Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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In Reply — Limitations of Safety Update on Convalescent Plasma Transfusion in COVID-19 Patients

To The Editor: The authors thank Dr Farag for his letter in response to our manuscript "Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients."[1] The letter raises important questions about the presentation of our updated safety report from the Convalescent Plasma Expanded Access Program (EAP). The fundamental element of our response to all of the questions raised by Dr Farag is the need to frame the context of the paper. Establishing clinical efficacy for a potential therapeutic agent deployed during a public health crisis involves a climb through an epistemic ladder, and the comments from Dr Farag primarily highlight future rungs of that ladder. Our response can be summarized in three key points:

1) SAFETY FIRST

The primary purpose of our paper was to describe the key safety metrics following transfusion of convalescent plasma in 20,000 hospitalized adults with severe or life-threatening coronavirus disease 2019 (COVID-19). As such, the data reported in our paper are descriptive. Although no comparator group was used in our safety report, there is substantial data about the range of expected incidence of key transfusion-related complications.[2-4] In this context, the incidence of complications in this patient cohort was (objectively) low relative to historical perspective and is especially noteworthy given the critically ill cohort of transfused patients.

2) EXPLORATORY ANALYSES OF EFFICACY ARE FORTHCOMING

This analysis, focused on safety signals, should not be construed as evidence of efficacy. Adjusted analyses of mortality were beyond the scope of the paper. The many putative confounding factors that are raised by Dr Farag are justified and are being considered as part of adjusted analysis that is ongoing.

3) PRAGMATIC STUDY DESIGN VERSUS RANDOMIZED CONTROLLED TRIAL

The issue of a randomized controlled trial is of great interest; however, the EAP was a pragmatic study design, organized to allow routine clinical care to dictate the timing and administration of plasma with the collection of real world data. Changes in patient characteristics at the time of enrollment over the first ~8 weeks of the pandemic should not come as a surprise as the world rapidly shared information on the treatment of COVID-19. Additionally, as more plasma became available during April and May, there was a shift toward earlier treatment in less severely or critically ill patients.

How the EAP evolved into a much bigger program to administer a product that — when the EAP started — scarcely existed across the country while obtaining rudimentary outcomes data will be addressed comprehensively in the coming months. This discussion will include the logistical issues associated with conducting a randomized controlled trial on convalescent plasma during the COVID-19 pandemic.

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