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Comparability of treatment arms does not prevent correlated trial results

In a simulation study [1], we identified possible dependence between trial results when conducting multiple trials within a cohort multiple randomized controlled trial (cmRCT) setting [2]. In their letter, Verkooijen et al. [3] argue that contrary to our results, there is "no concern for dependency" as long as eligible patients for any given new trial are randomly selected into either of its arms. We disagree with this assertion.

In a cmRCT design, the issue to consider is not just the comparability of treatment arms—which may indeed be achieved in expectation by randomization—but is the reuse of the same outcome information for multiple comparisons. Consider a three-arm trial (say, intervention A, intervention B, and placebo). Even if treatment arms are perfectly comparable, the comparison between intervention A and placebo will be correlated with the comparison between intervention B and placebo, for the simple reason that the information on placebo-treated subjects is the same in both comparisons. Instead of a three-arm randomized trial, we can imagine two consecutive randomized trials within a cohort. In the first trial, a random selection of eligible patients receives intervention A. Those who receive the control intervention in that first trial may be considered eligible for the second trial, and a random selection of them is invited to receive treatment B. Those who receive neither treatment A nor treatment B provide information on the control intervention. Provided selection for intervention A and B is a random process, the comparison will not be affected by incomparability of treatment group, yet—like in the three-arm trial—result of the two comparisons will be correlated. This design option is not fictitious. For example, Kwakkenbos et al. describe their cmRCT design as follows: "Once interventions are developed, patients from the cohort will be randomly selected and offered interventions as part of pragmatic RCTs. Outcomes from patients who are offered interventions will be compared with outcomes from trial-eligible patients who are not offered the interventions" [4].

Verkooijen et al., however, argue that cmRCTs are more commonly of our scenarios 1 (subjects can participate in a single trial only) and 4 (all subjects can participate in multiple trials). There are several reasons to be concerned about these designs too. Ethical concerns may play a role when embarking on a cmRCT compatible with scenario 1, when subjects receiving the control intervention not only remain ignorant of the ongoing trial but are also kept unaware of the fact that they cannot participate in future trials. The elegantly designed stratified randomization procedure proposed by Verkooijen et al. may indeed improve comparability of treatment arms for scenario 4. But we anticipate this procedure (or any other multidimensional stratification) quickly becomes less feasible as the number of trials conducted increases. Moreover, while the procedure may account for past or ongoing trials, it cannot account for future ones, which may already commence when the current trial is still ongoing.

The apparent increase of cmRCTs in the medical literature calls for more methods research to better understand its properties. For this, we need to move beyond the standard ways of thinking about trials to better appreciate the full complexity of statistical and ethical elements involved in conducting multiple RCTs within a cohort. Comparability of treatment groups is only one of those elements.

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Selective outcome reporting is present in randomized controlled trials in lung cancer immunotherapies

Selective outcome reporting (SOR) is a type of in-study publication bias that occurs when only some outcomes listed in trial registries are reported in published articles often to increase the appearance of positive findings [1]. SOR contributes to distorting the scientific literature [2−4]. We investigated the presence of SOR in randomized controlled trials (RCTs) of lung cancer immunotherapies and noted the presence of trial registration, reporting of trial registration numbers, prospective registration, and compliance with CONSORT guidelines.

Detailed methods can be found in the Supplementary Materials (Appendix 1) at www.jclinepi.com. Briefly, we searched MEDLINE and the Cochrane Central Register of Controlled Trials for eligible RCTs. We found corresponding trial registration entries by checking to see if authors reported the registration numbers in the text of their articles or by hand-searching ISCRCTN.org. Using Fisher's exact test, we compared whether the presence of SOR was associated with study significance ($P \leq 0.05$ vs. $P > 0.05$), prospective registration (yes/no), and funding source (industry/other).

Supplementary Fig. 1 and Table 1 in the Supplementary Materials show the study selection process and study characteristics. Characteristics are also summarized in Supplementary Fig. 2. Of 42 articles that met our criteria, 20 did not report a trial registration number in the text. Overall, we identified 26 trial registrations, 22 on account of reported registration numbers, and four through manual searching of trial registries [5−8]. Ideally, all studies should provide registration numbers in published reports to comply with International Committee of Medical Journal Editors recommendations and CONSORT guidelines [9]; however, individual journals enforce compliance differently [10].

Of 26 articles, 19 had prospective registration, and seven were registered during the trial or after completion, with six of seven articles published before 2013. Twenty-four articles met criteria for SOR analysis; the most common SOR was the addition or omission of secondary outcomes (Supplementary Table 2; Fig. 1 below). Five articles did not have any SOR present [11−15]. Only two of the 24 articles adhered to CONSORT guidelines [7,16]. SOR was found to be associated with study significance ($P = 0.04$), but not prospective registration or funding source (Supplementary Tables 3−5).

Researchers may alter secondary outcomes more often than primary outcomes because doing so is unlikely to change the primary study question or design. Thus, researchers might believe that a comprehensive list of secondary outcomes is not necessary for trial registration, and subsequent changes to the list do not require updates to the registry.

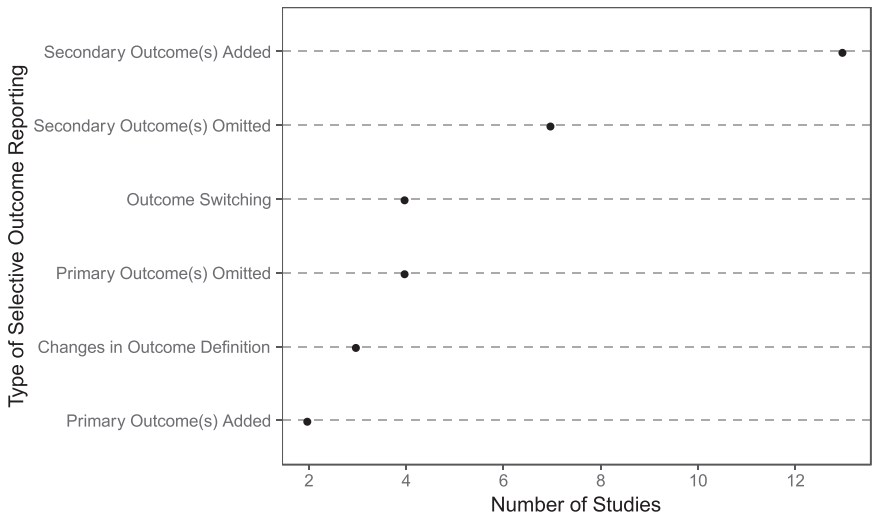

Fig. 1. Types of SOR present in studies ($n = 24$). *Note.* Summary of the different kinds of SOR present in eligible studies ($n = 24$). Outcome switching refers to either a primary outcome switched to secondary or a secondary outcome switched to primary. SOR, selective outcome reporting.