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

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To the Editor:

Soon after the start of the coronavirus disease 2019 (COVID-19) pandemic, in May 2020, more than 1300 trials were registered worldwide, 82% of which were devoted to assessing drugs or biologics [1]. Most of them were non-randomised trials or randomised controlled trials (RCTs). A few were adaptive, platform trials. However, in March 2020, the public hospitals of Paris (France) registered a cohort study, CORIMUNO-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.

The CORIMUNO-19 collaborative group has published several open-label RCTs comparing various medicinal products on top of usual care *versus* usual care in hospitalised patients. Among these are tocilizumab (TOCI-1) [2], anakinra [3], sarilumab (SARI-1) [4] and tocilizumab plus dexamethasone *versus* dexamethasone [5]. Hermine *et al.* [6] have just published the results of the second tocilizumab trial (TOCI-2) and the second sarilumab trial (SARI-2). Why did these investigators decide 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 a cmRCT have some feature that prevents many other researchers from using it?

Relton *et al.* [7] first proposed the cmRCT design, highlighting three main features: 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 cmRCTs, all patients in the cohort consent at the beginning to provide data, but only some eligible patients are randomised and included in each RCT to receive the intervention of interest: the outcomes of this latter group will be compared with those of eligible patients that were not randomly selected [7]. Only those patients randomised 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 the CORIMUNO-19 RCTs were informed about this. Deferred consent was permitted. The fact that only those participants randomised to receive the intervention of interest were informed about all the 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 being included in the trial and thus, prior to randomisation. 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 fulfil 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 Council for International Organizations of Medical Sciences 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. CORIMUNO-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

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In the cohort multiple randomised controlled trial design, consent is not sought from control group participants in each trial conducted within the cohort, so it is ethically inappropriate for assessment of medicinal products in COVID-19 patients https://bit.ly/3xtBX3m

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hospitals in March 2020, it was reasonable to think that, at the time this cmRCT was conceived, any trial could be carried out after obtaining participants' informed consent prior to randomisation. This was the approach taken by successful adaptive, platform trials conducted across many countries (*e.g.* Recovery (ISRCTN50189673) and Solidarity (ISRCTN83971151)), including in 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]. It seems clear that in March 2020 only the last of these four features could be applied to the conduct of RCTs in hospitalised COVID-19 patients. The need of explanatory trials was paramount: CORIMUNO-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 the CORIMUNO-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 randomisation.

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 CORIMUNO-19 investigators' objectives and all ethical and scientific standards.

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