Author's response to reviews

Title: Conducting research in individual patients: lessons learnt from two series of N-of-1 trials

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Author's response to reviews: see over
Reply to comments of the reviewers

Reviewer: Roman Jaeschke

General
Generally, this paper reinforces the observations and suggestions of previous authors in the field. It is written (and potentially useful) for those who are interested in conducting their own N-of-1 RCTs.

- Major Compulsory Revisions: Nil
- Minor Essential Revisions: Nil
- Discretionary Revisions: Nil
- Conclusion: Accept without revision

Reply: We would like to thank the reviewer for his positive evaluation of our manuscript.

Reviewer: Chris Del Mar

General
This is a study that produces little new data, but reports on the barriers to and difficulties in conducting n-of-1 trials from this group already published. The Discussion is interesting to people undertaking research in this method of investigation, although this is a very small group of us! The main sections of concern are: outcomes; ways of analyzing the results; withdrawals and drop-outs. Although this is of interest, the lack of good solutions to the problems makes the paper of limited usefulness.

- Major Compulsory Revisions
It would be better if the paper were expanded to include the data of all the trials done by n-of-1, like a systematic review, perhaps in primary care, or perhaps in use as a diagnostic tool.

Reply: Following the recommendation of the reviewer and the advice of the editor (see below), we have expanded our discussion to include a more comprehensive review of the literature on N-of-1 trials. In the literature search we have focussed on N-of-1 trials carried out in primary care settings, and on studies addressing methodological issues of N-of-1 trials. We have indicated this in the Background section of the revised manuscript (last few lines). The results of the search have been included in the debate section of the revised manuscript. When discussing each problem, we added solutions and recommendations from the literature to our own suggestions. The revised manuscript, therefore, offers a wider of scope on the methods used for conducting N-of-1 trials, and provides alternative solutions reported in the literature.

Minor Essential Revisions: Nil

- Discretionary Revisions
I would also have enjoyed some discussion about what use these methods might have in clinical practice. Might we one day look forward to all GPs using these techniques to enable better decisions about what drugs doctors should be using for individual patients?

Reply: In the revised manuscript we have added a section on the usefulness of N-of-1 trials in clinical decision making, and possible barriers to implementation in practice (Summary, 2nd paragraph).

- Conclusion: Unable to decide
Reviewer: Janet Pope

- **Major Compulsory Revisions:** Nil
- **Minor Essential Revisions:** Nil
- **Discretionary Revisions**

Their experience is recommended from 2 small trials they have done and not from a summary of the literature. However, there is likely generalizability of their comments for Family Practitioners that may want to do these studies.

**Reply:** As mentioned above, we have expanded our discussion to include a more comprehensive review of the literature. This has possibly also increased the generalizability of our suggestions.

**Some overall recommendations could be stressed:**
- These trials are only good with meds that are rapidly acting and stop rapidly (in order to decrease the carryover effects)

**Reply:** We have added prerequisites of conducting N-of-1 trials in the background of the revised manuscript (Background, 2nd paragraph, last 5 lines). These include the requirement that medication has to act rapidly, and becomes ineffective soon after discontinuation.

- Patient outcomes may be different, but could be homogeneous as you could ask each patient their preference in each couplet of treatment (first, second or neither) and this usually takes into consideration their benefit to side effects profile and benefit is patient centred.

**Reply:** This is a good suggestion. We have added this possibility in our revised manuscript, and referred to trials that have used patient preferences as outcome measure (Discussion, Recommendations regarding outcome assessment, page 6, lines 18 to 20).

- There are 3 problems with N of 1 trials
  1. It is difficult to get a placebo, so unblinded trials may have a role (not usually done to date).

**Reply:** We have briefly mentioned the difficulties in producing placebo’s in the newly added paragraph on barriers to implementation of N-of-1 trials (Summary, paragraph on usefulness and implementation, page 16-17).

  2. Most doctors will not do any statistics, so patient preference is a good surrogate (with overall a win for a drug if 2 of 3 cycles prefer it or 3 of 5, etc, unless if pt will not go further as they are convinced one is superior or more toxic or inferior to the other and that achieves the outcomes of the individual study) and this would allow for variable cycles in one patient and another “there is no point of going to further cycles if objectives are met already.

**Reply:** We have addressed alternative methods for analysing the results of N-of-1 trials in the revised manuscript, including the use of patient preferences (Discussion, Recommendations regarding analysis, page 10, lines 3 to 21).

  3. Later the results are not acted on. Another trial (NSAID for OA, Pope et al) followed the patients after the trial was completed and at 3 months, there were many who returned to treatment even if it was not preferred during the N of 1 trials.

**Reply:** We encountered this problem in both our N-of-1 series. In the revised manuscript (discussion) we have referred to other studies that reported on patients reverting back to their old (or active) medication, even if the results of their N-of-1 trials indicated insufficient effectiveness (Discussion, Recommendations regarding follow-up, page 14-15).

- **Conclusion:** Accept after discretionary revisions

**Comment by the editor**

As you will see one of the reviewers has suggested that you expand your paper, making it more of a systematic review. As your paper is currently a debate we would only ask you to expand your discussion to include more of your published work or a more comprehensive literature review-no new data is required. If you do wish to make your paper into a systematic review, that is entirely up to you.

**Reply:** We would like to maintain our paper as a debate, rather than rewrite it into a systematic review. We have, however, conducted a Medline search focussing on reports of N-of-1 trials in primary care settings,
and on papers on methodology of N-of-1 trials. The results have been included in the debate section of the revised manuscript. When discussing each problem we added solutions and recommendations from the literature to our own suggestions (see our reply to Pope and Del Mar). In order to limit the length of the manuscript we have slightly rewritten some sections of the paper.