Peer-review Comments and Author Responses

Reviewer 1

1. *I'm very happy to see your enthusiasm through your work on this study protocol. As I was reading, I got a notion of your aim and what you desire to study. Firstly, the writing of the manuscript is good, although I added some grammar suggestions, it still holds validity throughout the entire manuscript. The introduction has some suggestions/comments on how to organize some sentences that maybe you would like to take and change. The methods section is impeccable, because you clearly stated each component of the trial. However, there are some parts that might need clarification (such as the trial being a superiority, the blinding with the pharmacist, etc.). These you'll see in the comments I posted there.*

Thank you for your positive feedback regarding our manuscript. We review the suggestions in the document and clarified some details about the methods section.

2. *The suggestions I made can be accepted/rejected by clicking directly on them. The conclusions go accordingly to what you stated and want to achieve, therefore I believe this protocol to be good and clear for publication. Congratulations on your hard work!*

Thank you for your suggestions and for your kind words. We reviewed them and accepted them.

Reviewer 2

3. *Dear authors,*
Congratulations for the great work on the RESPIRE protocol. I appreciated a lot the paper due to its relevance and prevalence in the population. Just minor revisions are needed.

Thank you for reviewing our manuscript!

4. *Disclosures of several of the authors are with wrong title of the publication. Discosures that need review: Nicole A. Sanchez Iriarte, Wilhelm Sebástian Basegoda Curiel, Roselyn Lemus-Martin, Lucas Maffioletti Gonçalves, Mira Reger, Jose Antonio Bustos Cabrera, Maíra Ribeiro, Christina Bothou, Daniela Alonso-Ruiz, Emilio Israel Wong-Valenzuela, Diego Rolando Chavez Fernandez e Bryan Monterroso Yancor.*

Thank you for noticing that. We have addressed that issue and put all the titles as it should be in the disclosures.

5. *Exclusion criteria: consider other vaccines recommendations to COPD patients beyond COVID-19.*

Thank you for the comment. Due to the relevance of COVID at that time we considered having this as exclusion criteria. Other vaccines should be recommended as guidelines per CDC. However, we do not consider their absence relevant for exclusion criteria.

6. Define better the Adherence : meetings or video... written or verbal information... This details should be already defined.

Thank you for the feedback. We mentioned using either meetings or video, written or verbal information because we want to individualize as much as possible. We suggest using any of those at the convenience of each patient so they can understand the trial's objective. For adherence we will use telephone follow-up, homework, in-person meetings and motivation.

7. Which COVID test will be performed during the visits ? Serology? Please define it better.

Thank you for noticing that. We clarified and the test to be used are COVID-19 antigen tests.

8. Sample size calculation: Please cite what is the standard deviation and the effect size, they are not clearly mentioned.

Thank you for your comment. Based on Squassoni et al, 2021 findings on FEV1 % changes postbronchodilator use. To calculate the sample size, we used the following: Mean1 = 48.33, Mean2 = 43.60, Delta = 4.73, SD1 = 12.86, SD2 = 19.11. This can be found inside the supplementary appendix of the article.

9. Please rewrite this phase in Sample Size Calculation part: "With a 15% drop-out rate, the recruitment goal is n = 444 subjects; n = 222 subjects per n = 444 using 1:1 randomization (treatment: placebo)". I believe it might be 222 per group.

Thank you for noticing that. We clarified that already. The total population n = 444. Each group will have 222.

10. *Not all references are in APA style*

Thank you. We did a second review and fixed the references accordingly.