Stopping a trial early in oncology: for patients or for industry?

Trotta et al. [1] raise interesting points regarding the size of a clinical trial and the consequences of stopping due to
evidence of efficacy. They list trials in which stopping rules have been applied, including some stopped due to superior efficacy in the experimental arm.

The objective of clinical evaluation of a new therapy is to collect valid and reliable information to allow the best decisions to be made for the benefit of current and future patients. As complete information will never be available, a balance has to be struck between collecting information and reaching a conclusion. Statisticians have developed methods to ensure that specified values of type I error ($\alpha$) and power are respected. R. A. Fisher, working with agricultural data that arrive all together at harvest time, developed fixed-sample experimental designs. These can be implemented even when data arrive sequentially, as in clinical trials. However, sample size determination is not an exact matter as it depends on anticipating parameters such as the variability of the data, the average response rate or the overall survival pattern. When data arrive sequentially, there is an opportunity to use the accumulating evidence to reach an ideal sample size in a way that is impossible in settings such as agriculture. This ideal value will not be fixed in advance, but the procedure for determining it from the emerging data can be. Using such rules does not amount to 'stopping a trial early': it is a matter of stopping at precisely the right time.

Trotta et al. point out that repeated analyses of accumulating data can lead to statistically significant results occurring only by chance (at a rate $> \alpha$) and that analyses of sequential trials on the basis of methods for fixed-sample designs can lead to biased overestimates of treatment advantage and overstatement of the strength of the evidence ($P$ values that are too small). They do not mention that proper sequential designs guaranteeing specified values of $\alpha$ and power have existed for many years, nor that methods exist for their analysis avoiding bias and leading to accurate $P$ values [2–4]. Neither do they report whether such methods were used in the trials that they reviewed, although they recognize that 'the studies analysed were formally well designed'. Certainly regulators are well aware of such methods and tend to insist on their proper use [5].

Trotta et al. indicate that the principal beneficiary from stopping a trial due to efficacy will be the trial sponsor. However, there is also benefit for patients otherwise randomized to control when it is already evident that the experimental treatment is efficacious, and for those outside the trial otherwise denied the new therapy while patients continue to be recruited. Although Trotta et al. provide evidence that stopping rules are being used, they provide no evidence at all for their misuse. They do not reveal how the sample size for a clinical trial can be fixed so accurately that anything smaller is clearly inadequate.

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references


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