When Factorial Design Randomized Control Trials are no plain sailing

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Description: Randomised controlled trials (RCTs) using a factorial design enable the assessment of multiple interventions within one trial. Compared to multi-arm, factorial RCTs are more efficient as they require fewer participants, assuming the interventions are independent (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.

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. Data from primary reports and protocol/SAP were extracted and compared on the trial characteristics (e.g. disease, sample size, funding, etc.) and approach to factorial design-specific methodology (e.g. account for interaction sample size/analysis) as indicators of potential challenges.

(Preliminary) Results: The review included a 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 non-industry funded. The rationale for a factorial design was often efficiency (44%, n=44/100); 12% (n=12/100) explicitly assumed no treatment interaction; 4% (n=4/100) reported a powered sample size to detect an interaction. The primary outcome analysis was conducted for the main effects in 43% (n=43/100). 60 articles reported testing for an interaction. Protocols/SAPs were available for 37% (n=37/100) of 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 present this in the primary results report.

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