

ANALYSIS

Problems of stopping trials early

When interim analyses of randomised trials suggest large beneficial treatment effects, investigators sometimes terminate trials earlier than planned. **Gordon H Guyatt and colleagues** show how this practice can have far reaching and harmful consequences

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In a seminal simulation study published in 1989, Pocock and Hughes showed that randomised control trials stopped early for benefit will, on average, overestimate treatment effects.¹ Since then, the warning implicit in this simulation study has been largely ignored.

Fifteen years later, we reported a systematic survey which showed that trials stopped early for benefit—which we will refer to as truncated trials—yield treatment effects that are often not credible (relative risk reductions over 47% in half, over 70% in a quarter), and that the apparent overestimates were larger in smaller trials.² We subsequently compared effect estimates from all the truncated trials we could identify that had been included in systematic reviews and meta-analyses with the results of non-truncated trials in those same meta-analyses. We found, on average, substantially larger effects in the truncated trials (ratio of relative risks in truncated versus non-truncated of 0.71). Again, we showed an association with the size of the truncated trial: large overestimates were common when the total number of events was less than 200; smaller but important overestimates occurred with 200 to 500 events; and trials with over 500 events showed small overestimates.³

The results of simulation studies and systematic surveys of truncated trials therefore show that when true underlying treatment effects are modest—as is usually the case—small trials that are stopped early with few events will result in large overestimates. Larger trials will still, on average, overestimate effects, and these overestimates may also lead to important spurious inferences. Uncritical belief in truncated trials will often, therefore, be misleading—and sometimes very misleading.

The tendency for truncated trials to overestimate treatment effects is particularly dangerous because their apparently compelling results often prompt publication in prominent journals,^{2 3} rapid dissemination in media, and speedy

incorporation into practice guidelines and quality assurance initiatives. Below we review three instances in which truncated trials have provided misleading estimates of treatment effect and the response of the clinical community possibly resulted in harm to patients.

β blockers in non-cardiac surgery

In 1999 a clinical trial of bisoprolol in patients with vascular disease having non-cardiac surgery with a planned sample size of 266 stopped early after enrolling 112 patients.⁴ Two of 59 patients in the bisoprolol group and 18 of 53 in the control group had experienced a composite endpoint event (cardiac death or myocardial infarction). The authors reported a 91% reduction in relative risk with a 95% confidence interval of 63% to 98%.⁴ In 2001 a prominent opinion piece recommended β blockers for all high risk patients having non-cardiac surgery, and in 2002 the first authoritative clinical practice guideline recommended β blockers for such patients.^{5 6} In 2001, a US quality assurance initiative identified the practice as an opportunity for improving safety.⁷

Although the enthusiastic reception of the results almost stifled subsequent trials, in 2008 a systematic review and meta-analysis, including over 12 000 patients having non-cardiac surgery, documented a 35% reduction in the odds of non-fatal myocardial infarction (95% CI 21% to 46%), a twofold increase in non-fatal strokes (odds ratio 2.1, 27 to 3.68), and a possible increase in all cause mortality (1.20, 0.95 to 1.51).⁸

Despite the results of the systematic review, subsequent guidelines published in 2009 and 2012 continued to recommend β blockers, sometimes with great enthusiasm.⁹ Enthusiasts for β blockers suggest that lower doses and ensuring an early start to treatment can prevent the increase in stroke seen in the overall population. The enthusiasts may be right, but there is limited

evidence supporting the claim, and if the results of pooled analyses are correct, recommending β blockers in patients having non-cardiac surgery is continuing to cause disabling strokes.

Another explanation for β blockers continuing to be recommended is cognitive dissonance¹⁰—after prolonged advocacy, it is painful to acknowledge that the policy may result in a large number of patients having a disabling stroke. Those producing, and profiting from, β blockers may also have encouraged their continued perioperative use.

Intensive insulin therapy in critically ill patients

Cognitive dissonance may also help explain responses to the unfolding story of intensive insulin therapy in critically ill patients. In 2001, a single centre randomised trial of an intensive insulin regimen in critically ill patients with raised serum glucose reported a 42% relative risk reduction in mortality (95% confidence interval 22% to 62%). The authors used a liberal stopping threshold ($P=0.01$) and frequent looks at the data, strategies they said were “designed to allow early termination of the study.”¹¹ The results were, again, met with enthusiasm and rapidly incorporated into practice guidelines, with recommendations published as early as 2003 for an upper limit of glucose of ≤ 8.3 mmol/L.^{12–13} Numerous protocols for achieving upper limits of ≤ 8.3 mmol/L were also published.

Fortunately, the investigators’ decision to stop early did not stifle subsequent research. A systematic review published in 2008 summarised the results of subsequent studies, which refuted the lower mortality with intensive insulin therapy and established an increased risk of hypoglycaemia.¹⁴ These findings were confirmed in a later systematic review including additional studies. Nevertheless, several guideline groups continue to advocate limits of ≤ 8.3 mmol/L. These recommendations contrast with those of guidelines that fully account for the results of more recent studies, which recommend a range of 7.8–10 mmol/L.¹⁵

Activated protein C

The latest example of the phenomenon of misleading results from truncated trials concerns the use of recombinant human activated protein C (rhAPC) in critically ill patients with sepsis. The original trial, published in 2001, was stopped early after the second interim analysis because of an apparent difference in mortality.¹⁶ In 2004 the Surviving Sepsis Campaign, a global initiative to improve management, recommended use of the drug as part of a “bundle” of interventions in sepsis.¹⁷ A subsequent trial, published in 2005,¹⁸ reinforced initial concerns about increased risk of bleeding with rhAPC and raised serious questions about the apparent mortality reduction in the original study. Nevertheless, the 2008 iteration of the Surviving Sepsis guidelines, mirrored in 2009 by another guideline,¹⁹ continued to recommend rhAPC. After further discouraging results, the drug was withdrawn from the market last year, providing no further opportunity for guideline panels to drag their feet in altering recommendations to reflect the latest evidence.

Stopping the rush to judgment

Simulations show that a systematic review of a series of adequately powered trials with similar stopping rules, some of which stop early for benefit and most of which do not, will not appreciably overestimate treatment effects. These simulations,

however, assume that the results of one trial will not influence how, or whether, another trial is undertaken.

This assumption is unlikely to reflect the real world. If a trial that by chance overestimates treatment effects, and therefore stops early for benefit, is one of the first, the correcting trials that would bring a pooled estimate towards the truth may never be conducted. Indeed, if the investigators’ judgment to stop the trial early—that it is no longer ethical for patients not to receive the experimental intervention—is sound, the correcting trials should never be undertaken.

Overestimation of effects from stopped early trials is therefore an extreme example of two related phenomena: large effects tend not to be replicated, and results from early randomised trials tend to overestimate effects. Increasingly, methodologists are producing guidance for clinicians and guideline developers on how to interpret clinical trial evidence. Such guidance must include a high level of scepticism regarding the findings of trials stopped early for benefit, particularly when those trials are relatively small and replication is limited or absent.

The stories in this article illustrate the linked phenomena of publication of stopped early trials with dramatic results in high profile journals, their rapid and perhaps uncritical uptake by the media and guideline panels, and the experts’ understandable disinclination to reverse previous recommendations in the face of new data. Humans tend to seek confirming evidence for previous beliefs and to devalue new evidence.²⁰ Discomfort with the possibility of having made widely followed recommendations that did more harm than good is natural. It may be equally natural to persuade yourself of the limitations of disconfirming evidence.

Furthermore, the continued use of drugs—particularly if they are expensive and yield large profits—is in the interest of those who produce them. The drug industry is extremely effective in influencing the behaviour of clinicians, and guideline panellists sometimes also have substantial conflicts of interest. Thus, industry influence may partly explain continued recommendations in the face of contradictory evidence.

One solution to this problem would be for investigators to refrain from stopping their trials early. Indeed, we may ask whether trials should ever stop early for apparent benefit. The justification for stopping early is that it is no longer ethical to randomise patients to not receive the experimental treatment. If, after a trial stops early, other investigators launch new trials of the apparently beneficial intervention, the original trial authors’ judgment was premature. That was the case in the three examples we have presented here. The standard for persuading the entire clinical community that further investigation is not ethical—that is, the appropriate standard for stopping early—should be extremely stringent, both in terms of the magnitude of the evidence and the plausibility of the result. Such stringent criteria are unlikely to be met before 500 events have accumulated.³

While awaiting the uniform application of such a cautious approach, opinion leaders and guideline panels should ensure that when the evidence base is modest and comes largely from truncated trials their recommendations and evidence summaries reflect the uncertainty in the evidence and that the effects are likely to be overestimated. This will decrease the likelihood of further possibly harmful, widely promulgated, and inappropriately persisting recommendations.

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