Author's response to reviews

Title: Participation rate in Designed Uneven Randomization Trials (DU-RANDOM): a methodological survey protocol

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Author's response to reviews: see over
Dear Editor,

We appreciate to the comments and suggestions of the reviewers, and thank you for providing us a chance to improve our paper. In this revision, we have very carefully revised the paper, and addressed all the concerns raised by the reviewer point-by-point.

We hope that you, the editor and the reviewer would find this revision acceptable. Should you have further comments or suggestions, please don't hesitate to let us know.

Kind regards,

Darong Wu and Holger J Schünemann, on behalf of all the authors
1. Will the study design adequately test the hypothesis?
I do not think that it will. There will be lots of confounding which will be practically impossible to allow for. At the very least, I would have expected to see concurrent controls. Surely the investigators should be comparing recruitment rates with trials reported by the same journals over the same period, with 1:1 randomisation.

Response: Thank the reviewer for raising it up. We aim to do a systematic literature review to evaluate the epidemiology and to explore factors, e.g. participation rate, associated with DUR. As we've stated in the title, this is a "methodological survey" study. We agree that if the study objective is to quantitatively estimate the effect of DUR on certain factor, for instance, participation rate, a concurrent control group with trials with 1:1 ratio of randomization should be needed. As a result, we've revised several sections in the manuscript (see abstraction on P2, first and last paragraph of discussion section on P14 and P16, respectively) to make sure that our hypothesis has been clearly described.

2. I cannot understand rationale for differences in thresholds for unequal randomisation dependent on trial size. The focus should be on the planned ratio, not that actually achieved (which may be influenced by trial size.

Response: We agree, that's why we've defined a DUR RCT to have pre-planned uneven numbers of participants in the experimental and control groups ("Definitions" section, see P5). And we'll contact the author to definitely establish whether the study was a pre-planned DUR trial, if we cannot obtain evidence from the published materials (including protocols, reports, supplementary, etc).

The point here is that, we have to make judgment for those we cannot get response. We know that actually achieved ratio may not always equal to pre-planned one (though most of the time they do). It's like an estimation of the likelihood that to what extent an actually achieved ratio is a pre-planned uneven ratio. We may consider it as a coin flipping test. The more number of tosses the less chance of imbalance between number of heads and number of reverse side, which means that larger sample size should have less chance to get a uneven ratio. As a result, the threshold ratio of DUR should be larger in smaller sample size trials than it is in larger trials.

Though we've set up a high sensitive threshold for identifying DUR trials (Second paragraph of "Definitions" section, see P5-6), we plan to do a sensitivity analysis to include all those trials, without response to establish whether DUR or non-DUR trial, ratio in between 1.05-1.25, despite their sample sizes (see P12). All these efforts may help us to achieve robust results.

3. If the protocol cannot be revised then a minimum requirement might be a discussion of the problems raised above.

Response: We've revised the corresponding paragraph in discussion section (see P15).