Reviewer's report

Title: Probiotics and oxytocin nasal spray as neuro-social behavioral interventions for patients with autism spectrum disorders: a pilot randomized controlled trial protocol

Version: 1 Date: 12 Dec 2019

Reviewer: Sarah Daisy Kosa

Reviewer's report:

Thank you for the opportunity to review this important manuscript. There are some typographical (e.g., consistent use of abbreviations) and referencing errors that take away from the paper. I make some minor suggestions to also improve the reporting of the protocol to reflect that it is a pilot study.

1. Suggest revising to the abstract from "This paper presents a protocol for a pilot randomized controlled trial testing oral supplementation of L. reuteri probiotics and intranasal OXT spray on the effect of social and behavioral functions in ASD patients. The main objective of this pilot trial is to investigate feasibility, tolerability, adherence, and preliminary efficacy of the proposed interventions in ASD patients." could be revised to "This paper presents a protocol for a pilot randomized controlled trial to evaluate the feasibility of conducting a full trial comparing oral supplementation of L. reuteri probiotics and intranasal OXT spray to placebo on the effect of social and behavioral functions in ASD patients at (TIME POINTS). The study will also capture preliminary estimates of efficacy of the proposed interventions in ASD patients." to adhere to the PICOT format and also to ensure that the primary outcome is not clinical (which you would be underpowered for), but rather the feasibility of the larger trial.

2. Consider a revision to this sentence in the introduction "For instance, patients with low baseline level of oxytocin may benefit from oxytocin treatment, while patients with gut microbiome abnormality may benefit from probiotics supplementation. Oxytocin (OXT) is...". Oxytocin should be abbreviated and the abbreviation defined the first time it is used. Additionally, it seems odd to discuss oxytocin treatment, before explaining what it is.

3. An overall comment, seems strange that the references are inside of the punctuation, I don't believe this is consistent with the journal style.
4. Another overall comment on references, the journal names seem to be sometimes capitalized (each word) and sometimes only capitalized on the first word. The same problem with the title of the articles. Suggest referring to journal referencing style.

5. Some references are missing issue number and page numbers, could include doi if no page and issue numbers available (online first?), e.g., Mechanisms Underlying Microbial-Mediated Changes in Social Behavior in Mouse Models of Autism Spectrum Disorder. Neuron. 2018. Suggest referring to journal referencing style.

6. You have started to define feasibility criterion, but you have several process related outcomes you mention capturing: track the number of patients who meet study criteria, the number approached for enrollment, the number enrolled, reasons why patients chose not to participate, dropout rate, and reasons for dropout, but for which you don't define thresholds of success / targets.


8. Agree with previous reviewer, while the SPIRIT guidelines are definitely appropriate, this protocol would benefit from following the CONSORT extension for pilot trials. There are several dimensions related to pilot trials specifically that could be better reported, as per the previous reviewer's comments, that are not fully addressed.

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