To the Editor:

The recently published article by Ranucci and colleagues is a randomized trial of a protocol for goal-directed perfusion of patients undergoing cardiac surgery that suggests efficacy of a goal-directed perfusion strategy aimed at maintaining oxygen delivery at a minimum of 280 mL · min⁻¹ · m⁻². I have serious concerns, however, regarding the conduct of interim analyses and early stopping of the trial.

In brief, Ranucci and colleagues planned 4 analyses: 3 interim analyses (25%, 50%, and 75% completion) and a final analysis at 100% completion. At 25%, an efficacy analysis was performed at an α level of 0.01 (per online supplement). I presume that results were not significant at this first interim analysis with P > .01 as the study continued; however, investigators and statisticians at the sponsoring institution may have observed suggestive interim efficacy results such that they changed their stopping boundary for the P value at the 50% interim analysis from .005 to .05 (per statistical analysis section, main text) for the efficacy analysis. This decision was not grounded in statistical or ethical principles for data monitoring of an ongoing clinical trial.

Among many issues with this decision, the combination of the first 2 interim analyses tested at α levels 0.01 and 0.05 levels, respectively, leads to an inflated type I error rate greater than 0.05 for this study design. I note that the actual type I error rate for this approach depends on the rule used to define suggestive results that would lead to an increase in subsequent efficacy boundaries; however, with certainty the type I error rate for this design is greater than 0.05. The 75% interim analysis, had it been needed, was also modified to stopping with P ≤ .05, and I presume that the final analysis would also have tested at P ≤ .05, leading to an overall type I error rate as high as 0.101—a doubling of the type I error rate!

Ranucci and colleagues should post their ethics board-approved study protocols before and after modification in a public repository and address the following questions: Were interim analyses specified before the first subject was enrolled (limited details were added to clinicaltrials.gov registration on February 9, 2017, well after the study was already halted for efficacy)? If so, were efficacy stopping boundaries specified in advance for interim and final analyses, with a plan to control the type I error rate, at the time that the study enrolled the first patient? Was the ethics board notified that modification would break any previously specified control of the type I error rate?

At the 50% interim analysis, the primary end point was analyzed with the result of P = .036 from a χ² test, which would not have met stopping rules for efficacy if not for this questionable change in the stopping rules. Unfortunately, because the trial was stopped early, we do not know whether results would still be compelling after observing another 350 subjects.

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References

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ON THE PREMATURE TERMINATION OF THE GOAL-DIRECTED PERFUSION TRIAL

Reply to the Editor:

I thank Dr Schulte for his letter, in which he strongly debates the reasons for the premature termination of the Goal-Directed Perfusion Trial (GIFT). His contribution gives me the opportunity to clarify some aspects of the GIFT study, and even to provide additional data. I actually agree with most of the points raised by Dr Schulte. Premature termination (for efficacy) of a randomized, controlled trial is of course a matter of strong debate.

The Editor welcomes submissions for possible publication in the Letters to the Editor section that consist of commentary on an article published in the Journal or other relevant issues. Authors should: Include no more than 500 words of text, three authors, and five references. *Type with double-spacing. *See http://jtcvs.ctsnetjournals.org/misc/ifora.shtml for detailed submission instructions. *Submit the letter electronically via jtcvs.editorialmanager.com. Letters commenting on an article published in the JTCVS will be considered if they are received within 6 weeks of the time the article was published. Authors of the article being commented on will be given an opportunity of offering a timely response (2 weeks) to the letter. Authors of letters will be notified that the letter has been received. Unpublished letters cannot be returned.