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Don't forget about the "R" in cmRCT: reply to Groenwold and van Smeden

With great interest, we read the paper "*Investigation of the 'm' in the cmRCT design revealed dependence between trial results*" [1]. We were particularly triggered by the rather alarming title. Upon reading the paper, however, our worries disappeared. It seems that, while focusing on the "m" in cmRCT, the authors forgot to think about the "R."

The authors describe four scenarios for conducting RCTs within one cohort. In scenario 1, subjects can only participate in a single trial. In scenario 4, subjects can participate in multiple trials, and trial allocation in subsequent trials is irrespective of the treatment status in the previous trials. The authors state that these scenarios bear no risk for dependence between trials.

The risk occurs, they state, in the other two scenarios. However, neither of these two scenarios represents true RCTs, as in both scenarios participants do not have an equal probability to be allocated to the treatment arms. In scenario 2, subjects in the active treatment arm in trial 1 cannot participate in trial 2, while those receiving the control treatment in trial 1 can only receive control treatment in trial 2. It is completely clear that patients in both treatment arms of trial 2 are not interchangeable (a requirement for randomization), as the control arm of trial 2 may include controls of trial 1, while the intervention arm may not. In scenario 3, subjects in the active treatment arm in trial 1 can only receive the control treatment in trial 2, while controls in trial 1 can receive either the active and control treatment of trial 2. Also here, the two arms of trial 2 are not interchangeable, as the control treatment arm of trial 2 may include participants from the active treatment arm of trial 1, while the intervention arm may not.

There are multiple examples of scenario 1 trials, where cohort members participate in one trial only (www.twics.global/use-of-the-design). An example of scenario 4 is seen in the PLCRC cohort of colorectal cancer patients [2]. Here, participants of the cohort-based BOOST trial (impact of a radiation boost on pathological response in rectal cancer) may subsequently participate in the SPONGE trial (impact of a retractor sponge on postoperative complications) [3,4]. Since patients who have received a radiation boost are prone to postoperative complications, participants in the SPONGE trial are stratified according to their BOOST trial status.

The authors do not provide examples of scenario 2 or scenario 3 trials. To the best of our knowledge, these trials do not exist. It therefore seems that the authors are using a straw man argument by setting up a scenario that hasn't been seen in reality.

As long as the multiple RCTs running within one cohort are designed as randomized controlled trials, in which patients are eligible for a new trial only if they are eligible for all of its arms, there is no concern for dependency between trials. Dependence may occur when the principles of randomization (interchangeability between groups) are abandoned, and cmRCT becomes cmCT.

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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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