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Early stopping of randomized clinical trials for overt efficacy is problematic

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Abstract

Objective: To illustrate controversial issues associated with stopping randomized controlled trials (RCTs) early for apparent benefit.

Study Design and Setting: The article presents our review of prior relevant work and our research group's reflections on early stopping.

Results: Compelling evidence suggests that trials stopped early for benefit systematically overestimate treatment effects, sometimes by a large amount. Unresolved controversies in trials stopped early for benefit include ethical and statistical problems in the interpretation of results.

Conclusions: The best strategy to minimize the problems associated with early stopping of RCTs for benefit is not to stop early. As an alternative, we suggest a threefold approach: a low *P*-value as the threshold for stopping at the time of interim analyses, not to look before a sufficiently large number of events has accrued and continuation of enrollment and follow-up for a further period.

Keywords: Randomized controlled trial; Data-monitoring committee; Stopping rule; Interim analysis; Stopping for benefit; STOPIT-2

1. General considerations of stopping a randomized clinical trial early

1.1. Four reasons for early termination

There are four major reasons for stopping a randomized clinical trial (RCT) early. First, the trial may show serious adverse effects and may be stopped for unacceptable safety. This was the case, for instance, in an RCT that investigated the effect of hydrocortisone treatment on survival without bronchopulmonary dysplasia in preterm infants [1]. This study was discontinued early because of gastrointestinal perforations in the hydrocortisone group [1].

Second, investigators may stop the trial if interim differences in outcomes between the intervention and control groups are so unimpressive that any prospect of a positive result with the planned sample size is extremely unlikely—so-called ''futility.'' In this case, the argument goes, continuing the trial may not be justifiable in terms of time, money, and effort. For example, Thistle et al. recently truncated their investigation of whether an ultrashort course of zidovudine therapy combined with a single dose of nevirapine would improve neonatal outcome compared with nevirapine alone [2].

Third, new external information may arise during the conduct of the study that either convincingly answers the primary study question or that raises serious safety issues. For example, the Steering Committee of the Canadian Atrial Fibrillation Anticoagulation trial decided that the evidence of benefit with warfarin from two RCTs published while their trial was ongoing was sufficiently compelling to dictate stopping recruitment into their trial without any preliminary examination of their data [3]. More recently, an RCT that enrolled men with prostate cancer and compared celecoxib, a selective cyclooxygenase-2 inhibitor with placebo [4] was terminated early after information about the cardiovascular safety of celecoxib prompted review of ongoing clinical studies [4].

Finally, investigators may terminate an RCT for apparent benefit, the issue we will focus on in this article.

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What is New?

- The prevalence of RCTs stopped early for apparent benefit is increasing.
- Results of trials stopped early for benefit should be interpreted with caution because statistical stopping rules are prone to stop a trial in a ''random high'' and exaggerate the estimated treatment effect.
- Unresolved controversies in trials stopped early for benefit include statistical problems in the interpretation of results, and ethical problems including implications for trial participants, clinicians, and society.
- The ongoing Study of Policy of Interim Truncation—2 (STOPIT-2) seeks to empirically determine the magnitude and determinants of bias that truncation introduces.
- An approach that requires a low *P*-value as the threshold for stopping, a sufficiently large number of events and confirmation of the positive trend may minimize the overestimation of treatment effects associated with early stopping for benefit.

Papanikolaou et al.'s trial comparing in vitro fertilization with single blastocyst-stage vs. single cleavage-stage embryos in infertile women represents an example of an RCT stopped early for efficacy [5]. The study was terminated early after an interim analysis showed a higher rate of pregnancy among women undergoing transfer of a single blastocyst-stage embryo [5].

1.2. Two principles of the decision-making process

The monitoring of response variables in clinical trials should adhere to the following two principles. First, an independent group of people, called a data-monitoring committee (DMC), should review analyses of a trial's accumulating data. Nowadays, some funding, ethics, and regulatory bodies consider an independent DMC essential for major RCTs. For instance, the Food and Drug Administration has published a draft guidance for clinical trials sponsors on the establishment and operation of clinical trials DMCs [6]. Several other experts have presented their ideas of DMCs' role in clinical trials [7–9]. Its independence protects the DMCs' decision-making process from the vested interests, and potential conflicts of interest, that may influence investigators or sponsors in their decisions about trial methods and potential termination.

In our view, safety should be the prime concern of the DMC. After any review, the DMC should decide whether to inform the management or steering committee of the interim results, and may make a recommendation about stopping or changing the trial protocol. The management of the trial and the final decision about stopping should, however, rest with the investigators. Second, unless unanticipated degrees of toxicity or benefit that the DMC feels is critical occur, the study investigators should not become aware of the emerging safety and efficacy data. Such knowledge may compromise the investigators' uncertainty about which of the treatments would benefit participants most (sometimes referred as equipoise), which is often considered an essential prerequisite of an RCT [10]. Early bad news could have a negative impact on the investigators' enthusiasm for proceeding with the trial and bringing it to its scheduled conclusion. Furthermore, much effort and discipline is required to avoid leaks and news about a trial's emerging data; such disclosures could compromise trial conduct and participation.

The remainder of our discussion addresses only RCTs stopped early for benefit. We do not address the more complex issues related to stopping early for harm. Our discussion is restricted to frequentist approaches to analysis, and does not address Bayesian strategies [11].

1.3. Values and preferences underlying decisions to stop early

RCTs stopped early for apparent benefit may lead to rapid dissemination of promising new interventions, whereas RCTs stopped early for other reasons (harm and futility) tend to decrease use of the treatments under study. Differences in thresholds to stop for one or another reason reflect values the decision makers hold: more stringent thresholds to stop early for benefit reflect a preference for avoiding the incorporation into practice of overestimates of treatment effect; less stringent thresholds to stop early for harm reflect a preference for foregoing potentially useful interventions rather than exposing patients to harm. These values and the thresholds will vary according to socioeconomical (e.g., availability of resources and opportunity costs of conducting the research) and clinical contexts (e.g., availability of effective agents and outlook of patients with current care). Researchers and DMCs consider these thresholds when designing and conducting interim analyses and choosing statistical stopping boundaries. Whatever thresholds decision makers choose, they should be aware of the serious dangers of stopping early for benefit. In the remainder of this article, we highlight these dangers.

2. Stopping an RCT early for apparent benefit

2.1. Motivations for early stopping

There are two potentially justifiable reasons for early termination of a trial showing apparent large benefit. First, one might make an argument that it is unethical to continue to randomize patients in the face of such a result. This consideration may be compelling for investigators, patients,

and their advocates, and DMCs. Second, scarce research resources might be better invested in addressing other questions if one believes an apparent large benefit has adequately addressed a research question, an issue of concern to the research community, and funding agencies.

There are, however, other motivations that some may consider problematic. The publication in high-impact journals that often accompanies the large effect size typically associated with RCTs stopped early for benefit generates honor and publicity for investigators, and positive press and attention for the trial funders. The journal itself may see an associated story in the lay press as increasing its profile and prestige, and ultimately its impact and its readership. These considerations may help explain the findings of STOPIT-1, a systematic review of RCTs stopped early for overt efficacy by Montori et al. that found an increasing prevalence of these trials [12]. In the early 1990s, about 0.5% of all RCTs in high-impact journals were stopped early for benefit. By the early 2000s, this figure had climbed significantly to 1.2% with clustering of publications in two particularly high-impact journals, the New England Journal of Medicine and The Lancet [12].

2.2. The quality of reporting in RCTs stopped early for benefit is limited

Many of the 143 trials stopped early for benefit identified by Montori et al. failed to report key methodological information regarding how the decision to stop was reached, including planned sample size, intervals, and numbers of interim analyses, and the statistical stopping rules used [12]. The CONSORT statement recommends reporting of these three characteristics [13]. Lack of details of the stopping process limits readers' ability to evaluate the decision to stop early and to draw their own informed conclusions.

The unsatisfactory reporting of studies that stop early is not limited to the RCTs themselves. In 2007, we published the results of a systematic literature search that identified 96 systematic reviews that include at least one RCT stopped early for benefit [14]. Over 70% of the systematic reviews that include at least one RCT stopped early for benefit failed to mention that some of the included RCTs were stopped early for benefit; though the Quality of Reporting of Meta-analyses statement does not explicitly call for identification of RCTs stopped early for benefit [15], including trials such as those in systematic reviews and meta-analyses without properly identifying and considering possible biases may lead to overestimates of treatment effect that ultimately influence clinicians and guideline developers [14].

2.3. RCTs stopped early for benefit often overestimate treatment effects

There are two statistical problems associated with stopping an RCT early for apparent benefit. The first is widely known and has to do with multiple testing. If investigators conduct repeated interim analyses at the same unadjusted level of significance, the probability that, at some time, the analyses will lead to significant results by chance alone will be larger than the significance level selected.

A number of strategies and procedures exist to deal with the problem of multiplicity. Statisticians have suggested rules for stopping early that, although sometimes disregarded (20% of RCTs stopped early for benefit have failed to report monitoring methods to justify early termination [12]), have become popular. The three most frequently used are the O'Brien–Fleming boundary (27%), the Lan–DeMets alpha-spending function (19%), and the Haybittle–Peto boundary (11%) [12]. These stopping rules ameliorate the multiplicity problem by having much more stringent significance levels in the early interim analyses while maintaining the study-wide significance level. The O'Brien–Fleming and Peto–Haybittle procedures set a predefined statistical stopping boundary for the primary outcome [16–18]. Although the O'Brien–Fleming boundary's last interim look slightly increases the significance level on each following test, the Peto–Haybittle method simply requires a low P-value of <0.001 at each interim analysis as evidence to stop early for benefit. The Lan–DeMets alpha-spending function allows the investigators to determine how they want to "spend" the type-I error or alpha during the course of the trial [19]. This method will lead to an overall type-I error at the end of the trial that matches the prespecified value of alpha.

The second problem, overestimating treatment benefit, is more challenging. Trials stopped early for benefit may overestimate the treatment effect no matter what statistical procedure ("stopping rule") investigators used to justify termination of the study. Bias arises because random fluctuations toward greater treatment effects may result in early termination [20]. If the decision to stop the trial did result from observing the apparent benefit of treatment at a "random high," the resulting estimate of the treatment effect will be misleading [21]. Indeed, the more stringent the P-value threshold results must cross to justify stopping the trial, the more likely it is that a trial stopped early will overestimate the treatment effect. Statisticians have offered methods for correcting for this overestimation [22], but none suggested thus far addresses the problem in a satisfactory way [23].

The findings from the review by Montori et al. demonstrate how these theoretical concerns play out in practice [12]. The 124 RCTs that used a dichotomous outcome reported a median relative risk reduction (RRR) of 47%, and a quarter reported an RRR of 70% or more. The magnitude of these effects is—unfortunately—not consistent with the modest effects we expect from most treatments [24–26]. Furthermore, trials that stopped on the basis of less than the median number of events (66) were far more likely to generate RRRs greater than 47% (odds ratio 31, 95% confidence interval: 12, 82). Montori et al. also

provide examples of truncated RCTs, the widely disseminated results of which subsequent RCTs contradicted [12].

2.4. Stopping RCTs early for benefit is ethically questionable

One of the primary motivations to include a DMC in an RCT is the concern that continuing a trial showing an apparent large benefit is unethical [27]. If a treatment really has large benefits, one would want to stop early both to protect the interests of trial participants (i.e., offer the beneficial intervention to participants in the apparently less effective control group), and to ensure that the good news spreads as quickly as possible.

Ethical trials must be scientifically valid [28]. Their validity, however, is seriously compromised when the RCT is at high risk of yielding a substantial overestimate of the treatment effect [27]. Scientific validity is further compromised by the reduced information on other outcomes and longer-term effects that would have accrued had the trial continued to completion. Truncated trials violate a second key criterion for ethical RCTs [28]. The social value of the research is severely compromised when overly sanguine estimates of treatment effect result in misleading risk–benefit ratios, misguided practice recommendations, and suboptimal clinical practice [27], as was the case, for instance, with an RCT that was stopped early for overt efficacy that included patients undergoing vascular surgery with and without beta-blockers [29,30].

One may be concerned, however, about the participants who gave informed consent to participate in the trial. Shouldn't they have the chance to choose the superior treatment?

Because of the lack of information on other clinical outcomes, the lack of precision, and the potential overestimation of treatment effect, it might be impossible for investigators to inform patients about the true benefit-to-risk ratio of the intervention and therefore give them a fair chance to choose the superior treatment [27].

The ethical mandate for early stopping in terms of enrolling new patients assumes that, should the trial terminate, such patients will have greater than the 50% chance of receiving the intervention. This seems overly optimistic given ubiquitous delays in dissemination, and uncertainties about magnitude and even existence of a beneficial effect that accompany the decision to stop early. For instance, when the ISIS-2 trial, an RCT of intravenous streptokinase, oral aspirin, both, or neither for suspected acute myocardial infarction [31] showed clear benefits early in the trial, the management committee decided that rather than stop they would inform all investigators and let them decide. Many continued recruiting as they were not persuaded by the interim results.

In another example, the early stopping for benefit of a trial of circumcision to prevent HIV infection in African men [32] did not lead to the immediate widespread adoption of the practice and the truncation of two ongoing trials. Rather—and appropriately—investigators launched two additional trials [33,34], both of which were later stopped early for benefit. Even when all three trials are complete, considerable effort (ongoing at the time we are writing) will be required for widespread dissemination. Furthermore, dissemination may be delayed by legitimate concerns regarding the behavioral consequences of a possible perception of complete protection against infection and the unintended decrease in other safe sex practices that may follow. The residual doubt about the magnitude of effect resulting from these stopped early trials adds an unnecessary and unfortunate uncertainty to the clinical and policy decision-making processes.

A trial stopped early for benefit, usually demands replication because it may overestimate treatment effects. Replications are likely to show smaller effects, leaving heterogeneity in the estimate of treatment effect. This heterogeneity might mandate further trials. Considerable effort may be avoided by completing the first trial without stopping early and therefore generating an unbiased estimate, ensuring that apparent treatment effects indeed really protects both scientific validity and social benefit and balances the need to protect the interests of study participants [27].

2.5. Unresolved issues and potential solutions

All statistical stopping rules are prone to stop a trial in a "random high" and therefore exaggerate the estimated treatment effect. Thus far, no satisfactory solution to deal with the problem of overestimation exists. Although it is consistent with statistical theory and empirical evidence that RCTs stopped early for apparent benefit may lead to overestimated treatment effects [12], the magnitude of bias, and the factors that are associated (and perhaps causally related) with the magnitude of bias in individual situations, are unknown. As we have mentioned, the systematic review by Montori et al. found a strong inverse association between the number of events and the estimated treatment effects and a median of 66 events observed at the time trials were stopped [12]. The 66 events would need to distribute as 46 vs. 20 events or a more extreme difference (RRR of 57%) to achieve a statistically significant treatment difference with the Peto–Haybittle method (i.e., $P < 0.001$) [35]. Because outcome is typically determined by multiple treatment factors, such treatment effects are usually implausible.

The STOPIT-2, an international methodological study funded by the British Medical Research Council (MRC) and led by four of the authors (P.G., D.B., V.M.M., and G.G.) promises to, in the future, provide some answers to the remaining questions. The study seeks to determine the magnitude and determinants of bias that truncation introduces by comparing treatment effects of studies stopped early for benefit with a pooled estimate of randomized trials addressing the same question as the stopped early studies. The primary research questions of STOPIT-2 are:

- What is the extent to which RCTs stopped early for benefit exaggerate the treatment effect compared with the best available estimate of treatment effect as determined by a systematic review of randomized trials addressing the same question as the stopped early study?
- What factors are associated to the size of the estimated difference in the treatment effect in the stopped early study and the respective meta-analytic estimate?
- Can Bayesian methods, using conservative priors, correct for the optimism of stopped early studies?

To answer these questions, we are searching the biomedical literature for systematic reviews addressing the same question as the stopped early studies we have identified. We are extracting data from the component studies of the systematic reviews and will conduct new meta-analyses addressing the outcome that led to the early termination of the stopped early RCT(s). We will then compare the relative risk (RR) generated by the truncated RCT with the pooled RR from all studies conducted to completion. Multivariable regression methods will help determine the influence that factors associated with the decision to stop early have on the magnitude of the treatment effect. Hypothetical determinants of the magnitude of difference include the particular stopping rule chosen, the methodological quality of the trials, and the number of events that had occurred at the time of early termination. Finally, we will compare possible methods for correcting the treatment effect estimates from stopped early studies. In particular, we plan to use Bayesian methods with priors chosen to ''regress to the mean'' the overoptimistic truncated RCTs, and use these ''corrected'' RCTs to repeat our comparisons with RCTs not stopped early.

2.6. What to do while awaiting the results of STOPIT-2?

Early inappropriate stopping for benefit is a powerful way to introduce bias in randomized trials [12]. Thus, the best solution to the problem is not to stop early for benefit. Furthermore, DMCs can avoid temptation by focusing on issues of harm, and not reviewing effectiveness data by group while the trial is ongoing.

Nevertheless, there will be rare situations when the observed benefit is truly large and the treatment is associated with minimal harm. In these circumstances, early stopping will lead to the happy outcome of treating as many patients as possible as quickly as possible. How should those who feel compelled by this tantalizing possibility maintain the possibility of stopping early for benefit proceed while awaiting the results from the STOPIT-2 study? After highlighting the controversies around stopping RCTs early for apparent benefit, we suggest an approach that includes three necessary steps if one considers stopping an RCT early for overt efficacy. First, set a low *P*-value (e.g., 0.001) as the threshold for stopping at the time of interim analyses. Second, do not look before a sufficiently large number of events have accrued. Because Montori et al. found a very strong association between number of events and the magnitude of treatment effects up to almost 200 events, that should be a minimal threshold—those who wish to be conservative might choose 300 or more events [12]. Third, continue enrollment and follow-up for a further period to make sure that the positive trend continues.

Such an approach is likely to minimize the overestimation of treatment effects inevitably associated with stopping trials early for apparent benefit. In the future, the results of STOPIT-2 will guide the interpretation of stopped early trials, and will inform investigators, institutional review boards, funding agencies, and DMCs about the appropriate use of stopping rules in clinical trials.

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