PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A systematic review with meta-analysis of different models of intervention for pre-school autism: study protocol
AUTHORS	Yoshiyuki Tachibana, Jonathan Green, Yeonhee Hwang and Richard Emsley

VERSION 1 - REVIEW

REVIEWER	Dr Iliana Magiati Assistant Professor/ Clinical Psychologist Department of Psychology National University of Singapore Singapore No competing interests
REVIEW RETURNED	05/12/2011

THE STUDY	I have included all my concerns, comments and suggestions in the section below.
RESULTS & CONCLUSIONS	N/A
REPORTING & ETHICS	I have included all my comments together in one section below.
GENERAL COMMENTS	Thank you for inviting me to review the study protocol of a proposed systematic review and meta-analysis of comprehensive early interventions for pre-school children with Autism Spectrum Disorders. The authors in this paper present their rationale and proposed protocol for such an analysis and I completely agree with them that such a meta-analysis/ systematic review could be highly significant as well as informative and useful for intervention and policy decisions. At the same time, I have two main concerns. Firstly, I am personally not aware of any systematic reviews or meta-analyses publishing their methodology/ protocol prior to publishing the actual study's findings. I have to admit that I wonder how useful it would be for the reader to read the proposed protocol of a meta-analysis without the actual findings of that particular meta-analysis. Published study protocols primarily present in detail the intervention protocol of an RCT trial and as such are potentially interesting and important, as often clinicians and professionals wish to find out more details about the theoretical background, structure, content and approach employed in different intervention outcome studies. I am also aware of a few study protocols on prospective longitudinal cohort studies, but not of meta-analyses. I am thus not sure that reading about the inclusion and exclusion criteria and proposed methodological process of a meta-analysis serves a similarly useful function. As a reader, what I really want to read – and I think most readers would agree- is the actual results of such a meta-analysis.

	The information presented in this paper could be concisely presented in the Methods section of such a publication. Clearly, this is the Editor's decision to make, but as a reviewer I question the significance of publishing a study protocol of a systematic review. Secondly, the significance and potential contribution of such an analysis to the field of early intervention in autism lies primarily in whether the proposed study is able to select, analyze and synthesize early intervention outcome studies reliably, validly and in a way that is informative and helpful. In its present form, it is my opinion that the manuscript does not achieve the aim of clearly describing the study protocol. I have some comments and suggestions regarding the proposed inclusion and exclusion criteria as well as the characterization and definition of the proposed interventions to be included – I outline these below and I hope they will be useful to the authors: TITLE I think the title can be more precise, accurate and describe with more exact terms what will be done (i.e. comprehensive pre-school interventions for pre-school children with Autism Spectrum Disorders). ABSTRACT Upon revision of the manuscript, the abstract also needs to be revised to be more accurate, specific and clear. Age range of children for example needs to be included in the abstract. Non-specific terminology such as "points are lacking" also needs to be avoided. INTRODUCTION The description of the "three models" could improve by clearly defining/ describing these models, including some key references for these models. I will also come back to this issue in the Methods section. I also believe, given the challenges and limitations of current research, that terms such as "this study will reveal which type of intervention is the most effective" are too strong to be supported by evidence and need to be revised. METHODS Types of studies – RCTs continue, unfortunately, to be rare in early intervention outcome studies in ASD. Thus, I wondered whether you are excluding too many studies by selecting only RCTs and that perhaps by including studies that are not RCTs but have a comparison/ control group and then rating them all on quality (where clearly RCTs will receive higher scores than non-RCTs) might be more informative and inclusive of a larger body of available research. Types of participants – the exact age range of participants and the exact diagnosis (i.e. autism, ASD, Asperger's PDD) need to be stated in this section and not later on, as the reader keeps wondering about these characteristics. Types of interventions – this section is, in my opinion, the most challenging one to characterize and define. You have organized interventions into three groups, but it is unclear on what basis such a structure has emerged, thus this needs to be theoretically explained and supported by evidence. In addition, a major issue is that of "overlap" or "eclectic" approaches, which I am sure you are aware

	can often be the “norm” in ASD interventions rather than the exception. ABA-based interventions are also multimodal, they also target a range of aspects of children’s development and they also have a developmental focus, so what is of paramount importance is to clearly define and explain how you will group the interventions and how you will deal with comprehensive “eclectic” approaches. The reader needs to be clear how and why you organize the different interventions in the proposed categories. Types of outcome measures- primary measures need to be defined more clearly and I think it would be helpful to include examples of tools/ measures you will accept as measuring primary outcomes. For example, it is not clear to me how qualitative impairments in social interaction and communication (primary outcome) may be that different to social communication in an interactive setting (intermediate outcome) and how you can clearly and unambiguously separate these (unless you do this by measure, in which case this section needs to be strengthened by including example measures). Adaptive behavior should also be clearly included (presumably in secondary outcome or primary outcome if you decide to measure socialization or communication subscales as primary). Searches - The words “treatment” and “therapy” were not included in your proposed search. Data collection and analysis – Inclusion criteria 5 is most likely going to result in inclusion of a very small number of studies in your proposed meta-analysis, if any. Ethically, most studies cannot withhold early intervention from the control/ comparison groups, thus it is unlikely that you will find a study with a control group of children who did NOT receive early intervention for autism. Most RCTs with a waitlist control will be studies evaluating effectiveness of short-term, time-limited interventions, not comprehensive, long-term multimodal interventions such as the ones you propose to evaluate. Thus, I think it may be worthwhile reconsidering this criterion. Also, in exclusion criteria 6 you mention “cognitive/behavioural” intervention. I am unclear why you included CBT (“cognitive”) here for pre-school children. Exclusion criterion 3 also needs to be defined carefully as stating that “study did not report adequately” can be open to selection bias. What are the important information that you need to have? Exclusion criteria 5 will also be problematic – most families of most children in most trials try a number of different interventions whether they are in the experimental or control group over and above the comprehensive intervention that is being evaluated and we know the percentages of families of children with ASD trying alternative medicine at some point are very high. If you exclude all these studies/ families, then it is likely your sample size of studies may be small and possibly not representative of interventions for pre-school children with ASD. You may want to consider these issues and revise the criteria. Measures of treatment effect – Could you provide a reference for the statistical analyses/ methods you are proposing for the readers (i.e. for random effects model using a standardized mean difference) as they are novel in this field? Similarly, please provide references for Chi2 test of consistently of results. Assessment of heterogeneity – if the meta-analysis includes such a small number of studies, I would argue that it would be more appropriate to revise the exclusion and inclusion criteria rather than

	set the p value to 0.10. Please see my comments above regarding some of the exclusion and inclusion criteria that I think will potentially be problematic and result in a very high exclusion of good quality published studies in the field. The same point goes for subgroup analyses, you need to have enough studies to be able to carry out these potentially very informative analyses. P. 11 (measures of treatment effect) and p. 13 (data synthesis) are repetitive and exactly the same sentences are used in some parts. Given the many challenges in trying to synthesize such complex literature, I would suggest that you consider including a section on "anticipated challenges and proposed course of action" so that the many difficulties discussed above can be openly and systematically addressed. One challenge I think is worth discussing in a little more detail includes how you will compare between findings from different studies with different time points (i.e. outcomes reported after 3, 6, 12, 24 months etc). Finally, you mention "parent-mediated" vs "child-mediated" intervention delivery – I think it is important to define and clarify what you mean as most comprehensive interventions target the child but also most emphasize training the parents and parents working as co-therapists.

REVIEWER	Sigmund Eldevik, Ph.D Associate Professor Oslo & Akershus Univeristy College No competing interests.
REVIEW RETURNED	14/12/2011

THE STUDY	I think the study is set up appropriately. However, with the suggested inclsuion criteria my guess you would not be able to find an adequate number of studies to include.
GENERAL COMMENTS	I think such a study should be done, but I think you need to adjust inclusion criteria so that a meaningful number of studies could be included.

VERSION 1 – AUTHOR RESPONSE

Our responses to the managing editor's and the reviewers' comments are in the supplementary file, since responses in text style here might be uncomfortable to read. Please find the attached file (Page 20 to 29 in the synthesized document).

VERSION 2 – REVIEW

REVIEWER	Dr Iliana Magiati Assistant Professor/ Clinical Psychologist Department of Psychology National University of Singapore No competing interests.
REVIEW RETURNED	09/01/2012

THE STUDY	Thank you for inviting me to review the revised manuscript bmj-open-2011-000679.R1 titled “A systematic review with meta-analysis of comprehensive interventions for preschool children with autism spectrum disorder: study protocol”. The authors have sufficiently responded to most of my comments and suggestions. Specifically, they have revised their title to make it more specific and precise; they have revised the abstract; they have better described the three models (behavioral, communication-based and developmental) by which they propose to organize their systematic review and meta-analysis; they have described the participants of the proposed study more clearly; they have included the terms “treatment”, “therapy” in their proposed search terms; deleted inclusion criteria that would have resulted in including a small number of studies only and clarified all inclusion and exclusion criteria. The study protocol reads much better compared to the original manuscript and is more clear. Where changes were not made, the authors have clearly and convincingly argued in favor or their initial decisions (i.e. regarding the importance of publishing a proposed study protocol for a meta-analysis; including RCTs only in their study). Thus, I believe this revision is stronger and more methodologically sound. I have some final minor comments and recommendation to further improve the manuscript, which the authors can consider: - Consider replacing the term “preschool autism spectrum disorder” with “preschool children with ASD” throughout the document in order to meet APA guidelines regarding best use of language to describe participants - Despite the good standard of English language, I would still advice the authors to review their manuscript one more time for grammar and syntax. - Change “most” individuals in final line of first paragraph to “many” individuals – in fact, many outcome studies in adulthood show that many individuals remain very vulnerable and in need of services. - Please consider including one or two references as examples of behavioral, social-communication and multimodal developmental interventions in the second paragraph of the introduction. - Can you clarify what you mean by “intermediate developmental endpoints” and “surrogate endpoints” (p.4, last line, p.5 first line)? - Clarify the “quality criteria” ratings mentioned in Methods, Type of Studies section. - I am not sure that “adaptive behavior functioning” as measured by the Vineland Adaptive Behaviour Scales constitutes an intermediate outcome – social and communication skills are primary areas of difficulty in ASD and I would think they are primary or secondary outcome. - Please consider including “trial” and “outcome” too in your search terms. - The exclusion criteria need to be more clearly written with more attention to language/ grammar. - With exclusion criterion 7 do you mean that you will exclude all studies who do not have a TAU comparison group? What if a study compares a behavioral with a developmental approach? Wouldn’t the findings of such a study be directly relevant to the aims of your systematic review and meta-analysis? - Please delete the age groups of adolescents and adults from your list in p. 13, point 3, as your study is only on pre-school children. - The first paragraph of the discussion needs to be written in a more “moderate” tone – i.e. “this study will provide the most reliable basis for decisions on early intervention”. Clearly this depends on the quality of the study eventually so best to rephrase to “can provide a more reliable basis”.

VERSION 2 – AUTHOR RESPONSE

Responses to Dr. Iliana Magiati's comments:

- Consider replacing the term "preschool autism spectrum disorder" with "preschool children with ASD" throughout the document in order to meet APA guidelines regarding best use of language to describe participants

The term "preschool autism spectrum disorder" has now been replaced with "preschool children with ASD" throughout the document.

- Despite the good standard of English language, I would still advice the authors to review their manuscript one more time for grammar and syntax.

Our manuscript has now been reviewed for grammar and syntax.

- Change "most" individuals in final line of first paragraph to "many" individuals – in fact, many outcome studies in adulthood show that many individuals remain very vulnerable and in need of services.

This has now been changed.

- Please consider including one or two references as examples of behavioral, social-communication and multimodal developmental interventions in the second paragraph of the introduction.

One reference for each model has now been included.

In more detail,

These programmes tend to fall into three models; i) those based on behaviour change which use applied behavioural analysis (ABA) (e.g. [5]); ii) those focused on therapies targeted at improving the social communication impairment, the core symptom of autism (e.g. [6]); iii) multimodal interventions targeted across areas of autistic children's development (e.g. [7]).

References:

5. Smith T, Groen AD, Wynn JW. Randomized trial of intensive early intervention for children with pervasive developmental disorder. American Journal on Mental Retardation 2000;105(4):269-85.
6. Green J, Charman T, McConachie H, Aldred C, Slonims V, Howlin P, et al. Parent-mediated communication-focused treatment in children with autism (PACT): a randomised controlled trial. The Lancet 2010;375(9732):2152-60.
7. Dawson G, Rogers S, Munson J, Smith M, Winter J, Greenson J, et al. Randomized, controlled trial of an intervention for toddlers with autism: the Early Start Denver Model. Pediatrics 2010;125(1):e17.

- Can you clarify what you mean by "intermediate developmental endpoints" and "surrogate endpoints" (p.4, last line, p.5 first line)?

'Surrogate endpoint' is a well characterized term in the trials and intervention literature – essential an intermediate outcome that is a proximal equivalent to the endpoint change desired (for in change in immune status after vaccine) and can in some way 'stand for it'. The text now clarifies our meaning here in relation to the intermediate developmental endpoints reported in studies.

In more detail,

Specifically, there has been variation in whether endpoints have been framed in terms of specific autism symptom outcomes, non autism-specific outcomes that are not specific to autism (such as for instance IQ), or 'intermediate' endpoints relating to aspects of development that may have some relationship to later autism symptoms – examples would be changes in joint attention or parent-child interaction. These latter two kinds of outcome are often reported, without necessarily strong justification, as if they were the equivalent of change in autism symptoms (i.e. as 'surrogate' endpoints); and this can cause real confusion.

- Clarify the "quality criteria" ratings mentioned in Methods, Type of Studies section.

This part has now been corrected as below.

We will include randomized controlled trials and subject these to a rating on the Cochrane Collaboration tool for assessing risk of bias.

- I am not sure that "adaptive behavior functioning" as measured by the Vineland Adaptive Behaviour

Scales constitutes an intermediate outcome – social and communication skills are primary areas of difficulty in ASD and I would think they are primary or secondary outcome.

We agree with the reviewer and "Adaptive behaviour functioning" has now been put into the secondary outcomes.

- Please consider including "trial" and "outcome" too in your search terms.

These have now been included in the search terms.

- The exclusion criteria need to be more clearly written with more attention to language/ grammar.

The exclusion criteria have now been corrected.

- With exclusion criterion 7 do you mean that you will exclude all studies who do not have a TAU comparison group? What if a study compares a behavioral with a developmental approach? Wouldn't the findings of such a study be directly relevant to the aims of your systematic review and meta-analysis?

We need to limit the studies to those using a TAU comparison group because of our statistical analyses. Following Cochrane Handbook for Systematic Reviews of Intervention, we are using an inverse variance method within a random effects model. This requires treatment of TAU arms in a standard way – excluding comparisons of two test treatments in which the baselines are not TAU.

- Please delete the age groups of adolescents and adults from your list in p. 13, point 3, as your study is only on pre-school children.

These have now been deleted.

- The first paragraph of the discussion needs to be written in a more "moderate" tone – i.e. "this study will provide the most reliable basis for decisions on early intervention". Clearly this depends on the quality of the study eventually so best to rephrase to "can provide a more reliable basis".

The first paragraph of the discussion has now been corrected according to these comments.

In more detail,

Meta-analysis of RCTs across types of intervention for preschool children with ASD is an important step in providing a reliable basis for implementation decisions. Since previous analyses have been essentially restricted to specific intervention types, and often with different outcome criteria, a study across three representative models: behavioural, multimodal developmental or communication-focused models will guide future clinical practice and research trials for children with ASD.

All correspondence should be sent to
Yoshiyuki Tachibana M.D., Ph.D.
Room 4.321, Psychiatry Research Group, 4th Floor (East), Jean McFarlane Building, University Place, University of Manchester and Manchester Academic Health Sciences Centre, Oxford Road, Manchester, M13 9PL, UK

Tel/Fax: +44 (0) 161 306 7941; E-mail: yoshiyuki-tatibana@hotmail.co.jp

We are looking forward to your replies.

Sincerely yours,

Yoshiyuki Tachibana