Early View

Correspondence

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COVID-19 drug research and the cohort multiple randomised controlled trial design

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Take home message: In the cohort multiple randomized controlled trial design, consent is not
sought from control group participants in each trial conducted within the cohort, so it is
ethically inappropriate to assess medicinal products in COVID-19 patients.
To the editor

Soon after the start of COVID-19 pandemic, in May 2020, more than 1,300 trials were registered worldwide, 82% devoted to assessing drugs or biologics [1]. Most of them were non-randomized trials or randomised controlled trials (RCT). A few were adaptive, platform trials. However, in March 2020, the public hospitals of Paris (France) registered a cohort study, CORUMINO-19 (NCT04324047), aiming to collect observational data to nest a series of RCTs to assess interventions for COVID-19 patients, i.e., a cohort multiple RCT (cmRCT). This clinical research approach has been exceptional in the COVID-19 pandemic.

CORUMINO-19 Collaborative group has published several open-label RCTs comparing various medicinal products on top of usual care versus usual care in hospitalized patients. Among these are tocilizumab (TOCI-1) [2], anakinra [3], sarilumab (SARI-1) [4], and tocilizumab plus dexamethasone vs dexamethasone [5]. Hermine et al have just published the results of the second tocilizumab trial (TOCI-2) and the second sarilumab trial (SARI-2) [6]. Why these investigators decided to conduct a cmRCT? Acknowledging that the conduct of a series of individual RCTs is much more complex, expensive, and time-consuming, why they did not conduct an adaptive, platform RCT? Does cmRCT has some feature that prevents many other researchers from using it?

Relton et al first proposed the cmRTC design highlighting three main features [7]: the recruitment of a large observational cohort, the regular measurement of outcomes for the whole cohort and the capacity of conducting multiple RCTs over time. In cmRCT all patients in the cohort consent at the beginning to provide data, but only some eligible patients are randomized and included in each RCT to receive the intervention of interest: the outcomes of these latter group will be compared with those of eligible patients that were not randomly selected [7]. Only those patients randomized to receive the intervention of interest are
informed of the trial specifics and must provide a second informed consent. The control group is not informed on the conduct of this RCT.

Participants (or legal representatives) in CORUMINO-19 RCTs were informed about this. Deferred consent was permitted. The fact that only those participants randomized to receive the intervention of interest were informed about all trial’s specifics, constitutes a modification of the usual informed consent process, in which all potential participants (which will constitute the experimental and control groups) receive the same information about the trial prior to be included in the trial and thus, prior to randomization. The well-accepted reason for consent is that all participants must know about the trial and agree to participate in it. Hence, the cmRCT approach does not fulfill the ethical requirements of informed consent [8].

The Declaration of Helsinki [9] does not consider the possibility of a modification of the informed consent process. However, the CIOMS guidelines [10] state that an alteration (or even a waiver) of the informed consent process could be applied to research fulfilling three requirements: the research has important social value, it poses no more than minimal risks to participants, and it would be unfeasible or impracticable to carry out without the modification. CORUMINO-19 trials fulfil the first two requirements since they assessed repurposed (well known) drugs for an unmet urgent medical need. However, with the huge number of COVID-19 patients admitted to hospitals in March 2020, it was reasonable to think that, at the time the cmRCT was conceived, any trial could be carried out after obtaining participants informed consent prior to randomization. This was the approach taken by successful adaptive, platform trials conducted across many countries [e.g., Recovery (ISRCTN50189673), Solidarity (ISRCTN83971151)], including France [Discovery (EU2020-000936-23)].

The cmRCT design is best suited for pragmatic trials, conducted in chronic conditions, conditions for which previous trials have struggled with recruitment and for which many trials will be conducted [7]. Seems clear that in March 2020 only the last of these four features could
be applied to the conduct of RCTs in COVID-19 hospitalized patients. The need of explanatory trials was paramount: CORUMINO-19 investigators considered their trials as phase 2 or phase 2/3 and were conducted following good clinical practice guidelines. Investigators could not foresee problems in the recruitment of participants in the middle of the first pandemic surge. Some may think that CORUMINO-19 cmRCT allowed the fast recruitment (in 2-3 weeks) of the limited number of cases needed (between 91 and 148 participants) to draw conclusions [2-4,6]. Yet, this seems not to be a reason to justify the conduct of trials in which half of participants are unaware of being included in a specific RCT, especially when these trials could have been carried out seeking participants’ informed consent prior to randomization.

It is concluded that there is no justification for using the cmRCT design in future pandemics, and that an adaptive, platform RCT approach would have fulfilled CORUMINO-19 investigators objectives and all ethical and scientific standards.
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References


https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ Date last accessed: 8 April 2022