GDP focused on AKI stage 1, with an odds ratio in favor of GDP of 0.3.³ Our results are in line with this finding and with previous observational studies,^{4,5} providing a confirmation of the hypothesis generated by nonrandomized, controlled studies.

I am happy to answer the direct questions of Dr Schulte. (1) All the documents related to the study protocol, its amendment, and the pertinent approvals of the ethics committee have now been placed as supplementary documents in clinicaltrials.gov and as supplementary material to this reply. (2) Yes, interim analyses were specified before starting the study, as per protocol version 1.0. (3) The initial *P* values for the stopping rules and the following changes were arbitrarily generated, without strict planning to control the type I error rate, and this is certainly a limitation and a potential flaw. A professional statistician with high expertise in study design and sophisticated statistical analyses was involved only in the late phases of the manuscript revision, to fulfill the requests for additional analyses from the statisticians of the *Journal*. (4) The ethics committee was not specifically informed that changing the stopping rules would result in an increased risk for a type 1 error; however, the committee includes a professional statistician (see the list in the document), and they had all the calculations available to draw their own conclusions. In addition, the amendment was presented as “substantial” and not “minor.”

In conclusion, I agree with Dr Schulte that our study design and planning were certainly not perfect from the point of view of a professional statistician. Nevertheless, I believe that the message delivered by the GIFT report is sound, albeit limited to minor degrees of AKI.

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PERFUSION-INDUCED ACUTE KIDNEY INJURY: CRITIQUES THAT DO NOT ROLL OFF THE TONGUES OF THORACIC SURGEONS

Reply to the Editor:

The letter to the Editor by Schulte¹ in this issue of the *Journal* raises some important critiques regarding a previously published randomized trial by Ranucci and coauthors.² The article by Ranucci and coauthors² was controversial from the day it was published, and likely before publication as well. The editorial process encompassed some difficult decisions both before and after publication of the article.³⁻⁵ There were questions raised about how oxygen delivery should be measured. There are at least 5 unmeasured variables that affect oxygen delivery at the cellular level and that confound the study of Ranucci and coworkers²:

1. Rate of oxygen delivery to the capillary.
2. Oxygen-hemoglobin dissociation curve.
3. Size of the capillary to cellular Po₂ gradient.
4. Diffusion distance from the capillary to the cell.
5. Rate of use of oxygen by cells.

Further, there are questions about the study design, some of which are addressed in the accompanying Letter to the Editor by Schulte.¹ Schulte¹ suggests that errors in measurements of statistical significance in the study design likely flawed the interpretation of results. At the heart of Schulte's comments¹ are the fact that the statistical significance levels for a difference between study groups (Acute Kidney Injury Network classes 1, 2, and 3) in the study of Ranucci and coworkers² were arbitrarily raised from *P* = .001 to *P* = .01 for questionable reasons during the course of the study.

TABLE 1. Overall type 1 error rate applying repeated significance tests for interpretation of interim results.

No. of tests	Error rate probability
1	0.05
2	0.08
3	0.11
5	0.14
10	0.19
20	0.25

Adapted from: Jennison C. Group sequential methods for clinical trials. Available at: http://people.bath.ac.uk/mascj/talks_2004/kl.pdf. Accessed January 31, 2019.

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The study design described in the article of Ranucci and coworkers² is a group sequential trial—sequential scheduled analyses in equal comparison groups during the time of the study. This sequential type of analysis provides a safer means of conducting a randomized trial and allows for early stopping of the trial if highly significant comparisons are identified. Schulte's comments¹ encompass the issue of type II statistical errors applied to group sequential clinical trials.⁶ At the heart of this concept is the fact that multiple comparisons of data that contain newer additions to baseline data requires more stringent *P* values (Table 1), not less stringent ones. This concept is not something that rolls off the tongues of most cardiothoracic surgeons. Nonetheless, when repeated significance testing occurs on additions to baseline data, adjustments have to be made to the hypothesis testing procedure to maintain overall significance and adequate statistical power.⁷ Specifically, to allow for repeated testing, it is necessary to use a more stringent significance level as a stopping rule, not a less stringent significance level as used by Ranucci and coauthors.² Table 1 gives an idea of how the number of comparisons of group sequential data alters *P* values. Starting with a *P* value of .05, as done by Ranucci and coauthors² in their secondary analysis, quickly becomes a much less significant *P* value on subsequent analyses.

So, what should we take away from the Ranucci publication and the subsequent editorial comments? There are several factors that affected the decision to publish the article of Ranucci and coworkers.² First, and perhaps most importantly, randomized, controlled trials that deal

with cardiopulmonary perfusion are few and far between, something that reflects both the procedural difficulty of performing these randomized, controlled trials and the attendant complexity of constructing and analyzing appropriate study designs. The trial of Ranucci and coworkers² is a semirigorous attempt at legitimizing the practice of cardiopulmonary perfusion, something that has evaded cardiothoracic surgeons since the days of John Gibbon and the first heart-lung machines. Establishment of an evidence-based approach for cardiopulmonary bypass opens up a whole new world that is all-inclusive and prepares for the future complexities of more and more difficult cardiac operations as the norm. The study of Ranucci and coworkers² provides hope for more robust and better-designed trials in the future.

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