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LETTER TO THE EDITOR

Letter by Hochman and Maron Regarding Article, "'Faith Healing' and 'Subtraction Anxiety' in Unblinded Trials of Procedures: Lessons From DEFER and FAME-2 for End Points in the ISCHEMIA Trial."

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To the Editor:

We recognize and value the open discourse surrounding the design and conduct of clinical trials. Recent discussion of the ISCHEMIA trial (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) has focused mostly on a change that amended the protocol to include additional components in the primary end point in 2017. The primary aim is to test whether an early invasive strategy has incremental value beyond optimal medical therapy for patients with stable ischemic heart disease and moderate–severe ischemia on clinically meaningful cardiovascular outcomes. Of note, the grant application funded by the National Heart, Lung, and Blood Institute (NHLBI) in 2011 was based on the current 5-component primary end point. However, we sought and received approval to implement the study protocol with a primary end point of cardiovascular death or myocardial infarction and to specify that a change to include resuscitated cardiac arrest and hospitalization for unstable angina or heart failure would be made in the event it became necessary to preserve power of the trial. The trial was designed to optimize precision around point estimates for the outcomes deemed most important to patients and clinicians, allowing them to make personalized decisions about their care, guided by robust data on risks and benefits. ISCHEMIA will have broad implications for the health of the millions of patients affected by stable ischemic heart disease.

As the study chair and co-chair/principal investigator for the ISCHEMIA trial, we wish to provide corrections of inaccuracies published in the Perspective by Rajkumar et al[1] in *Circulation: Cardiovascular Quality and Outcomes*. That Perspective misinformed the scientific community and other interested stakeholders about the ISCHEMIA trial.

First, the statement that "… on January 17, 2018, over 99% of the way through the recruitment period, an amendment was made to the clinicaltrials.gov website" is misleading. In May 2017, NHLBI convened an Independent Advisory Panel to review the potential change in the primary end point as prespecified in the protocol. An independent panel was necessary because the Data and Safety Monitoring Board had already reviewed outcome data by treatment group. The prespecified primary end point change was recommended by the Independent Advisory Panel that only had access to aggregate outcome data. This panel was independent of study leadership, NHLBI, and the Data and Safety Monitoring Board. The Data and Safety Monitoring Board reviewed the recommendation of the panel in alignment with their oversight duties, and NHLBI approved the recommendation in June 2017. https://www.clinicaltrials.gov was updated in January of this year to reflect that decision, consistent with the requirement to update this type of protocol change annually. All changes are reflected in the publicly accessible https://www.clinicaltrials.gov database.

The article, now titled "'Faith Healing' and 'Subtraction Anxiety' in Unblinded Trials of Procedures: Lessons From DEFER and FAME-2 for End Points in the ISCHEMIA Trial," was originally titled "Moving the Goalposts Into Unblinded Territory: The Larger Lessons of DEFER and FAME 2 and Their Implications for Shifting End Points in ISCHEMIA."

http://circoutcomes.ahajournals.org

The second inaccuracy relates to the statement (bold font added), "…we must reflect on whether there is any meaning to the term primary end point if these goalposts can be moved *at will* after a trial has begun recruiting—and especially if a very prominent trial does *so shortly before reporting its result*." In addition, the Perspective also states that "…readers should retain their focus on the primary end point that was prespecified and not one that was *post-specified*." The original study protocol, dated January 2012, *pre-specified* the potential change to the 5-component end point and adjudicated all components throughout the trial. A statistical plan developed in 2012 for the Independent Advisory Panel process specified that a decision about changing the primary end point would occur before 75% of the final number of primary end point events had accrued. Although the final number of primary end point events is not yet known because the trial is ongoing, estimates performed at the time of the Independent Advisory Panel meeting suggested that the ratio of accrued end point events to final end point events was <50%.

It is important to note that the original primary end point, cardiovascular death and myocardial infarction, remains of major interest and will be reported.

Finally, on the statement "The trial… is expected to report within the next few months," the Independent Advisory Panel also recommended extension of follow-up during their May 2017 meeting. The last patient visit is now planned for June 2019, so trial results will likely be reported in early 2020.

The ISCHEMIA trial has been conducted in accordance with the most rigorous clinical trial standards. The process described above to change the primary end point was extensive, deliberate, and carefully considered, involving not only the Independent Advisory Panel but also the trial Leadership Committee, Steering Committee, NHLBI program staff, and statisticians.

This brief response to the Perspective by Rajkumar et al[1] is intended to provide timely corrections to the factual errors. As study leads, if we had been given the opportunity to vet the information about the trial included in the manuscript before the article's publication, we might have prevented the dissemination of misinformation. We plan to follow up with a detailed article that addresses the rationale for the addition of hospitalization for unstable angina or heart failure and resuscitated cardiac arrest to cardiovascular death and myocardial infarction in the primary end point, and the rigorous methods used to maximize reporting of all events.

ARTICLE INFORMATION

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1. Rajkumar CA, Nijjer SS, Cole GD, Al-Lamee R, Francis DP. 'Faith healing' and 'subtraction anxiety' in unblinded trials of procedures: Lessons from DEFER and FAME-2 for end points in the ISCHEMIA trial. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004665. doi: 10.1161/CIRCOUTCOMES.118.004665.

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