Dear Drs. Hornby and Landray:

We congratulate you on publishing the findings of the RECOVERY trial of convalescent plasma. To advance the academic discussion on convalescent plasma, we wonder whether you could provide some additional information on three points below.

1. As acknowledged in your discussion, a key question is whether the experiment undertaken in this population, who were treated on average after 9 days of symptoms, and with a high 28-day mortality rate (24%) is generalizable to recipients of plasma earlier in the disease, such as the participants in the Libster et al trial which treated in the first 3 days of illness (*N Engl J Med. 2021 Feb 18;384(7):610-618*).

In this light, we note that in all four categories suggestive of earlier treatment presented in Webfigure 4 in the supplement (short time to treatment, not receiving oxygen, not receiving steroids, and having yet to form endogenous antibodies) convalescent plasma trends towards benefit, as seen below. We suspect that examining outcomes in individuals who had *combinations of these indicators*, especially participants who had all four, might shed light on the results, and we would be most appreciative of your undertaking and publishing such an analysis. Sub-group analysis in trials is of course hazardous but has already been undertaken in Webfigure 4. Our suggestion is based on the hypothesis that benefit is most likely to be seen in people treated when the disease has not progressed very far. Numbers will unfortunately be small, but perhaps the overlap among the four indicators will not reduce the sample size as much as might be expected.

LOW RISK CONDITION	CONVALESCENT PLASMA ARM	CONTROL ARM	ODDS RATIO (95% CONFIDENCE INTERVAL)
< 7 days since symptom onset	690/2149 = 32.1%	741/2156 = 34.4%	0.93 (0.86 – 1.02)
No oxygen received	60/442 = 13.7%	75/455 = 16.5%	0.82 (0.60 – 1.13)
Not receiving corticosteroids	66/360 = 18.3%	90/375 = 24%	0.76 (0.58 - 1.01)
Negative antibody test result	709/1935 = 36.7%	649/1586 = 40.9%	0.90 (0.82 – 0.97)

2. We wonder if you could shed light on the discrepancy in the number of deaths reported in the news release posted on your website on January 15th from the preliminary analysis that led you to suspend enrollment, and the number of deaths in the paper uploaded onto the Med Archive server. The information in the news release was the largest contributor to a recent JAMA meta-analysis of trial findings, and although the relative risk did not change, it is remarkable to see that the paper had 49.8% more deaths than described in the news release, with only a modest increase (11.1%) in the number of subjects. We think it would be helpful to clarify the discrepancy.

Jan 15th news release:

"The preliminary analysis based on 1873 reported deaths among 10,406 randomised patients shows no significant difference in the primary endpoint of 28-day mortality (18% convalescent plasma vs. 18% usual care alone; risk ratio 1.04 [95% confidence interval 0.95-1.14]; p=0.34). Follow-up of patients is ongoing and final results will be published as soon as possible."
https://www.recoverytrial.net/news/statement-from-the-recovery-trial-chief-investigators-15-january-2021-recovery-trial-closes-recruitment-to-convalescent-plasma-treatment-for-patients-hospitalised-with-covid-19

March 15th paper on Med Archive server:

There was no significant difference in 28-day mortality between the two groups: 1398 (24%) of 5795 patients allocated convalescent plasma and 1408 (24%) of 5763 patients allocated usual care died within 28 days (rate ratio [RR] 1·00; 95% confidence interval [CI] 0·93 to 1·07; p=0·93).
https://doi.org/10.1101/2021.03.09.21252736

3. A very high fraction of the study population received corticosteroids, and while you and others have shown the value of corticosteroids in patients with COVID-19 who require mechanical ventilation, corticosteroids do not seem useful early in the course of the disease (K*eller MJ, et al. J Hosp Med. 2020;15(8):489–493.*) We note above that the strongest protective odds ratio for convalescent plasma in your data was in patients not treated with steroids.

We are concerned that early corticosteroid use might have impaired therapeutic antibody function in a subset of your patients and wonder whether you have any immunologic-related biomarker data that might shed light on this issue. Steroids suppress phagocytosis of antibody-bound phagocytic cell functions and complement activity. Indeed, viral clearance was slower in patients with SARS and MERS who were treated with steroids (*Arabi YM, et al. Emerg Infect Dis. 2016;22(9):1554–1561; Lee N, et al. J Clin Virol. 2004;31(4):304–309).*

Sincerely,

Nigel Paneth MD MPH, University Distinguished Professor, Departments of Epidemiology & Biostatistics and Pediatrics & Human Development, College of Human Medicine, Michigan State University.

Jeffrey P. Henderson MD, PhD, Associate Professor of Medicine and Molecular Microbiology, Division of Infectious Diseases, Washington University School of Medicine in St. Louis.

Michael J. Joyner MD, Professor of Anesthesiology, Mayo Clinic School of Medicine.