

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy of Parent- mediated communication-focused treatment in toddlers with autism (PACT) delivered via videoconferencing: a randomised controlled trial study protocol
AUTHORS	Jurek, Lucie; Occelli, Pauline; Denis, Angelique; Amestoy, Anouck; MAFFRE, Thierry; dauchez, tom; Oreve, Marie-Joelle; Baghdadli, Amaria; Schroder, Carmen; Jay, agathe; Zelmar, Amélie; Revah-Levy, Anne; Gallifet, Natacha; aldred, Catherine; Garg, Shruti; Green, Jonathan; Touzet, Sandrine; Geoffray, Marie-Maude

VERSION 1 – REVIEW

REVIEWER	Kathleen Baggett Georgia State University
REVIEW RETURNED	21-Oct-2020

GENERAL COMMENTS	<p>This manuscript, "Efficacy of Parent- mediated communication-focused treatment in toddlers with autism (PACT) delivered via videoconferencing: a randomised controlled trial study protocol", reflects an important topical area of research. However, as written, there are numerous concerns and limitations that severely restrict enthusiasm about contribution of this manuscript to the field. Notable limitations are detailed below along with suggestions for addressing when possible:</p> <ol style="list-style-type: none">1. ASD prevalence statistic of 1-1.5% is outdated. Current data indicate nearly double this prevalence rate- of 1 out of 54.2. The manuscript incorrectly states that "PACT (Preschool Autism Communication Trial) is the only parent-mediated therapy that has shown a significant and sustained impact on autism symptom reduction". In fact there are numerous published randomized controlled trials showing short and long term effects. See recent review- Moore et al. 2020 as one example of several reporting numerous RCTs demonstrated effects of parent mediated interventions on toddlers with ASD.3. The background support for conducting the study states: "The symptom severity as measured by the Autism diagnostic Observation Schedule version 2 (ADOS-2) was significantly reduced between both groups". This is not compelling. If the treatment group was not significantly different than the other group, evidence of efficacy or effectiveness is unclear.4. Combining the treatment of interest with intervention as usual and comparing this to no intervention is a serious design limitation for which no rationale is provided. The stated purpose of the study cannot be achieved with this design as described. Typically, rigorous
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	<p>RCTs examine treatment of interest against treatment as usual- not no treatment.</p> <p>4. Research questions are not presented and need to be added.</p> <p>5. In general, measures are not sufficiently described relative to psychometric integrity or their procedural use within the study. For example, no description of how or why the Vineland Assessment Behavioral Scale by videoconferencing would be used to qualify study inclusion. More information is essential for assumptions about generalizability of the sample to be recruited. Measurement indices and procedures need to be thoroughly described.</p> <p>6. No consort plan or description are provided.</p>
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REVIEWER	Sallie Nowell The University of North Carolina - Chapel Hill, USA
REVIEW RETURNED	16-Nov-2020

GENERAL COMMENTS	<p>This study protocol proposes an RCT of PACT delivered via teletherapy to rural French families of toddlers with autism symptoms. Extending PACT to rural families who may not otherwise receive these services is an area of research and clinical need. the mixed methods approach is an innovative way to learn about the effectiveness of PACT delivered via telehealth. Thank you for inviting me to review this protocol.</p> <p>Study protocols published in BMJ Open are required to report study dates. I see your start date but not your anticipated end date.</p> <p>Participant consent and human subjects protections are mentioned several times but ethical approval from the 6 institutions involved in the study is not discussed. Further, the consent process seems to be happening after the diagnostic eligibility assessments. In similar studies I have worked on, we have to consent families before we do any assessment with them. So we consent to the assessment/eligibility phase and then if families are eligible, we consent them again to the intervention/randomization phase of the study. Please check with your institutions about requirements for seeing research subjects for eligibility assessments without consent.</p> <p>I recommend having a native English speaker review the manuscript for copy edits. It's clear what you're trying to say, but the message would be more effective if the English were cleaned up. Some of this could be edited by another read-through by the authors.</p> <p>Line 44 - please the name of the person and date of communication for the personal communication as per APA 7 guidelines</p>
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VERSION 1 – AUTHOR RESPONSE

ANSWERS TO THE REVIEWER 1

1. We thank the reviewer for this commentary. Prevalence is at least 1.5% in developed countries, with recent increases primarily among those without comorbid intellectual disability according to the last review of Lyall and colleagues (2017). A study of Kogan and colleagues (2018), Parent-Report

based, reported that prevalence of Autism Spectrum Disorder among US Children (3-17 years old), is 2.5%. We changed our Introduction and bibliography according to these data.

Kogan MD, Vladutiu CJ, Schieve LA, Ghandour RM, Blumberg SJ, Zablotsky B, Perrin JM, Shattuck P, Kuhlthau KA, Harwood RL, Lu MC. The Prevalence of Parent-Reported Autism Spectrum Disorder Among US Children. *Pediatrics*. 2018 Dec;142(6):e20174161. doi: 10.1542/peds.2017-4161. PMID: 30478241; PMCID: PMC6317762.

Lyall K, Croen L, Daniels J, Fallin MD, Ladd-Acosta C, Lee BK, Park BY, Snyder NW, Schendel D, Volk H, Windham GC, Newschaffer C. The Changing Epidemiology of Autism Spectrum Disorders. *Annu Rev Public Health*. 2017 Mar 20;38:81-102. doi: 10.1146/annurev-publhealth-031816-044318. Epub 2016 Dec 21. PMID: 28068486; PMCID: PMC6566093.

2. We assume that the reviewer is referring to her recent co-authored systematic review (Moore, D. M., Baggett, K. M., & Barger, B. (2020). Measuring parent positive support of social communication among toddlers with autism: A systematic review. *Psychosocial Intervention*. Ahead of print. <https://doi.org/10.5093/pi2020a20>). As we read this review, it was specifically focused on the use of parent-child interaction measures within early parent-mediated interventions, rather than the efficacy of the early interventions themselves on standard outcomes. We based the specific assertion in our paper on systematic reviews of intervention efficacy; for instance that of French and Kennedy (2018) which included use of the Cochrane Risk of Bias tool to evaluate study quality. We felt the issue of study quality was salient, since these authors showed that among the 48 relevant RCTs identified in their search, only six met criteria for low risk of bias across domains of the Risk of Bias Tool. Among these 6 studies, PACT was the only one that showed efficacy on objectively assessed autism symptom outcomes specifically, and has also demonstrated sustained effects six years from intervention end (Green, 2010; Pickles, 2016). The more recent high quality metaanalysis from Sandbank and colleagues (2020) supports these conclusions and also identifies the strength of evidence of the PACT model.

While we consider that this evidence does therefore support the specific statement we made in the paper (relating to 'significant and sustained impact on autism symptom reduction'); we do of course acknowledge that there are a considerable number of other early intervention models for autism with other efficacy evidence apart from specific autism symptoms and long-term outcomes. We have therefore changed the text to remove the inference of 'uniqueness' – and have further referenced the SRs mentioned.

French L, Kennedy EMM. Annual Research Review: Early intervention for infants and young children with, or at-risk of, autism spectrum disorder: a systematic review. *J Child Psychol Psychiatry*. 2018 Apr;59(4):444-456. doi: 10.1111/jcpp.12828. Epub 2017 Oct 20. PMID: 29052838.

Sandbank, M., Bottema-Beutel, K., Crowley, S., Cassidy, M., Dunham, K., Feldman, J. I., Crank, J., Albarran, S. A., Raj, S., Mahbub, P., & Woynaroski, T. G. (2020). Project AIM: Autism intervention meta-analysis for studies of young children. *Psychological Bulletin*, 146(1), 1–29. <https://doi.org/10.1037/bul0000215>

3. We thank the reviewer for highlighting this unclear sentence. The results represented the effect size on between-group comparison in a parallel group RCT. We have altered the text to clarify:

“In a trial of PACT intervention compared to regular care, PACT showed a statistically significant effect at 13 month endpoint to reduce of autism symptom severity measured on Autism diagnostic Observation Schedule version 2 (ADOS-2) (effect size 0.64; 95%CI 0.07-1.20); and an increase in parental communication synchrony with the child and child communication initiations with parent [13]. The follow-up study showed evidence of sustained effect on autism symptom severity six years after intervention end, with a significant overall reduction in symptom severity over the course of trial and follow-up period (effect size=0.55, 95% CI 0.14 to 0.91, p=0.004)[14]”.

4. We apologize for the typo error here. The design is for a comparison of PACT plus TAU (usual care) against TAU alone. This has now been made clear in the text.

This is the design used in the original Green et al study (2010). It is done for pragmatic reasons. We are not ethically able to tell and control families randomized to PACT not to access other treatments and in practice. However, we think it unlikely on our population that a great deal of TAU will be accessed. We will be collecting full data on all TAU used in both arms and will describe that in the study report. In Green et al 2010, TAU use was largely balanced across both study arms.

Green J, Charman T, McConachie H, Aldred C, Slonims V, Howlin P, Le Couteur A, Leadbitter K, Hudry K, Byford S, Barrett B, Temple K, Macdonald W, Pickles A; PACT Consortium. Parent-mediated communication-focused treatment in children with autism (PACT): a randomised controlled trial. *Lancet*. 2010 Jun 19;375(9732):2152-60. doi: 10.1016/S0140-6736(10)60587-9. Epub 2010 May 20. PMID: 20494434; PMCID: PMC2890859.

4'. The research question is stated in the following sentence (p.3) at the end of the introduction; we added “on the autistic symptoms” to clarify: “The proposed protocol is for a large RCT in children under 3 years with ASD to evaluate the effectiveness of PACT therapy delivered to parents by videoconference.” We emphasized this sentence in adding “research question “at the beginning of the sentence.

5. To be online and the number of words allowed by the journal in the main text, the description and the procedural use of each test has been put in the appendix. We updated the description as recommended by the reviewer.

We used VABS by videoconferencing to check if the family have at least a sufficient connection to do a videoconference. We stated that in the inclusion criteria “are able to do videoconferencing with therapists from the center (assessed through the conduct of the Vineland Assessment Behavioral Scale by videoconferencing)”. The procedure is the following: A first assessment will be proposed to the parents. In case of technical difficulties during the first meeting, a second, and if necessary, a third meeting will be proposed. Tips to improve videoconferencing will also be provided to the parents. In case of failure of every remote assessment, the family will be considered as not eligible for the study as the remote PACT session require the ability to conduct a videoconferencing meeting. We added that in the appendix too.

We can also note that the use of videoconferencing is interesting to reduce the journeys and burden of the families (particularly with young children) who participate to the studies (Pagano, 2017).

Pagano-Therrien J, Sullivan-Bolyai S. Research Participation Decision-Making Among Youth and Parents of Youth With Chronic Health Conditions. *J Pediatr Health Care*. 2017 Mar-Apr;31(2):167-177. doi: 10.1016/j.pedhc.2016.07.002. Epub 2016 Aug 20. PMID: 27553117.

6. We presented a consort flow-chart in figure 1. We added the term “consort” to the title for clarity. <http://www.consort-statement.org/consort-statement/flow-diagram>

ANSWERS TO THE REVIEWER: 2

We thank the reviewer for this commentary. We added the anticipated end date following the start date. “The anticipated end date will be the 30th June, 2023. “

In France, we are using a centralized IRB Review Process and the study protocol is approved by one committee for every institution involved in the study within France.

Concerning the consent process, it is indeed happening after the diagnostic eligibility assessments. The diagnostic process used in the study is not different from the usual diagnostic process performed in our different centers. It involves a measure of autistic symptoms in a semi-structured interview (ADI-R), a direct measure of autistic symptoms (ADOS-2), a measure of global development (with MSEL) to ensure the symptoms are not part of a global delay diagnostic and finally, a measure of adaptive behavior (VABS-2) to evaluate the level of disability. As this is the usual process, the written consent is not required. Parents are consenting to the assessment by showing up to the center for the different assessments.

We thank the reviewer for her comments and a native English speaker now reviewed the manuscript.

Line 44 –

We updated this form according to APA 7 guidelines. Thank you for reviewing this protocol.

<https://apastyle.apa.org/style-grammar-guidelines/citations/personal-communications>

VERSION 2 – REVIEW

REVIEWER	Sara Nowell, PhD UNC-Chapel Hill, USA
REVIEW RETURNED	16-Feb-2021
GENERAL COMMENTS	Thank you for the opportunity to review this revision. The revised manuscript reflects all of the changes that I suggested and is now ready for publication, in my opinion. I look forward to hearing the results of this exciting trial and wish you the best with the work.