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



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*Reply to R. Dal-Ré*:

We read with interest the comment of R. Dal-Ré on the CORIMUNO-19 trials design [1–5]. The key argument is that the cohort multiple randomised controlled trial (cmRCT) design implies an alteration of the informed process that can only be justified if three requirements are fulfilled: the research has important social value, it poses no more than minimal risks to participants, and it would be impracticable to carry out without consent process modification [6]. R. Dal-Ré acknowledges that the first two requirements were fulfilled for CORIMUNO-19 trials, but argues that, given the huge number of patients hospitalised with severe or critical coronavirus disease 2019 (COVID-19) in March 2020, trials would have been feasible without consent modification.

At the time when CORIMUNO-19 trials were designed, the huge number of COVID-19 patients in French hospitals did not mean that conducting clinical research was facilitated. Indeed, physicians were overwhelmed, the whole hospital and care systems were de-organised, and clinical research infrastructures were not fully operational, for instance because staff were not allowed to go onsite. Let us first recall the situation we faced:

1) It was difficult to plan a trial with scarce knowledge on the disease (*e.g.* what was the prognosis of patients);
2) Knowledge on the disease was expected to move quickly;
3) Usual care and the prognosis of patients would likely change rapidly;
4) There would be the need to evaluate many different treatments, all of which were not yet identified.

Accordingly, our choice of a cmRCT was based on the following considerations:

1) We wanted to plan a series of trials with the same master protocol to be quick and reactive and respond to the urgency of the situation, while keeping high ethical standards;
2) We wanted to set up a cohort to standardise data collection for COVID-19 patients even if they were not eligible/included to a trial;
3) The foreseen rapid evolution of disease management and prognosis, and differences in centre practices, would necessitate comparing patients receiving the evaluated intervention to controls treated in the same sites at the same time.

For instance, this third point led us to discard platform designs where new intervention groups are compared to a shared control group comprising participants who have been enrolled to the trial before this new intervention arm was added [7].

Instead of a cmRCT design, R. Dal-Ré recommends using a platform trial. Actually, the CORIMUNO-19 is a platform trial. Indeed, there is no unique platform trial design, which corresponds to a specific form of trial in which substudies can possibly be added or terminated dynamically during the course of the trial, under a common trial infrastructure [8]. This is exactly what the CORIMUNO-19 trials aimed at. The design allowed to quickly set up trials in the early pandemics in France.



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Concerning CORIMUNO-19 consent, individuals (or legal representatives) gave informed consent to participate in the cohort, which implied data being recorded and analysed, and agreeing to be possibly randomised in a trial comparing usual care to a specific intervention, under the provision that eligibility criteria were met. In case of randomisation to the intervention arm only, a second consent was asked, so that no participant would receive an intervention she or he would not deem acceptable. For individuals for whom the randomisation would not modify care, no second consent was sought. We considered this process easier to implement, and it was deemed acceptable by both the IRB (Comité de Protection des Personnes Île-de-France VI) and competent authorities (Agence Nationale de Sécurité du Médicament, ANSM). Of note, a wide majority of inclusions to the cohort and randomisations were performed on the same day. More generally, ethical issues with the asymmetric consent in cmRCT have already been debated, and the consent for participation to the cohort and to being possibly randomised would mitigate issues over the ethics of obtaining a trial-specific consent only for individuals allocated to the intervention arm [9]. Ethical superiority over Zelen randomised consent design has also been claimed.

Last, if all CORIMUNO-19 participants consented to being possibly randomised, it is true that they did not explicitly consent to be randomised between two specific treatment arms. There are other situations where consent is not so explicit. For instance, in some trials, individuals are recruited and randomised, after consent, but blinded to the study hypotheses [10]. Other similar situations occur in group-randomised trials, when potential participants are identified before their physician would be randomised to the intervention or control.

In conclusion, and looking retrospectively at CORIMUNO-19 trials, we have been able to test rapidly several hypotheses during this epidemic crisis, which have been the basis of designing more classical registration trials that have led to the definition of new standards of care using tocilizumab and dexamethasone, for instance. Thus, it is tempting to claim that cmRCTs are also appropriate during epidemic crises.

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