Author’s response to reviews

Title: Dealing with indeterminate outcomes in antimalarial drug efficacy trials: A comparison between complete case analysis, multiple imputation and inverse probability weighting

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Title: Dealing with indeterminate outcomes in antimalarial drug efficacy trials: A comparison between complete case analysis, multiple imputation and inverse probability weighting

Dear Dr Hodges,

Thank you for giving us the opportunity to revise and resubmit our paper. The reviewer’s suggestions were very constructive and we have revised the manuscript to address the comments raised.

Thank you for your attention.

Yours sincerely,
Prabin Dahal

Julie A Simpson

Alexander Robitzsch (#Reviewer 1): No further comments.

Author’s response: We would like to thank the reviewer for accepting our revision and supporting the publication of our manuscript.

Roderick Joseph Little (#Reviewer 2):

#Reviewer 2: Line 96. It is not clear what "this" is referring to -- CC analysis, not Eq. (2), right? Author’s response: “This” referred to the Kaplan-Meier method, which has now been explicitly stated.

#Reviewer 2: Line 261. But the model did include regimen as a covariate, right? I think you mean the sample size was too small to stratify on treatment, but this could be more clearly phrased.

Author’s response: Our imputation model included the treatment regimen as a covariate. We have now rewritten the sentence for clarity.

#Reviewer 2: Line 329. It is odd to include the analytical estimate based on Eq. (2) here, but not include it as a method to be compared elsewhere, particularly given that it corrects the bias. RMSE is easy, and estimates of SE are readily computed for this method. I wonder if none of the other methods did any better, somewhat deflating the findings of the simulation.

Author’s response: We have now presented the additional performance measures (empirical and mode based standard error, root mean squared error and the coverage probability) for the analytical solution. An expression for the variance for the analytical solution is provided in the Additional file 1(Section B2). The other performance measures indeed are much superior to the complete case estimators and are reported in Table 6 of main text with further results provided in Tables 7, 8 and 9 of Additional file 1.

#Reviewer 2: Line 339. ML is fully efficient, and MI is asymptotically efficient as the number of imputes increases. I think you mean the variance of the estimates increase, but this reflects loss of information in the data, not statistical efficiency.

Author’s response: We will like to thank the reviewer for pointing this out. Indeed, we meant that the variance of the estimates increased. We have rewritten the sentence to clarify this and
have added the following sentence: “The variance of the estimates increased as the proportion of missing outcomes increased for all the approaches used for handling missing data”

#Reviewer 2: Discussion. The simple analytical method in Eq. (2) does not appear to be discussed at all, but to me it captures the main idea, though MI and weighting may be useful for including covariates.

Author’s response: We have discussed the advantages of the analytical method in equation (2) in lines 390-392 in the revised draft of the manuscript. We have now further re-iterated the advantages of analytical solution in the abstract (lines 55-56, and 61-62), in main results (lines 352-354; 370-374; 382-384; 390-392), in discussion (lines 418-419; 446-449), and in our concluding remarks (lines 508-510).

#Reviewer 2:. Acknowledgement. Thanks for now acknowledging my "substantial contribution", but (admittedly on a self-serving note) you might say what that contribution is…

Author’s response: We have explicitly stated the contribution now (lines 557-558).