**Project Title:** An evaluation of informative cluster size in mental health trials to determine whether standard statistical methods are robust and reliable

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**Introduction**

Many individually randomised mental health trials evaluate interventions which are delivered by healthcare professionals (HCPs), e.g. cognitive behavioural therapy (CBT) delivered by a psychologist. Typically, multiple patients would be treated by each HCP, leading to a nested structure where patients assigned to the intervention group are ‘clustered’ by HCP. Because usual care patients are not typically treated by a HCP, these trials are referred to as ‘partially nested designs’.

In partially nested trials the treatment effect may depend on the skill or expertise of the HCP delivering the intervention. For instance, psychologists with more experience may be more effective at delivering CBT, which may lead to better patient outcomes. This can lead to correlation between patients treated by the same HCP, and this ‘clustering’ by HCP must be accounted for in the trial analysis to obtain valid standard errors and p-values. Common methods of accounting for such clustering is to use a mixed-effects model which fits a random intercept for HCPs in the intervention arm, or generalised estimating equations (GEEs), which typically fits an exchangeable working correlation structure to patients in the intervention arm.

However, recent research into fully clustered designs (i.e. cluster randomised trials) has found that mixed-effects models and GEEs can lead to biased estimates of treatment effect when there is informative cluster size (ICS). ICS refers to the setting where the outcome or treatment effect differs according to the size of the cluster (e.g. if the intervention works better in larger clusters than in smaller clusters).

ICS could occur in partially nested mental health trials if:

* Higher skilled HCPs are asked to treat more patients than lower skilled HCPs
* The intervention delivery has a learning curve, such that HCPs who treat more patients become more skilled
* The characteristics between patients who present to high-volume HCPs differ to those presenting to low-volume HCPs (e.g. if those presenting to high-volume HCPs are more urban and have different socioeconomic statuses), and these characteristics influence their response to treatment

If ICS poses the same issues for partially nested designs as it does for fully clustered designs, this could have profound implications for how mental health trials are designed and analysed, including choice of statistical model; how sample size calculations are performed; and how patients are assigned to HCPs within the trial.

However, it is currently unclear whether ICS does affect mixed-effects models and GEEs in the same way for partially nested designs as it does for full cluster randomised trials. Furthermore, even if ICS could affect results from mixed-effects models and GEEs in the partially nested setting, it is not clear how often ICS occurs in mental health trials, or when whether it would be severe enough to materially affect results.

Thus, there is urgent need to (a) identify whether ICS can introduce bias into mixed-effects models and GEEs in the partially nested setting; and (b) evaluate whether ICS is likely to occur in mental health trials, and if so, whether it is severe enough to affect results.

**Objectives**

To:

1. Identify whether ICS can introduce bias into mixed-effects models and GEEs in the partially nested setting
2. Evaluate whether ICS is likely to occur in mental health trials, and if so, whether it is severe enough to affect results
3. Develop dissemination materials in conjunction with PPI members to explain results to key stakeholders

We carried out objective 1 by performing a simulation study comparing the performance of mixed-effects models and GEEs to independence estimating equations when there is ICS in partially nested trials.

We carried out objective 2 by performing a re-analysis of the SlowMo trial, which was a partially nested trial comparing a digitally supported reasoning intervention plus usual care vs usual care only in patients with psychosis.

**Progress**

The simulation study in objective 1 is complete. The simulation study demonstrated that:

* Mixed-effects models and GEEs demonstrate bias when there is informative cluster size
* Independence estimating equations are unbiased, even when there is informative cluster size
* Independence estimating equations did not lead to material reductions in precision or power compared to mixed-effects models and GEEs

The main conclusions from this simulation study are that when informative cluster size is considered a possibility, investigators should consider moving away from standard analysis approaches (mixed-effects models/GEEs) in favour of methods which are more robust (independence estimating equations), as these models are able to maintain unbiasedness without sacrificing much in the way of efficiency.

The re-analysis in objective 2 is complete. The re-analysis demonstrated that:

* Several outcomes appeared to be affected by informative cluster size (i.e. outcomes from individuals in larger clusters were higher than from those in smaller clusters)
* For these outcomes, estimates from mixed-effects models and GEEs were notably different to those from independence estimating equations, indicating that results from these models may have been affected by informative cluster size

The main conclusion from this simulation study is that informative cluster size appears to be a plausible concern in mental health trials, and should be considered by investigators at the design stage.

An infographic to explain results from the re-analysis (objective 3) is complete, and an infographic related to the simulation study in objective 1 is in progress.

**Outputs**

The infographic related to the re-analysis is displayed as figure 1 in the appendix. This will be published alongside a manuscript (currently in preparation) describing results from the re-analysis, and will be used on social media to promote the results.

We will shortly begin work on a manuscript describing the simulation study, and aim to publish this in a peer-reviewed journal.

**Future plans**

We aim to:

* Publish results from the re-analysis and simulation study in separate peer-reviewed publications
* Release infographics on social media promoting results from these studies
* Potentially seek further funding to develop additional methods of analysis for partially nested trials with informative cluster size, as well as to develop sample size formulas and guidance on design considerations

**Appendix**

***Figure 1 – Infographic related to re-analysis objective***

A screenshot of a diagram

AI-generated content may be incorrect.