## General Response

We would once again like to thank both reviewers for taking the time and effort to review our Stage 1 Registered Report. We are very grateful for all of their feedback, which has vastly improved the quality of our work.

Richel Bilderbeek had no additional comments on the manuscript, and the below responses relate to comments from Marietta Papadatou-Pastou. Reviewer comments are in **bold** and our responses are in regular text.

## Responses to Reviewers

**1. Risk of bias: The authors state that they will not conduct a risk of bias analysis, but they actually are - risk of bias is another term used for quality assessment (which is one of the three aims of the review). So, risk of bias (with a note maybe that it is performed under the term "quality assessment"?) could be added to the checklist and the abstract.**

Although risk of bias assessment is a type of quality assessment, the specific quality assessment we are performing in this project is a reporting quality assessment (using the PRISMA-Pre checklist). Risk of bias and reporting quality are related and overlap to a degree, and a formal risk of bias assessment of systematic reviews would be performed using the ROBIS checklist. The use of ROBIS is not part of our study design, and the ROBIS tool is specifically designed for systematic reviews of clinical intervention studies and would have to be substantially adapted before we could use it to assess in vivo systematic reviews.

We have made minor edits to the text to clarify in every instance that we are specifically referring to reporting quality and not any other form of quality assessment.

**2. One of my main suggestions (I also included it in the first round of reviews), is that an explanation of why NDC were chosen as the conditions that will be the focus of this review, should be given. Moreover, why are you interested in those specific 102 genes (or Rett or Fragile X)? What is their clinical importance, for example? Moreover, why did you focus on genetically modified animals and not other animal models? These choices are fine, but they need to be justified in the introduction. In their response to my comment in the previous round of reviews the authors comment that they now mention the "litter effect" in terms of NDC research, but this does not justify why they want to focus on NDC in the first place.**

Thank you for this comment and we apologise for not adequately addressing it in our last round of revisions. We have altered the text of Introduction Paragraph 1 to better justify our focus on genetic models of autism.

**3. In the PRISMA 2015 protocol checklist it is stated by the authors that the CRediT taxonomy was used, but it was not (e.g. "critical insights, preliminary searches", etc. are not part of the CRediT taxonomy; https://credit.niso.org). I do not object with the way credit is given now, but if the authors want to state that they used the CRediT taxonomy, they should make appropriate changes to their "Contributors" section.**

Thank you for highlighting this. We apologise for this discrepancy and have updated the contributors section to use CRediT taxonomy.

**4. Item 5c in the PRISMA 2015 protocol checklist states: "Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol" - I believe the answer here is "none" (as the funders should have had no role in developing the protocol" and not "PhD studentship".**

Thank you for clarifying this. We have edited the PRISMA protocol checklist and the abstract text accordingly.

**5. Correct me if I am wrong, but I do not think preprints are included in PubMed, Embase, or Web of Science (and I think this also applies to conference abstracts). If this is the case, then where will preprints and conference abstracts be sought from?**

Pubmed contains BioRxiv with publication dates from January 2020, so not all preprints will be available. However, we believe it is likely that systematic reviews published on BioRxiv prior to this date would have been published in a peer-reviewered journal by this time. Both Web of Science and EMBASE contain conference abstracts. We will also contact authors of PROSPERO registrations of systematic reviews relating to autism to establish if their review has been published (and have added this to our methodology).

**6. Abstract: "...however, methods differ depending on the type of research being reviewed". Is this sentence necessary? I mean, will "type of research" be a variable of interest in your review?**

Thank you for highlighting this. When we wrote this sentence, we intended “type of research” to describe how the differences between preclinical or in vivo and clinical research relate to differences in systematic review methodology. We have clarified this by editing the sentence to read “In vivo research has unique characteristics not shared with clinical research, meaning approaches to systematic review must be adapted to this context.

**7. Abstract: “We will annotate various characteristics from included systematic reviews and assess the reporting quality of each included review <u>will be assessed</u> using an adapted version of the PRISMA checklist (PRISMA-Pre). We will not conduct a risk of bias assessment.” This sentence has a grammatical issue.**

Thank you for highlighting this, we have edited the sentence to fix the grammatical error.

**8. Abstract: “We will not conduct a meta-analysis.” I don’t think this sentence is necessary (and eats away your precious word count!)**

Thank you for this suggestion, we have removed the sentence as you have suggested. Our abstract word count is now 249, which will hopefully make it acceptable to most journals with a maximum word count of around 250.

**9. Minor comment: Please add a comma “,” before “and” only if three or more items are listed (if you decide to use this “Oxford comma” please do it consistently).**

Thank you for pointing this, we have gone through and made sure Oxford comma usage is consistent.

**10. Introduction (first sentence): “De novo genetic alterations have been implicated in several neurodevelopmental conditions (NDCs), characterised by intellectual disability (ID), epilepsy, and autism spectrum condition (ASC). “ Is this sentence needed? I mean, you do not focus on “de novo alterations” (in fact they are not mentioned again in the manuscript), so there is no reason to start the manuscript with this information. Do you mean genetics in general maybe?**

Thank you. Indeed, whether a mutation occurs de novo or has been inherited is not a defining characteristic for inclusion, and we have amended the text accordingly.

**11. Introduction (paragraph two): All these variables (that introduce error) are not an object of this review. Then why mention them in the introduction (esp. so early on)? You will not investigate bias on a study level, but on a systematic review level (and in fact only one of the many items of the PRISMA-Pre checklist, is “Report the risk of bias of the primary studies (individual studies/across outcomes)” – so, this cannot be so central in the introduction. Maybe if the introduction is restructured to first say how clinicians use systematic reviews, what systematic reviews are, how they can help identify bias and then (briefly) which are the forms of bias? In any case, the focus of this review is the quality of the systematic reviews, not the quality of the primary studies included in said reviews. I trust that the introduction might be improved if the senior authors used some of their expertise to build the rationale.**

Thank you. While the quality of individual studies is of critical importance (and indeed the topic of other work from this group), it is, as the reviewer notes, not an objective of this review. We have therefore remover this paragraph.

**12. Introduction (paragraph two): Please explain what the "litter effect" is.**

This paragraph has now been removed. However, by way of explanation, there may be circumstances where a maternal phenotype (driven by the genetic manipulation of interest) has effects on developing pups, to which all pups would be exposed. In Het x Het crosses, wild type progeny would also be exposed to this maternal phenotype. Further, the consideration of transgenic pups as individual units of assessment ignores any shared maternal effects and is a form of pseudo replication.

**13. Inclusion and exclusion criteria: “We will include systematic reviews or meta-analyses that include animal studies, either as a review limited to animal studies or ones which include them alongside other study types (e.g. clinical studies). We will exclude publications which are not systematic reviews or meta-analyses, as well as systematic reviews or meta-analyses which do not include animal studies.” These two sentences say the same thing -why not say “We will only**

**include…" and remove the second sentence? (Similarly for the second criterion, it feels like the second sentence repeats info already presented in the first sentence.)**

Thank you for making this suggestion, we have edited the two criteria as you suggested to avoid repetition.

**14. Minor comment: Quite a number of typos are to be found in this version of the manuscript (e.g., abstract, "Search Strategy", second like "models" should be "model").**

Thank you. We have gone through the full manuscript and fixed any typos.

**15. The following bullet points are not needed (as they are subheading that appear straight after anyways):**

- **Bibliographic data**
- **Characteristics**
- **Reporting quality**

Thank you, we agree that these bullet points are redundant considering they are repeated in the sub headers, so have removed them.