Author’s response to reviews

Title: Accounting for centre-effects in multicentre trials with a binary outcome - when, why, and how?

Authors:

Brennan C Kahan (brk@ctu.mrc.ac.uk)

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Author’s response to reviews: see over
Reviewer:
Jinhui Ma
Reviewer's report:

I only have some minor essential revisions.

1. The presentation of the manuscript improved a lot compared to the previous version. But I still think that the paper can be much improved through organizing the information more precisely and appropriately to ensure the key message (when, why, and how) be easily caught by readers.

**Response**
I have added a section to the discussion highlighted the key points regarding the when/why/how of accounting for centre-effects, which should help readers to identify the key messages.

2. In the Methods – ICC consideration section, the author mentioned “For a binary outcome analyzed using odds ratio, the ICC can be defined as \#2/\( \#2+\#2/3 \), where \#2 is the between-center variance.” and “When centre is not accounted for in the analysis, the standard error for treatment effect is increased by a factor of \((1-\text{ICC})^{-1/2}\)”. The author should provide references for these two pieces of information, especially the definition of ICC since the it is used in the simulation study.

**Response**
This has been done.

3. In the simulation study, the simulated data were generated according to the mixed-effects model, which gives more preference to the mixed-effects model in the analysis. This can be part of the reasons why the performance of the mixed-effect model is super to other models.

**Response**
I have added a section to the discussion highlighting this point, and have referenced previous research which found that (with a continuous outcome) random-effects still outperformed fixed-effects even when the data were generated based on a fixed-effects model.

4. As the author already stated in the manuscript that GEE method (a marginal model) and random-effects model (conditional model) estimate different treatment effects and their interpretations are different as well. GEE method is expected to have larger bias for some
simulation scenarios if random-effects model is used for data generation. Since the objective of this paper is to investigate when, why, and how to account for center-effects in multicenter trials with binary outcome, the author should address the issues like when one method (such as GEE) is superior to the other method (such as random-effects model).

**Response**

In many scenarios there are several methods of analysis which perform equally well, and the choice of which to use must be based on personal preference. This is generally the case for random-effects and GEE; both perform equally well across all scenarios, and so neither method appears to be superior to the other. I have addressed when each method should and should not be used; when multiple methods of analysis are appropriate, the reader may choose the method they prefer.
The author has answered my earlier comments well. The revised paper discusses two types of models to account for the strata effects – marginal models and conditional models. It is quite clear now. The revised paper has improved a lot, although I have a few suggestions.

Minor revisions:

1. On page 2, the author states:

“However, this was only true for GEEs with non-robust standard errors; using a robust ‘sandwich’ estimator lead to inflated type I error rates across most scenarios.”

This statement is not clear without further explanation. The author discusses this issue in the simulation study. Without the further discussion, it is a misleading statement indicating that the robust sandwich estimator is worse than the non-robust one.

Response
I feel this sentence is both a clear and accurate representation of what the simulation results showed. GEE with robust SEs led to inflated type I error rates in many scenarios, and as a consequence, the non-robust estimators gave much better results than the robust sandwich estimator.

Also, I suspect that it is due to the simulation scheme chosen by the author. In the simulation study, the true model (on page 11) assumes that the random centre effects follow a normal distribution with variance \( \sigma^2 \). If the random centre effects have a complicated structure, the non-robust estimator based on “exchangeable” correlations might not be good.

Response
This point has been addressed in the section on GEEs:

“Robust SEs can be extremely useful when analysing longitudinal data (where patients are followed-up at multiple time points), as this type of data leads to many possible correlation structures, and it may be difficult or impossible to know which is correct. However, in multicentre trials, correlation structures other than exchangeable are unlikely; therefore, we focus mainly on non-robust SEs in this article.”

As stated, I feel that correlation structures that are more complicated than ‘exchangeable’ are extremely unlikely in multicentre trials. Therefore, the fact that robust SEs may be more appropriate for complex correlation structures does not mean they are more appropriate in multicentre trials.
2. On page 6, the notation of ORMH uses ‘i’ to represent the ith centre. Because all models in the paper use ‘j’ to represent the jth centre, it would be good to make notations consistent by replacing I with j for ORMH.

Response
This has been done.

3. On page 10, the author states:

“uj is the centre effect for j centre and follows a normal distribution with mean 0 and standard deviation σj.”

Is it σj or σ?

Response
This should be σ. This has been corrected.

4. On page 10, the author states:

“We generated σj and ǫij independently.”

Is it σj or uj?

Response
This should be μj. This has been corrected.

5. On page 10, the author states:

“The ICC was set to 0 (equivalent to setting σj = 0).”

How to generate values from N(0, 0)? I assume that the author sets a small number of σ, e.g. σ = 10−6. Also, shouldn’t the notation σj be σ?

Response
We have changed σj to σ. Generating from N(0, 0) indicates that every value will be 0 (as the variance is 0) – this is equivalent to removing the random effect from the model.

6. On pages 13 and 14, I am not confident about the argument against the GEE robust variance estimator. See my comment #1.

Response
See response to #1.