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Reply to Hasford and to Spinola et al

TO THE EDITOR—We proposed human challenge trials (HCTs) as a possible alternative or complement to conventional phase 3 trials for expedited severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine efficacy testing [1]. Hasford [2] argues that a large, simple, randomized trial, as proposed by Yusuf et al [3], could work better. We note that the latter design is similar to that implemented by the World Health Organization for the SOLIDARITY platform trial [4]. If vaccine efficacy can be assessed rapidly in such trials, then HCTs might prove unnecessary, but preparing for HCTs would still be a valuable hedge against the possibility of too low an incidence of coronavirus disease 2019 (COVID-19) in field trials in such a fluid situation.

Spinola et al argue that HCTs are generally limited to diseases that can be fully treated. We recognize that COVID-19 is not in that category, but have explained elsewhere why the risks remain tolerable [5, 6]. We note also that since we wrote our original manuscript, 2 specific therapies have been shown to reduce the risks to patients hospitalized with COVID-19 [7, 8], and it is possible that further treatments will be developed in the coming months that reduce the risks even further. It is true that we necessarily have no information on the long-term outcomes associated with SARS-CoV-2 infections. The informed consent statement must include specification that there may be long-term effects of which we are currently unaware. As we explained elsewhere, this in no way invalidates participants' informed consent [9]. Nor does the uncertainty otherwise make the trials impermissible [10]. We agree with Spinola et al that such trials should not target minority groups for recruitment [5].

Spinola et al argue that "it is unlikely that a SARS-CoV-2 model could be ready to evaluate vaccines for years." But the circumstances of the COVID-19 pandemic have changed the paradigm for the time it takes to develop and test new vaccines. If sufficient resources are devoted to developing HCTs for SARS-CoV-2 vaccines, then we believe they could be available much sooner. Of note is the recent report that HCTs might be conducted at Oxford University "by the end of this year" [11].

Spinola et al are also concerned that HCTs would not provide adequate data regarding vaccine safety and that, even with a parallel large short-term safety trial, such testing could not detect long-term adverse effects. However, even in the type of conventional phase 3 trial that it is hoped might produce efficacy data in 3–6 months sufficient to justify widespread vaccine use [4], longer-term adverse effects will remain unknown, and must be studied in postlicensure studies.

Notes

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Convalescent Plasma Therapy in Patients With Severe or Life-Threatening COVID-19: A Metadata Analysis

To the Editor—Current therapeutic options to mitigate severe COVID-19 cases remain limited. Prior experience with convalescent plasma (CP) to treat severe acute respiratory syndrome (SARS), influenza H1N1, and Ebola patients suggested that passive immunization by plasma transfusion suppresses viremia and improves clinical outcomes, reducing the number of deaths and length of stay in the intensive care unit (ICU) with minimal side effects. These findings are not universal, as Zeng et al described discouraging effects of CP therapy on survival in coronavirus disease 2019 (COVID-19) patients [1], and a recent COVID-19 study stratified by disease severity (n = 103 participants) did not show significant improvement following CP administration, when compared to standard care alone [2]. However, a subanalysis suggested a potential CP therapeutic benefit in those with advanced disease, including patients with COVID-19 severe disease (respiratory distress and/or hypoxemia) but not in patients with life-threatening disease (shock, organ failure, or requiring mechanical ventilation) [2].

In order to add more information on whether CP administration is effective as a treatment over the continuum of care of COVID-19 patients, we performed a metadata analysis, including random-effects meta-analysis and metaregression, based on available data [1–9].

The following measures, before and after CP transfusions, were assessed: (1) viral load expressed as reverse transcription polymerase chain reaction (RT-PCR) cycle threshold (Ct) values (where Ct values ≥ 40 were considered SARS coronavirus 2 [SARS-CoV-2] negative); (2) C-reactive protein levels as a surrogate marker of inflammation resolution; and (3) clinical disease severity (World Health Organization 6-point clinical scale) [8]