Author’s response to reviews

Title: A review of clinical trial designs used to detect a disease-modifying effect of drug therapy in Alzheimer's disease and Parkinson's disease

Authors:

David McGhee (mailto:davidjmmcghee@gmail.com; mailto:david.mcghee@abdn.ac.uk)
Craig Ritchie (mailto:craig.ritchie@ed.ac.uk)
John Zajicek (jz45@st-andrew.ac.uk)
Carl Counsell (carl.counsell@abdn.ac.uk)

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Author’s response to reviews:

Reviewer #1:

(1) I think this is a really well written, helpful and timely contribution.

• We thank reviewer one for their kind comments.

(2) Why were trials testing intraventricular or intrathecal treatments, foetal or embryonic stem cells, striatal delivery of growth factors, or deep brain stimulation excluded? Patients always ask about these things!

• We were interested in developing non-invasive treatments and so excluded these procedures. Furthermore, we are aware that deep brain stimulation is not felt to my disease-modifying.

(3) Page 17 line 1. Do the authors want to keep their thoughts on delayed start more general across AD and PD rather than flagging the basal ganglia as a site of compensatory changes.

• We have altered the text to keep this paragraph more general rather than PD specific.

(4) Page 19, line 49. The authors should probably acknowledge that the amount of a symptomatic treatment taken will also be highly variable between individual patients depending on the neurobiology, metabolism, body weight, resistance to taking medication (e.g. L-dopa phobia).
• We have inserted the sentence: ‘Furthermore, the amount of symptomatic treatment taken varies greatly between individuals (e.g. due to body weight, metabolism and levodopa phobia).’

(5) Typo: Page 8, line 45: "...practically defined off phase..."

• ‘define’ changed to ‘defined’.

(6) Typo: Page 15, line 35: "...irreversibly..."

• ‘irreversibility’ changed to ‘irreversibly’.

Reviewer #2:

(1) Thank you for this review.

• We thank reviewer two for their detailed and constructive comments.

(2) Change the title to a review: line 2 and line 16 - search and data extraction was done by 1 reviewer and not 2 therefore a review is an appropriate title.

• We respectfully disagree with the suggestion that we change the title of our systematic review. Not all systematic reviews are double data extracted and our methods are clearly systematic.

(3) line 9 (page 2) and line 11(page 4): can you please explain validity and what it refers to in your review.

• We have tried to make this clearer by making the following changes.

• Page 2: ‘A systematic review was undertaken to examine which trial designs have been used in Alzheimer’s disease (AD) and Parkinson’s disease (PD) to detect disease-modifying, as opposed to symptomatic, drug effects. In addition we aimed to identify novel clinical trial designs used in the past or planned for use in the future. We aimed to critique whether the methods used would have identified true disease-modification.’

• Page 4: ‘We, therefore, undertook a systematic review to determine which trial designs have been used in AD and PD to detect disease-modifying, as opposed to symptomatic, drug effects. In addition we aimed to identify any novel clinical trial designs used in the past or
planned for use in the future. We aimed to critique whether the methods used would have identified true disease-modification.’

(4) line 23 (page 3): please spell out AD.

- We have corrected this to ensure both the abbreviations ‘PD’ and ‘AD’ are spelt out in full at first use in the main body of the manuscript.

(5) Methods (page 4): can you please mention your efforts in obtaining non published literature and were authors contacted?

- We have inserted the sentence ‘We used Google to identify websites and press releases related to unpublished trials’.

(6) Study selection (page 5): can you please clearly state your inclusion criteria in terms of study design, population, intervention, comparison, outcomes. Clearly state what main points for exclusion.

- We have reworked this section in keeping with the reviewers comments to make our inclusion and exclusion criteria clearer.

(7) Data extraction (page 6): did you extract or assess sources of funding of RCTs? as this may introduce some bias.

- We did not examine the sources of funding for included RCTs as our systematic review was not a quantitative review of RCT results but rather a review of their methodology.

(8) Methodological quality (page 6): you mention in your review that you will critique clinical trial designs therefore the assessment of the quality of included RCTs is necessary.

- In keeping with our answer to point 7, our systematic review aimed to critique clinical trial designs of included RCTs rather than their results. Therefore, we feel that an assessment of bias is not necessary: we were not trying to identify whether a particular intervention works or not but simply whether a trial design and the way it was implemented/analysed would allow a firm conclusion of disease modification rather than a symptomatic effect to be made if an effect had been found.

- We have altered the methodological quality section, as follows, to make this clearer: ‘We did not formally assess study quality in terms of methods to reduce bias (e.g. methods of
generating and concealing the randomisation sequence, blinding, source of funding) in this
review as our primary aim was to examine what clinical trial designs have been used or are
planned in RCTs to demonstrate disease-modification. However, we did examine losses to
follow-up and how this was dealt with as this would clearly impact on interpretation of
whether a given treatment had disease-modifying properties.’

(9) Data synthesis (page 6): change to narratively synthesised.

• Requested change made.

(10) Results: please mention total number randomised.

• We have inserted the following sentence: ‘The total number of participants randomised in
the completed RCTs in AD was 24,173 and in PD 10,652.’

(11) Results: please remove 20 to 26.

• We have removed this section.

(12) Results: when referring to trials in your results please ensure you insert the reference of
the trials mentioned (line 46). Please mention the number of studies when referring to
study characteristics (line 46, line 14 page 8, line 34 page 8, line 32 page 11).

• Our aim in the results section was to summarise the data presented in the tables and
additional files. For each summary comment we have not individually referenced every
study the comment relates to as this information is available in the corresponding tables. For
example, to reference every PD RCT which stipulated patients must be drug naïve on study
entry would require the insertion of 22 references into the main manuscript. However,
additional file 4 clearly indicates in which studies patients were drug naïve at baseline.

• We have, however, inserted references to accompany the comment in line 32 page 11 as
the number of trials that statement relates to is smaller.

(13) Characteristics of participants (line 6): if you conducted any statistical analysis please
mention the methods in your analysis section.

• We have inserted the following sentence into the ‘Data analysis and synthesis’ section of
the study methods: ‘The number of participants randomised into RCTs in AD and PD was
compared using the Mann-Whitney test.’
(14) Line 42 page 9: please spell out CSF

- Requested change made.


- Requested change made.

(16) Line 57 to 61: there is no need to constantly mention published and unpublished studies.

- We have adjusted the manuscript to reduce the use of these terms.

(17) Line 60 page 10: define long term follow up

- We have moved our definition of ‘long-term follow-up’ studies into the methodology section to improve clarity. The section in question states: ‘In this review the term ‘long-term follow-up’ was applied to studies that: (1) formally examined for sustained divergence in outcome measures between groups over time (i.e. through slope analyses); (2) did not formally measure sustained divergence but published figures (e.g. Kaplan Meier plots) from which the presence or absence of sustained divergence could be inferred; or (3) used no alternative design strategy to try to demonstrate disease-modification.’

(18) Results comments and recommendations: the results section is very lengthy and does not include quality assessment of included studies which is very important when assessing trials design. Recommend: condense the descriptive results and include methodological assessment of included trials and then discuss by trial design (as you already did in your discussion). Please mention within the text the (n) of study designs of included studies.

- Although the results section is fairly long, we feel this is necessary as it contains the critique of each trial design to explain in more detail why they might not truly separate disease-modification from symptomatic effects.

- The issue of bias from poor methodological quality affecting results if not relevant (except for losses to follow-up and missing data, which we do explore) as we were not summarising the results of RCTs but rather the methods used to demonstrate disease-modification. Giving details of factors such as randomisation, concealment and blinding is not relevant to the aims of our systematic review.
• In the results section we frequently give the number of trials in both PD and AD which used a particular trial methodology. These are also given in full within table 1. An example of an area of text including such numbers if given below:

• ‘Biomarkers of disease progression, most notably brain imaging (n=39/84 (46%) of included AD RCTs) and cerebrospinal fluid (CSF) biomarkers (n=27/84, 32%), were also frequently used as primary or secondary outcome measures to demonstrate disease-modification. In eleven AD studies (13%) a wash-out analysis [3,4] was employed to try to demonstrate disease-modification, and in three studies (4%) a wash-in analysis [3] was used to try to show the absence of an early symptomatic effect. A randomised delayed-start design [5] was used in nine (11%) included AD RCTs.’


• We have rephrased this section to make it easier to read.

(20) page 14 - end: when describing a trial design please insert reference.

• References have been inserted as requested.

(21) Flow diagram: please mention reasons of exclusion for others (n = 5)

• Figure one altered to include the details for the ‘other’ five studies.