Challenges in Factorial Design Randomized Control Trials

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Description: Randomised controlled trials (RCTs) using a factorial design enable the assessment of two or more interventions within a single trial. Compared to multi-arm trials, factorial RCTs are more efficient as they require fewer participants, with the assumption that the interventions act independently of each other (i.e. no interaction effect is present). This supposition creates specific challenges in the design, analysis and reporting of a factorial RCT, which if ignored can lead to biased results [1, 2].

Objective: To evaluate current methodology and reporting of published reports of 2x2 factorial design RCTs. Additionally, to assess how frequently trial design methods differ in reporting of results compared to those pre-specified in the protocol/statistical analysis plan (SAP).

Methods: We searched PubMed to identify primary reports of 2x2 factorial design RCTs published between 01 January 2018 and 04 March 2020. The corresponding trial protocol and/or SAP were collected, where available. Data from both primary reports and protocol/SAP were extracted and compared on the trial characteristics (disease, sample size, funding, etc.) and approach to factorial design-specific methodology, such as design rationale or consideration for a treatment interaction in the sample size and analysis as indicators of potential challenges.

(Preliminary) Results: The review included a purposeful sample of 100 factorial RCTs. The majority (23%, n=23/100) were conducted in cardiology; the median sample size was 258 (interquartile range 120 to 693); 44% (n=44/100) were multicentre; 61% (n=61/100) were funded by non-industry. The rationale for a factorial design was often efficiency in assessing multiple treatments in one RCT (44%, n=44/100). 12% (n=12/100) explicitly assumed no treatment interaction in the outset and 4% (n=4/100) reported powered sample size to detect an interaction. The primary outcome analysis was conducted for the main effects in 43% (n=43/100), as a four arm comparison for 25% (n=25/100) and both in 32% (n=32/100). Of 60 articles reporting testing an interaction, 83% (n=50/60) reported non-significant interactions. Protocols/SAPs were available for 37% (n=37/100) of the published primary reports. 65% (n=24/37) intended to assess for an interaction in the analysis (as reported in the protocol/SAP) and 17% (n=4/24) did not report this in the final report.

1 Montgomery AA, Astin MP, Peters TJ. Reporting of factorial trials of complex interventions in community settings: A systematic review. Trials. 2011;12. doi:10.1186/1745-6215-12-179

2 Kahan BC. Bias in randomised factorial trials. Stat Med 2013;32:4540–9. doi:10.1002/sim.5869