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)	Comparative efficacy and tolerability of pharmacological interventions for Attention-Deficit/Hyperactivity Disorder in children, adolescents and adults: protocol for a systematic review and network meta-analysis
AUTHORS	Cortese, Samuele; Adamo, Nicoletta; Mohr-Jensen, Christina; Hayes, Adrian; Bhatti, Sahar; Carucci, Sara; Del Giovane, Cinzia; Atkinson, Lauren; Banaschewski, Tobias; Simonoff, Emily; Zuddas, Alessandro; Barbui, Corrado; Purgato, Marianna; Steinhausen, Hans-Christoph; Shokraneh, Farhad; Xia, Jun; Cipriani, Andrea; Coghill, David

VERSION 1 - REVIEW

REVIEWER	Mark Stein University of Washington U.S.A. Receives research support from Shire, and advisor to Shire, Alcobra, and Medici.
REVIEW RETURNED	27-Sep-2016

GENERAL COMMENTS	This is a well-timed and very well designed meta analysis with appropriate inclusion and exclusion criteria.

REVIEWER	Darren Moore University of Exeter, UK
REVIEW RETURNED	09-Oct-2016

GENERAL COMMENTS	This is a very good protocol that is clear, detailed and uses the PRISMA-P checklist to signpost where the recommended detail is included. The systematic review and network meta-analysis will be a highly useful contribution to the field and therefore publishing the protocol in BMJ Open will help to raise awareness as well as assist in assessing the final review against the intentions outlined here. Systematic review search and methods follow best practice guidelines, the process of network meta-analysis and how data will be processed is clear. There are a few points below that warrant consideration or minor edits below and would strengthen an otherwise very good manuscript: While it is a positive that the prevalence of ADHD draws upon Polanczyk et al (2014), just stating the prevalence as 5% without at least acknowledging the heterogeneity in estimates seems a little sweeping.

	Citing some examples of systematic reviews and meta-analyses that have compared two different medications in the introduction (e.g. Hanwella et al. 2011 BMC Psychiatry for methylphenidate versus atomoxetine) would add to the previous literature and still show the inherent benefit of network meta-analysis over these comparisons. There ought to be reference to previous and ongoing network meta-analyses and justification for what this systematic review offers in advance of them (e.g. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4357151/; Roskell et al 2014, Current Medical Research & Opinion). To be clear the wide inclusion criteria and comparisons of the current protocol offer much to advance the field over existing and ongoing reviews. For those interested and/or less familiar it might be useful to cite an example of NMA that has been conducted and made an impact in a different field. Make clear whether e.g. a study with sample of 10-14 year olds would be included – types of participants suggests it might not be as children, adolescents and adults are distinct. Clinical guidelines recommend some flexibility about ages guidelines apply to, so studies may not neatly only sample children, adolescents, adults. Check that Ukoumunne et al (1999) does not suggest an estimate of the intraclass correlation coefficient should be obtained from previous studies if not reported in the study in question, before relying on an arbitrary ICC. Provide justification for defining acceptability of treatment as the proportion of patients who left the study early for any reason during the first 12 weeks – is this always acceptability, or at the very least acknowledge that there may be other measures of acceptability.

VERSION 1 – AUTHOR RESPONSE

Reply to Reviewer #1
This is a well-timed and very well designed meta analysis with appropriate inclusion and exclusion criteria.
Re: We thank the Reviewer for this very positive comment.

Reply to Reviewer #2
While it is a positive that the prevalence of ADHD draws upon Polanczyk et al (2014), just stating the prevalence as 5% without at least acknowledging the heterogeneity in estimates seems a little sweeping.

Re: The Reviewer highlights an important point. The meta-analysis by Polanczyk et al. (2104), (updating the previous one, published by the same group in 2007) showed that most of the heterogeneity between studies was accounted for by differences in either the method of assessment or the diagnostic criteria employed. Following Reviewer's suggestions, we have rephrased the text as follows: " The worldwide-pooled prevalence of ADHD is estimated at around 5% in school-age children, albeit with a substantial heterogeneity between studies, accounted for by differences in either the method of assessment or the diagnostic criteria employed."

Citing some examples of systematic reviews and meta-analyses that have compared two different medications in the introduction (e.g. Hanwella et al. 2011 BMC Psychiatry for methylphenidate versus atomoxetine) would add to the previous literature and still show the inherent benefit of network meta-

analysis over these comparisons.
Re: We thank the reviewer for this valuable suggestion. We have added the following: “Importantly, previous systematic reviews or meta-analyses also attempted to address the comparative efficacy of some available drugs for ADHD, considering either different formulations of the same drug class (e.g., 27) or different classes and agents (e.g., 28). Such systematic reviews/meta-analyses have relied on comparison of effect sizes from individual RCTs or on the qualitative/quantitative summary of head-to-head studies; most of them focused on the comparison of two drugs only. Overall, evidence from these reviews is inconclusive and/or mixed. For example, while some of them found comparable efficacy between psychostimulants and atomoxetine 29-30, others pointed to significantly higher efficacy of psychostimulants compared to other drug. 31-33”

There ought to be reference to previous and ongoing network meta-analyses and justification for what this systematic review offers in advance of them (e.g. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4357151/; Roskell et al 2014, Current Medical Research & Opinion). To be clear the wide inclusion criteria and comparisons of the current protocol offer much to advance the field over existing and ongoing reviews.
Re: Thanks, we do appreciate the Reviewer’s suggestion. We have made a reference to published (Bushe et al., J Psychopharmacol 2016; Roskell et al., Curr Med Res Opin 2014) and ongoing (Catala-Lopez et al., Syst Rev 2015) network meta-analyses on the efficacy and tolerability of ADHD medications, pointing out how our meta-analysis will add to the results from these meta-analyses. The revised text reads as follows: “Whilst previous or ongoing network meta-analyses focused on children with ADHD only 43-44 or on the comparison of only two medications in adults 45, the present one, to our knowledge, is the first NMA addressing the efficacy and tolerability of a set of ADHD medications in children as well as in adults, using stringent criteria to adhere to the methodological assumptions underpinning the validity of a network meta-analysis (see below)”.

For those interested and/or less familiar it might be useful to cite an example of NMA that has been conducted and made an impact in a different field.
Re: We agree with the Reviewer that this will be helpful for the readers and have added an example, as follows: “NMAs addressing the efficacy and tolerability of medications for other psychiatric disorders have been instrumental in providing novel evidence supporting clinical decision making. For instance, a recent NMA35 concluded that, with the possible exception of fluoxetine, antidepressants do not seem to offer a clear advantage for the acute treatment of major depressive disorder in children and adolescents”.

Make clear whether e.g. a study with sample of 10-14 year olds would be included – types of participants suggests it might not be as children, adolescents and adults are distinct. Clinical guidelines recommend some flexibility about ages guidelines apply to, so studies may not neatly only sample children, adolescents, adults.
Re: Studies with sample of 10-14 year olds will be included in the overall analysis, however, we have pointed out that it will be impossible to include these studies in the subgroup analyses comparing children vs. adolescents, unless data separately for children (aged < 12 years), and adolescents (aged ≥ 12) are obtained.

Check that Ukoumunne et al (1999) does not suggest an estimate of the intraclass correlation coefficient should be obtained from previous studies if not reported in the study in question, before relying on an arbitrary ICC.
Re: We thank the Reviewer for raising the issue about intraclass correlation coefficient and agree that our wording in the original version of the protocol should be amended. We therefore deleted the previous sentence (“If the ICC is not reported, it will be assumed to be 0.1”) and reported as follows:”The ICC will be estimated by using the between-cluster variance component and the within-cluster variance component of the study”.

Provide justification for defining acceptability of treatment as the proportion of patients who left the study early for any reason during the first 12 weeks – is this always acceptability, or at the very least acknowledge that there may be other measures of acceptability.
Re: Whilst there may be other measures of acceptability, we have pointed out that this is consistent with Cipriani et al. (2016).

VERSION 2 – REVIEW

REVIEWER	Darren Moore University of Exeter, UK
REVIEW RETURNED	05-Nov-2016

GENERAL COMMENTS	I would thank the authors for carefully responding to the reviewer comments. I believe that these revisions strengthen the protocol, which I would recommend is accepted. The only issue I identified was lines 39-43 of the revision: "It will be to include in this analysis studies assessing, e.g., individuals aged 10-14 years, unless data separately for children (aged <12 years), and adolescents (aged >12) are obtained" I do not follow this and wonder if the intention is to include studies whose samples span childhood and adolescence only if data are reported separately for each?

VERSION 2 – AUTHOR RESPONSE

The following is our specific response to Reviewer #2.

Reviewer #2: The only issue I identified was lines 39-43 of the revision: "It will be to include in this analysis studies assessing, e.g., individuals aged 10-14 years, unless data separately for children (aged <12 years), and adolescents (aged >12) are obtained" I do not follow this and wonder if the intention is to include studies whose samples span childhood and adolescence only if data are reported separately for each?

Re: We apologise for the lack of clarity in the sentence. We have rephrased the sentence as follows: “[if study data are not available for children (aged < 12 years) and adolescents (aged ≥ 12) separately, they will only be included in the main analysis (i.e. combining children and adolescents together - see above: “Synthesis of results”)]”

We hope that with the modifications made, our revised manuscript would be now suitable for publication in BMJ Open.