

Dear Mr Grüninger,

Thank you for submitting your report on "The "Completely randomised" and the "Randomised block" are the only common experimental designs which can avoid bias and irreproducibility in pre-clinical research." by Dr Festing et al. A copy of this report is attached below for your reference.

Best regards,

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We greatly welcome your feedback as a peer reviewer for Scientific Reports. Please follow [this link](#) to complete a brief survey on your experience in reviewing this paper.

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Is the manuscript technically sound?: Yes

Could the manuscript become technically sound with revision?: Yes

Are the conclusions supported by the evidence presented?: No

Are additional experiments or data required to support the conclusions?: No

Does the manuscript only duplicate previous work?: No

Appropriate use of statistics and treatment of uncertainties?: N/A

References: appropriate credit given to previous work?: No

Is the manuscript written clearly using Standard English?: Yes

Images (including electrophoretic gels and blots) are free from apparent manipulation?: N/A

Technical Comments to the Author:

I apologise that some comments were not clear enough in the previous version of my review. I restated them - if not already made obsolete by the revision - in the comments below.

In general:

- I agree with the key claim of the author that "randomization to treatment group" should not be adopted \*if\* the experimental unit is the single animal. This limitation should be specifically mentioned. In addition, I believe that calling the completely randomized and the randomized block design the "only" common experimental designs suitable avoiding bias and irreproducibility in pre-clinical research is too

strong a claim to be made based on the insights provided by the manuscript, especially given the wide range of experimental designs available to researchers. Even the necessity of randomization itself is topic of an ongoing debate within the statistical community (see for example Kadane and Seidenfeld (1990), Randomization in a Bayesian Perspective or Senn (1994) Fisher's Game with the Devil). Hence, I'd recommend to change the key claim insofar that CR and RB are superior to "randomization to treatment group" (i.e. without claiming that CR and RB are the *\*only\** suitable designs) or to provide additional arguments supporting the claim that CR and RB are the only common designs able to avoid bias & irreproducibility.

- It is important imo to explicitly state somewhere that the blocks need to be included into the final statistical analysis for the desired reduction in variability to have an effect on the outcome of the analysis. In other words: The best design efforts are thwarted if they're not mirrored by an adequate statistical analysis which incorporates the key elements of the initial design. What I often encounter is that researchers do match for certain variables such as sex or weight but then completely ignore these variables in their final analysis, thereby heavily undermining their initial efforts. They seem to believe that the matching itself is already enough to achieve better statistical results. The author alludes to this problem repeatedly in the manuscript, but the importance of including the blocks into statistical analysis might escape the statistically less trained researchers who read the manuscript.

- There are some minor repetitions in the text which should be removed (e.g. the reference to an increase in power by 40% and the claim that the observed irreproducibility in research might be caused by randomisation issues are both mentioned twice throughout the text).

Minor remarks & corrections:

- page 3, paragraph 3: Could you add the specific pages/passages in "The Design of Experiments" in which the inclined reader can find the origins of these attributions? (the book is quite voluminous)

- page 4, paragraph 2: Some text is missing - what comes here?

- page 7, paragraph 5: According to PubMed Central: "The default sort order for search results is based on an algorithm that analyzes the full text of every PMC article that contains any of your search terms. For a given search query, "weight" is calculated for each article depending on how many search terms are found, which fields they are found in, and the size of the article. Although recently-published articles are given more weight, this is not a major sorting factor." (<https://www.ncbi.nlm.nih.gov/books/NBK3825/>) Hence, there seems to be at least a temporal dependence between the search results"

- page 8, paragraphs 2-5: These paragraphs appear to contain several direct quotes from publications. Hence, it's necessary to cite these publications.

Recommendation: Minor Revision

Remarks to the Editor:

As stated in the technical report, I deem the manuscript worthy for publication if some minor changes are adapted and if the main claim is change to something that is directly supported by the arguments and data provided by the author.

Remarks to the Author:

see technical assessment

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