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The cohort multiple randomized controlled trial design was found to be highly susceptible to low statistical power and internal validity biases

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Abstract

Objectives: The ''cohort multiple randomized controlled trial'' (cmRCT) is a recent innovation by which novel interventions are trialed within large longitudinal cohorts of patients to gain efficiencies and align trials more closely to standard clinical practice. The use of cmRCTs is outpacing its methodological understanding, and more appropriate methods for designing and analyzing such trials are urgently needed.

Study Design and Setting: We established the UK Comprehensive Longitudinal Assessment of Salford Integrated Care cohort of 4,377 patients with long-term conditions within which we are conducting a cmRCT (''Proactive Telephone Coaching and Tailored Support'') of telephone-based health coaching.

Results: We identify some key methodological challenges to the use of the cmRCT in actual practice. Principal are issues around statistical power, sample size, and treatment effect estimation, for which we provide appropriate methods. Sampling procedures commonly applied in conventional RCTs can result in unintentional selection bias. The fixed data collection points that feature in cmRCTs can also threaten validity.

Conclusion: The cmRCT may offer advantages over conventional trial designs. However, a cmRCT requires appropriate power calculation, sampling, and analysis procedures; else, studies may be underpowered or subject to validity biases. We offer solutions to some of the key issues, but further methodological investigations are needed. Cohort multiple RCT–specific Consolidated Standards of Reporting Trials guidance may be indicated.

Keywords: cmRCT; Trials within Cohorts; Sample size calculation; Bias; Methods; Cohort study

1. Introduction

Randomized trials are fundamental in evidence-based medicine but often struggle to recruit, leading to problems in both internal validity (especially power) and external validity. There is widespread interest in the development of innovative trial designs that can more effectively recruit and retain patients and make trials more efficient and patient centered. One such innovation is the ''cohort multiple

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Ethical approval and informed consent: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individuals who participated in the CLASSIC and PROTECTS studies.

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What is new?

Key findings

- The cohort multiple randomized controlled trial (cmRCT) is a recent innovation in ''efficient'' trial design that is gaining in popularity. However, design and analysis of a cmRCT requires appropriate power calculation, sampling and analysis procedures, or such studies can find themselves underpowered or subject to selection and other validity biases.

What this adds to what was known?

- We identify key methodological challenges to the use of the cmRCT in actual practice. Principal are issues around statistical power, sample size, and treatment effect estimation. We also describe hitherto unidentified validity risks inherent in the design, such as sampling practices commonly applied in pragmatic trials, which when applied to a cmRCT can result in selection bias, and validity issues related to the fixed data collection points that feature in cmRCTs.
- We provide appropriate methods for power calculation and show that unless levels of participant eligibility and consent are substantial, the sample size requirements for a cmRCT may be impracticably large.

What is the implication and what should change now?

- Pilot studies are essential to determine likely rates of eligibility and nonconsent for the purposes of cmRCT sample size estimation.
- It is important that trials using the cmRCT design publish sufficient detail on their processes, along with summary statistics, to reassure users of the research that the validity threats specific to this design have been appropriately addressed. Cohort multiple RCT−specific Consolidated Standards of Reporting Trials guidance may be advised.

randomized controlled trial'' (cmRCT) [1], a form of ''Trials within Cohorts'' (TwiCs) design in which novel interventions are trialed within much larger, typically longitudinal cohorts of patients to take advantage of potential recruitment, cost, and other efficiencies [2].

It is claimed that the cmRCT design can overcome many of the shortcomings of traditional pragmatic randomized controlled trials (pRCTs) [1]. Under a pRCT potential participants are provided with information about the trial and the available interventions, and consenting participants are then randomized between trial arms. All patients are told about the different treatments in the trial arms, including any new treatment, but only half are randomized to that new treatment. Patients who have a strong preference for a particular treatment (on offer within the trial or outside of it) or who are concerned about the risk of being randomized to an unproven treatment may be less likely to agree to participate [3]. Even among participants, there is a risk that randomization to the nonpreferred arm may cause dissatisfaction affecting withdrawal and outcome reporting [3,4].

In contrast, the cmRCT design aims to make the trial consent procedure more like standard health care, where people are only asked to consent to treatments they are being offered and are not told about treatments they cannot access. Under this design, a substantial cohort of participants is first established and then followed up at regular time intervals. To conduct a cmRCT of a new intervention, all cohort participants eligible for the treatment are first identified and then a random sample selected and offered the treatment, which they can either consent to receive or decline. All remaining eligible patients—that is, all patients eligible for the treatment but not offered it—constitute the control arm. These patients are not informed about the trial or the randomization, so they never hear about treatments that they will not receive. Relevant outcomes and other measures are taken on all patients in both arms as part of the regular follow-up process. Further cmRCTs of other interventions can be conducted within the same core cohort of patients.

Advocates of the cmRCT design claim significant advantages regarding recruitment, patient centeredness, and efficiency including costs. Enhanced recruitment stems from basing the trial within an established cohort and from the simplified consent process, which offers a straightforward choice between agreeing to the experimental treatment or not; while disappointment bias and cross-over may be reduced by eliminating randomization to the control arm. Efficiencies can be gained by conducting multiple RCTs within the same cohort, while the availability of large numbers of potential controls allows the number offered treatment to be reduced without loss of statistical power, thus saving treatment costs. Since the design was first proposed, a number of patient cohorts and related cmRCTs have been established [5−14]; however, very few of these have yet reported, and good evidence to support these claims is lacking. We conducted a search for articles reporting the results of cmRCTs and found only two that have reported actual recruitment figures [15,16]. In a small pilot cmRCT of a homeopathic treatment for menopausal hot flushes, 17 of 24 women accepted the offer of treatment (71%) [15]. The Depression in South Yorkshire (DEPSY) trial achieved 40% consent to treatment (74/185) and reported that recruitment was more efficient and overall attrition smaller than other depression trials [16]. However, differential attrition was high, both between arms (13% among controls vs. 32% among intervention patients) and between intervention group patients who did (12%) and did not (66%) consent to treatment. No control