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THE AUTHORS REPLY:

Carolyn T. Bramante, M.D., M.P.H.,
University of Minnesota Medical School, Minneapolis, MN

John B. Buse, M.D., Ph.D.,
University of North Carolina at Chapel Hill, Chapel Hill, NC

David R. Boulware, M.D., M.P.H.
University of Minnesota Medical School, Minneapolis, MN

Randomized trials with a 2-by-3 factorial design allow three parallel but separate trials to efficiently share controls. Although quickly publishing the results for all three of the medications in the COVID-OUT trial was important, the sheer volume of data prevented us from presenting results as complete as those usually expected from phase 3 randomized trials.[1-3]

In response to Shukla and Misra: our median ivermectin dose of 430 μg per kilogram per day was higher than the doses used in other ongoing or completed trials at the time that we were developing the protocol (see Section 2.7.2 in the Supplementary Appendix of our article, available at NEJM.org). The safety of higher, repeated doses was unknown. The in vitro study of ivermectin plus niclosamide was published after enrollment for our trial had ended.[4]

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bramante@umn.edu .

Since publication of their article, the authors report no further potential conflict of interest.