In reply: Should we ever stop clinical trials for efficacy?

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To the Editor,

We thank Mr. Fergusson and Dr. Griesdale for presenting a well-reasoned discussion of the consequences of stopping a trial such as ours early.^{1,2} We generally agree that effect overestimation and lack of precision are unfortunate by-products of stopping a trial early. Nevertheless, we disagree with their suggestion that clinical trials should be stopped only “when it is obvious that clinical equipoise no longer exists.” The existence of different stopping rules indicates that deciding whether to stop or continue a trial is neither straightforward nor trivial.³ While *P* values are what lie on the surface, there are ethical reckonings involved. It requires weighing the current patients' good against the potential benefit to society.⁴ Each physician is required to balance the duty of care with the search for truth.⁵ Each patient desires the most effective treatment for themselves, not to serve an abstract scientific goal. To reconcile these interests, the power to stop or continue is rightfully vested with an institutional review board (IRB).

Though IRBs follow the principle of equipoise, this equipoise depends on what evidence is available at a given time. The editorial by Andrade (and the majority of its supporting references) summarizing the inconsistent results in ketamine trials was unavailable during our interim

analysis.⁶ Instead, the evidence with respect to our primary and many important secondary clinical outcomes significantly favoured ketamine over propofol. Together with findings from a paper published around the same time, our results may have led the IRB to conclude that equipoise no longer held.⁷

A larger sample number could give results that show either a greater or a lesser effect size, and would likely be a better estimate of the true treatment effect of our own study intervention. Nevertheless, IRBs are not required to stop or continue trials based on effect size, but rather on whether there is an effect at all.⁷ We are aware that our trial's small size and single-site nature are unlikely to change practice. We do believe that our results contribute to the scientific evidence and warrant a larger multi-centre trial.

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Conflict of interest No author has any commercial or other affiliations that are, or may be perceived to be, a conflict of interest.

Editorial responsibility This submission was handled by Dr. Hilary P. Grocott, Editor-in-Chief, *Canadian Journal of Anesthesia*.

References

1. Fergusson NA, Griesdale DE. Should we ever stop clinical trials for efficacy? Can J Anesth 2018; 65. DOI: <https://doi.org/10.1007/s12630-018-1207-y>
2. Gamble JJ, Bi H, Bowen R, et al. Ketamine-based anesthesia improves electroconvulsive therapy outcomes: a randomized-controlled study. Can J Anesth 2018; 65: 636–46.
3. Pocock SJ. Clinical Trials: A Practical Approach. NY: Wiley; 1983.
4. Goodman SN. Stopping at nothing? Some dilemmas of data monitoring in clinical trials. Ann Intern Med 2007; 146: 882–7.

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5. *Weijer C, Shapiro SH, Cranley Glass K.* For and against: clinical equipoise and not the uncertainty principle is the moral underpinning of the randomised controlled trial. *BMJ* 2000; 321: 756-8.
6. *Andrade C.* Ketamine as anaesthesia for ECT: is there room to improve a gold standard treatment? *Br J Psychiatry* 2018; 212: 129-30.
7. *Zhong X, He H, Zhang C, et al.* Mood and neuropsychological effects of different doses of ketamine in electroconvulsive therapy for treatment-resistant depression. *J Affect Disord* 2016; 201: 124-30.