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Research Briefing

Cohort Multiple Randomised Controlled Trial (cmRCT) design: efficient but biased? A simulation study to evaluate the feasibility of the Cluster cmRCT design

Alexander Pate, Jane Candlish, Matthew Sperrin and Tjeerd Van Staa
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Summary

Simulations were ran to look into the effect of treatment refusal on the estimation of the treatment effect when running a Randomized Controlled Trial (RCT) using the Cohort Multiple Randomised Controlled Trial (cmRCT) design [1].

Key points

- The cmRCT design is pragmatic by nature and is suited to being embedded into routine practice.
- cmRCT design can offer efficiency gains over standard randomized controlled trials.
- Treatment refusal happens post randomization so excluding these patients will lead to selection bias.
- Both an intention to treat (ITT) and instrumental variable (IV) analysis should be carried out. An IV analysis will calculate the causal treatment effect amongst compliers (CACE).
- Interpretation of the treatment effect can be difficult given the timing of treatment refusal. Whether an ITT or IV analysis is more relevant will depend on what extent treatment refusal is related to participation in the trial.
- When the outcome is the time until an event, correlation between refusal probability and patient risk can lead to high levels of bias in the estimation of the CACE even when IV assumptions are met.
- The cmRCT design is appealing for its pragmatic factors, however many statistical issues arise, only one of which is covered by this work.

Introduction

Randomised controlled trials (RCTs) often fail to meet recruitment targets and are costly [2]. Furthermore, the results from most randomised controlled trials may not be generalisable to routine practice [3], yet we use the results from these trials to inform clinical decision making [4]. There is a clear need for more pragmatic trials to address these needs and address the clinical questions that current RCTs cannot [5], [6]. The cluster cmRCT design is one such trial, where after consent is initially gained for data to be used comparatively, a random sample of patients from an observational cohort are offered the intervention and the control arm are not notified of their participation in the study until the end. Refusal is therefore only possible in the intervention arm and can lead to unbalanced trial arms if refusing patients are excluded, or a dilution of the treatment effect is all patients are retained. Treatment refusal will also lead to a drop in statistical power.

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Methodology and findings

A series of simulations conducting cluster TwiCs trials were ran to test the operating characteristics of the trial design. The simulations were based on a cohort of patients at risk of developing cardiovascular disease (CVD), comparing a novel intervention to treatment as usual. The simulated population was heterogeneous different scenarios were induced by controlling the probability of refusing treatment, the probability of a clinician refusing to offer treatment to a patient and the correlation between these probabilities with unique patient risks.

We compared the performance of four methods: ITT, Per Protocol (PP), Two Stage Predictor Substitution (2SPS) and Two Stage Residual Inclusion (2SRI). The latter two are instrumental variable methods which are starting to garner more use in the analysis of both trials where treatment refusal is present and observational data. We also considered the effect on statistical power of treatment refusal and how best to account for this.

This study found, as expected, that refusals can lead to a large underestimate of the CACE when ITT is used. Many published protocols of cmRCTs propose ITT for the primary analysis, the main argument for this is that treatment refusals do happen in actual clinical practice and ITT would thus evaluate the value of offering a treatment. However refusal rates may be different in trials and the ITT effect calculated in the trial will not reflect the ITT effect in routine practice. 2SRI was found to minimize bias in calculating the CACE in the majority of scenarios and is the recommended IV method. We believe the effect of the treatment is routine practice is often likely to lie somewhere between these two estimates. These simulations also highlighted a large drop in power due to treatment refusal which must be factored into the design stage. The required sample size is dependent on the level of refusal and adaptive sample size calculations should be adopted in order to maintain the power of the trial or stop over recruitment when refusal rates are low.

Importance of this project

- The cmRCTs design is novel (proposed in 2010) and its operating characteristics are unknown. This study explores the statistical aspects of the design which have not been scrutinised to much extent.
- We provide guidance to decision makers considering different pragmatic trial designs by providing information on the advantages and disadvantages of the cmRCTs design.
- The statistical consequences of using such a design are highlighted which must be considered when running a cmRCTs in practice, at both the design stage and analysis stage.

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