03-Oct-2022
BMJ-2022-070464.R1
Efficacy and Safety of an Inactivated Virus-Particle Vaccine for SARS-CoV-2, BIV1-CovIran: Findings from a Randomised, Placebo-Controlled, Double-Blind, Multicenter Phase III Clinical Trial amid the Delta Variant Peak

Dear Prof. Salehi

Thank you for sending us your revised paper and for your patience while we have been considering it. We have read it carefully and still have a number of comments and questions that we would like you to clarify please.

We hope very much that you will be willing and able to revise your paper as in the notes from our statistical and research editors below, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

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Yours sincerely,

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Research Editor
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Comments from research editors

Further to the comment from the statistical editor below, have there been any changes to the study protocol in response to its peer review process?

We thought that the primary outcome discrepancies between registration, protocol, and study still require further explanation, for example the protocol stated the primary outcome would: “VE for non-severe, severe, critical cases and deaths due to COVID-19, 1`4-180 days after vaccine” - can this be included?

Relatedly - is follow up information now available for 180 days?

** Comments from reviewers**

Reviewer: 1

Recommendation:

Comments:
The authors have now added the study protocol as a supplement in preference to publishing elsewhere. The reviews of their attempts to publish elsewhere are not given and there is no information as to whether those comments are addressed in the version presented here.

The authors do not directly address several of my previous queries:

1. Follow up duration verified as 90 days with each participant contributing at most 90 days. How does this accord with a maximum of 131 days within the dataset?

2. The response re sample size is unclear. Are the authors anticipating a reduction from 1 per 100 to 0.4 per 100? Given 13350 receiving vaccine, 10% dropout = 12105 x 0.004 = 48 cases;
6650 controls, 10% dropout = 5985 x 0.01 = 60 cases.
Therefore total participants 20000, gives expected 108 cases (not 150) if reduction mooted is achieved. However, I note that in the revised tracked version of the paper, it now states that the incidence rate is estimated to be 1% PER MONTH, which is probably the crucial amendment? Please clarify how this relates to the proposed sample size and the 150 mooted.
The statement/query re lack of adjustment for within centre correlation has not been addressed.

3. Query re bias and generalisability issues of using volunteers: Whilst it is useful to know that internet penetration exceeds 84% (?source), this does not mean that the sample will be representative (16% did not have chance to respond and those that did may be a biased subset of those with internet access). Is there any evidence that those recruited were unbiased and representative? There should be at least some discussion of this. It may be informative to know which social media platforms were used and whether those receiving/reading the adverts might be biased too.

4. Similarly, the response re the convenience sample also misses the point – could this subgroup be biased? How were they selected from those available? Tehran was chosen for all (and this might not be totally representative? You have information to compare the sites, does selecting this one seem reasonable?) Within this selected site, how were the convenience sample chosen? And might this have led to any biases that could influence the findings?

5. The authors seem to imply that there were no missing values in those that completed the study. However, the response to the editors' comment 10 suggests this is not the case – that there were actually exclusions due to missing covariates. How many and how did this affect numbers included in the models? Imputation should be considered.
Although some were lost to follow up, overall dropouts appear less than the anticipated 10%. Given those completing, would expect 65 (1% of 6456) and 52 (0.4% of 12945) = 117 cases (still less than the 150 anticipated in the sample size calculation).

6. Regarding the discrepancy in serious AE, the authors have rechecked the numbers and given a potential explanation. It seems to me that this is a difference worth reporting in the paper – the difference in serious AE between groups with 95% confidence interval needs to be presented and commented on.

I have an additional comment to make re the immunogenicity analysis that requires addressing:

7. The statistical analysis section states that chi-square/fishers will be used for categorised variables and t-tests for the continuous. Results are given in tables 3 and S5. Differences and confidence intervals between groups should be presented. The figures show that the distribution of the values is skew and t-tests/means may not be appropriate summaries. Since there are only 400 participants in this analysis, the figures could show the actual values (and/or within person changes) rather than the box-plot

summaries only. It may be that the within person differences are normally distributed and therefore t-test the appropriate analysis to compare within person changes between the intervention and control groups. The analyses performed and validity do require some clarification.
Where is there any comparison of categorised data and usage of chi-square/fishers?

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