar to those in other high-income countries 11.

“Page 5. Top of page. The issue of psychiatric symptoms, psychiatric diagnoses and the link between these and methamphetamine addiction, withdrawal and protracted abstinence is not fully developed. This section reflects this struggle. In this paragraph, there is a struggle with the concept of psychiatric symptoms versus psychiatric diagnoses, a key concept that needs to be sorted out from the start. Depression, anxiety and other symptoms co-occur frequently with the experience of methamphetamine use and quitting meth, but are not interpreted as having diagnostic importance until these occur 6 months or more independent of meth use (see DSM IV-TR and DSM5; ICDM-9 and 10). Some effort to specify exactly what symptoms are being measured and how these are understood relative to methamphetamine addiction, withdrawal and protracted abstinence is vital. For example, in this paragraph is a sentence that conflates symptoms with diagnoses. There is no indication of how the data collected in the review will be sorted (or if it will). Will reviews be sorted such that there is one for meth outcomes, one for meth outcomes by psychiatric symptoms and one for meth outcomes by co-morbid psychiatric disorders? This is a key problem is never resolved and if not addressed, is in my mind a fatal flaw to this work. Here are the kinds of questions that come to mind: Within the psychiatric symptoms area, how would different symptoms be grouped? There are differences in scales used to measure symptoms. How would these be harmonized in the review? How would the team control for differential influence on outcomes for the review/meta-analysis from studies that have include extensive batteries for measuring psychiatric symptoms while others have less data? Would separate review/analyses be done for depression symptoms? Anxiety? Insomnia? Other symptoms?”

We anticipate that trials will report a variety of mental health outcomes assessed using a variety of

assessment tools and be reported in various units of measurement including either/both continuous and/or binary outcomes. Continuous outcomes will be pooled and reported as a mean difference if trials report the same mental health outcome measure and unit of measurement, or as a standardised mean where different measurement tools/units of measurement are used to report comparable underlying constructs. Binary outcomes will be pooled and reported as risk ratios where outcome and assessment tools are homogenous. We will not pool data where measures or assessment tools are heterogeneous. In such instances, intervention effects will be described narratively.

Different outcomes will not be combined in pooled synthesis (e.g. anxiety, depression, or hostility together). Only measures of the same outcome (e.g. measures of depression) will be pooled using a random effects model. Separate meta-analysis will be conducted for each outcome. Meta-analysis, will however, be contingent on the availability of appropriate data and following assessment and consideration of heterogeneity (described in the manuscript under 'data synthesis and analysis').

Upon further exploration there appear to be 9 studies incorporating psychological interventions for MA that use the BDI assessment to measure symptoms of depression. Therefore, data collected in the review will be sorted as follows: studies will be grouped by methamphetamine outcomes, methamphetamine outcomes by psychiatric symptoms and one for methamphetamine outcomes by co-morbid psychiatric disorders. Please see table below for how different symptoms would be grouped. Separate analyses will be conducted for depression, anxiety, psychosis and hostility symptoms.

Psychological Interventions

Mental Health diagnosis or group e.g. BDI
No MH diagnosis
Methamphetamine Use
Reduction (means)

Abstinence (%)
MH symptoms/diagnostic status
Depression
Anxiety
Psychosis
Hostility

"Page 5, Line 33. This sentence that opens the rationale for the review is simplistic. It's hard to stay in meth treatment. Period. It is not due solely to psychiatric symptoms. This section does not serve the proposed work well and confuses rationale for reviewing outcomes from pharmacotherapy studies in the area. How are psychiatric outcomes measured in the meth trials distinguished? Line 52 in the paragraph would seem to present evidence for NOT including medication studies in the review. A better rationale is needed here."

This section of the rationale has been rewritten according to the above comment. As this review is now only focusing on psychological interventions, this paragraph that discusses evidence for not including pharmacological studies will remain the same.

This has been addressed in the manuscript (page 5 and 6):
Treatment retention can be difficult for MA users in psychosocial treatment 22. Pharmacotherapies have been used in conjunction with the aim of improving treatment engagement and retention 22. However, research on the efficacy of pharmacotherapies to date has produced inconsistent results 23. There is no evidence to suggest that agonist drug treatments can reduce psychological distress associated with MA use 24 25. In a review conducted by Elkashef, et al. 26, pharmacotherapies such as bupropion and sertraline did not increase abstinence from MA in groups who received this drug compared to controls 27. The evidence base for pharmacological approaches for MA use is limited, with conflicting evidence for medication approaches, either for withdrawal, maintenance or relapse prevention treatment 28.

“Page 6, Line 33. This rationale for how this review is organized is not satisfying. My read is that what is being proposed is more of the same, an update of what is known, without guiding the reader to expect that some new information is going to come from this effort excepting more similar findings, though with a few more studies tucked in. If the team wants to go in this direction, then I see no useful purpose for this review. A more useful approach seems necessary. If this is the proposal for an update to a Cochrane review, I see no need to publish the protocol.”

This has been addressed in the manuscript (page 7 and 8):
Cochrane reviews conducted thus far have not focused on psychological treatment for MA and co-occurring mental health symptoms 35 37 40. The present review will focus on studies which have measured MA use and mental health symptoms or diagnoses at baseline and posttreatment. It will report on MA use outcomes, MA use and mental health symptom outcomes, and MA use and co-existing mental disorders. A review of this kind will contribute to the literature by highlighting psychological interventions that can reduce the global public health burden of in terms of MA use and mental health outcomes 41. Thus, this review will assess the effectiveness of psychological treatments in reducing MA use and associated symptoms of mental ill health 41. Results will assist public health and clinical utility of treatment for co-existing MA use and mental health symptoms 42. This systematic review represents an important step in summarising the available evidence for psychological treatment for MA use and will allow for identification of areas for future research.

“The dependent variables are not well described. There has been a host of literature over the past 15 years or so that highlight problems in measuring outcome for meth trials. Some clear definition of outcomes (even abstinence can vary how it’s measured) seems essential to organize this review so that findings will provide new and useful information. For example, in analyzing abstinence vs harm reduction outcomes across both behavioral and medication trials, a rationale needs to be presented why this is an important distinction. In our field there is heated controversy over abstinence as the only desirable outcome compared to value in reductions in methamphetamine use (and corresponding harms). The outcomes collected would seem to go a long way in this proposed comprehensive systematic review/meta-analysis toward helping organize this area of science.”

Refer to table above.

“The concept of dose of treatment to outcomes in trials is not mentioned and is conspicuously absent. For behavioral studies, this could involve dose measured by session attendance (or missing data/drop outs), metrics assessing knowledge/skills learned, etc that could be analyzed relative to outcomes. But in medication studies, dose is essential and is to date poorly and inconsistently measured. Drop

out and pill count data have been used to measure dose, but this metric remains woefully inadequate (see the Anderson bupropion trial for an embarrassingly low rate of confirmed medication taken. The authors pay only lip-service to the fact that a conclusion is made that bupropion is a failed drug when data show the majority of subjects took no study medication. This is bad science!). Highlighting biological confirmation of study medication doses taken in reviewing the pharmacological trials would offer a great advancement to the science. Dosing is THE single factor that presents significant risks for Type 2 errors simply because investigators didn't verify that meth users were taking their study meds."

This has been addressed in the manuscript (page 9):

Review question number 4 page 9 in protocol paper addresses session attendance for psychological interventions.

4. Is the effectiveness of psychosocial treatment for MA use influenced by treatment engagement (quantity, frequency and/or duration of therapy attendance)?
"Page 6, Line 38. Another example of conflating depression symptoms and co-occurring depression condition. These are not the same thing, though this paragraph again is confused on this issue."

This has been addressed in the manuscript (page 7):
Hellem, et al. 4 conducted a review on MA and co-existing depressive symptoms, reviewing nine studies incorporating psychological intervention only; psychological combined with pharmacological interventions; and pharmacological only, and found no research supporting one single treatment approach over others on either MA or depression outcomes. It appears that psychological therapies remain the most effective treatment option, and that pharmacotherapies may be used as an adjunct 21. As it is difficult to maintain enduring behaviour changes in people who experience problems with drug use 29, the longevity of treatment effects relating to long-term abstinence and psychological wellbeing should be further assessed 38 39.

We thank the reviewers for their comments and feel that the manuscript is much improved as a result of the changes. We hope that BMJ Open finds the modified version of the manuscript acceptable for publication.

We look forward to receiving your reply.

VERSION 2 – REVIEW

REVIEWER	Steve Shoptaw, PhD David Geffen School of Medicine Department of Family Medicine University of California, Los Angeles Los Angeles, California, USA
REVIEW RETURNED	25-Jun-2017

GENERAL COMMENTS	I have no further comments.