Reviewer's report

Title: Accounting for center in the Early External Cephalic Version trials: An empirical comparison of statistical methods to adjust for center in a multicenter trial with binary outcomes

Version: 1 Date: 10 February 2014

Reviewer: Freedom Nkhululeko Gumede

Reviewer's report:

General comments: The paper considers fixed effects models, marginal models (GEEs) and conditional models (mixed effects/ generalised linear mixed models) for correlated binary data from a multi-center clinical trial. The main purpose of the paper is account for center effects in assessing the treatment effect.

- Major Compulsory Revisions

1. General comment:

   The basic idea of marginal models is to make inferences about population averages, i.e. the regression parameters have 'population-averaged' interpretations such as describing the effect of the measured covariates on the mean response. Whereas generalise linear mixed models/mixed-effects (GLMMs) assume that some of the regression coefficients are assumed to vary across subjects/clusters according to some distribution.

   While under marginal models the dependence among the repeated measures on the same cluster is modelled via a 'working' covariance matrix, whereas under GLMMs the dependence is modelled via random effects.

   GLMMs are most useful when we wish to make inferences about clusters/subjects rather than population averages, i.e. the interest is on clusters and the influence of explanatory variables on a typical cluster's responses.

   For the multi-center clinical trial in this study it seems the original scientific objective was on population-average inferences. Can the authors motivate why mixed effects model (GLMM)s would be considered in their study.

Specific Comments:

1. Page 9: 2nd paragraph: GEEs are not mentioned here yet they are referred to in the Abstract and Results sections.

2. Page 11: Last paragraph, 2nd sentence: Include the names 'generalized linear
mixed models, multilevel models”.

3. Pages 12: Equations (3) and (4): Specify the assumptions for b0k and b1k, i.e. both random effects have normal distributions with zero means and variances sigma^2(1) and sigma^2(2), respectively.

4. Pages 12: Equations 4: It is misleading to call model (4) a random intercept and random slope model since the explanatory variable X is not continuously but a factor for the treatment.


6. Figure 3, 4 and 5: Specify the covariance structures for the GEE models fitted.

- Minor Essential Revisions

1. Page 3: Abstract: Keywords: add the words: random effect, mixed-effects, generalized estimating equations, generalized linear mixed model

2. Page 19: 3rd paragraph, 2nd sentence: Rephrase as "GEE use covariance matrices/structures to estimate..."

3. It is known that when the response is missing completely at random (MCAR), GEE yield consistent estimators of the regression parameters provided the model for the mean is correctly specified. The missingness in the dataset used in this study is unlikely to influence the results of this study because it is not substantial. The authors must acknowledge the influence missingness might have on the results when the methods they suggest are used to account for center effects.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.