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A comparison of statistical methods to compensate for missing data in longitudinal cluster-randomised controlled trials

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Introduction: Clinical trials are the preferred method in the evaluation of medical interventions. However, missing data causes loss of power and may introduce biases, potentially leading to researchers over- or underestimating intervention effects. This is a particular issue in studies where data are correlated, such as in longitudinal cluster-randomised controlled trials (LCRCTs). Despite advances in statistical methods, many researchers choose to simply exclude cases with any missing values from the analysis (complete case analysis).
Multiple Imputation (MI) and Structural Equation Modelling (SEM) are two sophisticated statistical techniques that may provide unbiased corrections in compensating for missing data. The aim of this research was to compare the performance of MI and SEM in compensating for missing data in LCRCTs using computer-simulated datasets. The performance of these methods was also compared to a common method used to analyse longitudinal data, mixed linear modelling (MLM).
Methods: Simulated datasets were generated to imitate data from a real LCRCT. Data from the outcome measures were deleted at 5%, 10%, and 20% and then analysed using the three aforementioned methods, in addition to complete case analysis (CCA). Missingness was introduced by three mechanisms: missing completely at random (MCAR); missing dependent on covariate x (MAR); and missing dependent on outcome value (MNAR).
Results: Regardless of missingness mechanism, MI, SEM, and MLM provided similar, unbiased results. SEM and MLM produced the least biased results, though the SEM generated the smallest standard errors, therefore recovering more of the lost sample size. CCA produces the largest standard errors and most biased results.
Conclusions: From the results of these simulations, MLM and SEM are the preferred methods to compensate for missing data in LCRCTs. These two techniques are able to recover most of the lost sample size, and therefore researchers are less likely to miss important intervention effects.

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Treatment effect adjusting for baseline covariates: a curious case of selection bias

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Introduction: In early phase often we have single arm trials with small patient population to generate evidence for treatment effect. A common approach in lack of randomized control arm is to compare outcome from treatment arm with potentially similar historical control arm adjusting for baseline covariates. Although we can minimize bias coming from the list of covariates at hand we may have unwanted factors which can potentially bias the treatment effect.
Methods: We will look into a case study from a Phase 2 trial. Treatment effect adjusting for baseline covariates using propensity scores and using adjusted Cox regression model will be demonstrated. Subsequent analysis with other factors in the model will be provided.
Results; Adjusted covariate analysis suggests significant treatment effect and potential planning for Phase 3 trial. However, subsequent analysis including other covariate in the model has raised questions about the magnitude of treatment benefit.
Discussion: Exploratory data analysis with statistically sound methodology can generate evidence of treatment effect from single arm trials. However, safeguarding against potential confounders is an issue. At the end we have to make decision based on risk benefit ratio. But questions should be raised and explored thoroughly to kill a drug before a fully planned Phase 3 trial is initiated.

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Simple correction of admixed RNA samples using cancer purity information

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Introduction: RNA expression data are very common in clinical research. In cancer, tissue samples, e.g. bone marrow aspirates, are usually a mixture of healthy and cancerous cells. The proportion of both types of cells varies across individuals. Downstream analyses are therefore affected by this source of error contributing to a reduction in power and increase in bias of parameter estimation. A simple tumor content correction is proposed to render RNA values more highly correlated with true levels of gene expression in cancer.
Methods: Assume the following simple admixture model:

$$E = pE\_c + (1-p)\,E\_n$$

,where E is the total RNA level for a given gene, e.g. log2(TPM*), Ec is the expression among cancer cells, and En is the expression among normal cells, and p is purity or cancer content in a 0-1 scale. A rearrangement of the equation above leads to:

$$E = E\_n + (E\_c - E\_n)p = a + bp$$

, which is equivalent to a simple linear regression with intercept a (expected expression in normal cells), and slope b (expected differential expression –DE-); which after adding a model error e (residuals after regressing E onto p) would render E=a+bp+e. The proposed correction is:

$$E\_c \cong a + b + e$$

Results: Simulation work showed that power to detect DE is reduced when sample purity decreases, but that power remained high after adjusting for purity differences. The method corrects equally well regardless of the levels of DE. There is some prediction bias that can reduced by selecting only samples with higher purities.
Discussion: All downstream analyses using RNA data, e.g. DE, gene signatures, prognostic modelling etc, would experience an increase in power and reduction in bias after using this correction in admixed cancer samples.

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Abstract withdrawn

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A new instrument to assess the credibility of effect modification analyses (ICEMAN) in randomized controlled trials and meta-analyses

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Introduction: Most randomized controlled trials (RCTs) and meta-analyses examine effect modification (also called subgroup effects or