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STATISTICAL NOTE

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How to interpret a randomized controlled study stopped early

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This issue of *Intensive Care Medicine* publishes data from a multicenter randomized controlled trial (RCT) by Joannes-Boyau et al. [1] on high-volume versus standard-volume hemofiltration for septic shock patients with acute kidney injury. The study was stopped early because of the authors' inability to recruit and enroll all planned participants, therefore calling into question how to interpret lower than the expected volume of data, which is a problem that occurs frequently in RCTs [2].

Reasons to stop a study early are the following:

(1) *Excess of treatment effect*: 'Stopping for benefit' is very well studied in the literature [3, 4] and two criteria should be considered: the quality of data reported and the effect estimation. First, the authors have to report adequately all the relevant information about the decision to truncate the trial, particularly when the number of events is small. In this case, the results that have been obtained up to that point may be considered reliable. In the absence of any adequate explanation as to why and how the study was stopped, the results should be regarded cautiously and with scepticism. Second, it has been well demonstrated that a major inflation of treatment effect can be related to an amount of information lower than 25 % of that planned. In turn, this effect may be considered trivial when the amount of information is higher than 50 % of that planned [5, 6]. Researchers need to be familiar with these issues, as the use of interim analysis is becoming more frequent, particularly in sponsored studies, and these interim analyses are used to continue or stop the investigation in order to avoid wasting financial resources [2].

(2) *Prevision of negative results at an interim analysis*: At the opposite pole of the previous 'stopping for benefit' effect, there is the possibility that, in the early stages of the study, no between-group differences are found. In the 1990s a cost-benefit index—the so called "futility index"—was developed [7], which was a probabilistic approach for early termination of a trial in which the accumulated data implies only a small probability of concluding that the new treatment in the study is superior to the standard treatment. However, the 'futility index' has received some criticism [8] and has not been used successfully.

(3) *Serious adverse events (SAR)*: SAR is a sufficient reason to stop an RCT. In this case, any statistical analysis of data obtained up to that point is useless and should not be performed.

(4) *New standard of care*: When new standard of care is available, the ongoing study becomes obsolete and should be stopped. In this case, analysis of the results obtained is unhelpful.

(5) *Inability to recruit and enroll an adequate number of patients*: This may stem from an inadequate estimation of the rate of occurrence of the event under study and/or the inability of the center(s) to recruit patients with the disease under study. In this case, by extension of the 50 % rule, it is logical to suppose that the recruited participants are a random sample of

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the patients that may be recruited. The data obtained up to that point are then an approximate estimation of definitive data, which may be as precise as the information obtained with >50 % of the planned information. If significant between-group differences are found, the results cannot be used to provide clinical positive statements, but only to design further trials taking into account past experience. If between-group differences are not statistically significant, there is no reason to carry on investigations in the specific subject of the trial.

In the RCT of Joannes-Boyau et al. [1], the recruitment of 460 patients was planned but only 140 (30.4 %) were enrolled in about 5 years. At the end of the study period (28 days) the two curves did not show different slopes and crossed at more than one point, as they also did during the follow-up period. It seems reasonable that the two treatments would not generate different outcomes, even if the study was completed, and the current results can be considered definitive despite only one-third of the planned sample being enrolled.

In conclusion, there is really no definite rule developed in the literature specifically for interpretation of a RCT stopped early. The decision is likely to rely on general rules of trial management, supported by an expert in clinical trial design and conduct. Therefore, this Statistical Note is to be considered a personal contribution for provisional guidelines on how to interpret a RCT stopped early.

Conflicts of interest The author states that there is no conflict of interest.

References

1. Joannes-Boyau O, Honoré P, Perez P et al (2013) High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicenter randomized controlled trial. Intens Care Med. doi:10.1007/s00134-013-2967-z
2. Friedlin B, Korn EL (2009) Stopping clinical trials early for benefit: impact on estimation. Clin Trials 6:119–125
3. Sargent D (2009) Early stopping for benefit in National Cancer Institute-sponsored phase III trials: the system is working. J Clin Oncol 27(10):1543–1544
4. Korn EL, Friedlin B, Mooney M (2009) Stopping or reporting early for positive results in randomized clinical trials: the National Cancer Institute cooperative group experience from 1990 to 2005. J Clin Oncol 27(10):1712–1721
5. Montori VM, Devereaux PJ, Adhikari NKJ et al (2005) Randomized trials stopped early for benefit. A systematic review. JAMA 294(17):2203–2209
6. Berry SM, Carlin BP, Connor J (2010) Bias and trials stopped early for benefit. Letters to the Editor. JAMA 304(2):156–159
7. Ware JH, Muller JE, Braunwald E (1985) The futility index. An approach to cost-effective termination of randomized clinical trials. Am J Med 78(4):635–643
8. DeMets DL (2006) Futility approaches to interim monitoring by data monitoring committees. Clin Trial 3:522–529