Journal of Clinical Epidemiology 82 (2017) 12−19

Randomized trials addressing a similar question are commonly published after a trial stopped early for benefit

M. Hassan Murad[a,b,c,*,1], Gordon H. Guyatt[d], Juan Pablo Domecq[e,f], Robin W.M. Vernooij[g], Patricia J. Erwin[h], Joerg J. Meerpohl[i], Gabriela J. Prutsky[f,j], Elie A. Akl[k,l], Katharina Mueller[m], Dirk Bassler[n], Stefan Schandelmaier[o], Stephen D. Walter[d], Jason W. Busse[p], Benjamin Kasenda[q,r], Gennaro Pagano[s], Hector Pardo-Hernandez[g], Victor M. Montori[b], Zhen Wang[a], Matthias Briel[o,d,1]

[a]*Evidence-Based Practice Center, Mayo Clinic, 200, 1st street, Rochester, MN 55905, USA*
[b]*Knowledge and Evaluation Research Unit, Mayo Clinic, 200, 1st street, Rochester, MN 55905, USA*
[c]*Division of Preventive Medicine, Mayo Clinic, 200, 1st street, Rochester, MN 55905, USA*
[d]*Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario L8S 4L8, Canada*
[e]*Department of Internal Medicine, Henry Ford Hospital, Detroit, MI, USA*
[f]*Unidad de Conocimiento y Evidencia, CONEVID, UPCH, Lima, Peru*
[g]*Iberoamerican Cochrane Centre, Institute of Biomedical Research (IIB Sant Pau), Barcelona, Spain*
[h]*Mayo Clinic Libraries, Mayo Clinic, 200, 1st street, Rochester, MN 55905, USA*
[i]*Cochrane Germany, Medical Center—University of Freiburg, Berliner Allee 29, 79110 Freiburg, Germany*
[j]*Department of Pediatrics, Children's Hospital of Michigan, Detroit, MI, USA*
[k]*Department of Internal Medicine, American University of Beirut, Beirut, Lebanon*
[l]*Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada*
[m]*Center for Clinical Pediatric Studies, University Children's Hospital Tuebingen, Frondsbergstraße 23, 72070 Tuebingen, Germany*
[n]*Department of Neonatology, University Hospital Zurich and University of Zurich, Frauenklinikstrasse 10, 8091 Zurich, Switzerland*
[o]*Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Switzerland*
[p]*The Michael G. DeGroote Institute for Pain Research and Care, Department of Anesthesia, and Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada*
[q]*Basel Institute for Clinical Epidemiology*
[r]*Department of Medicine, Royal Marsden Hospital, London, UK*
[s]*Federico II University of Naples, Naples, Italy*

Accepted 1 October 2016; Published online 8 November 2016

Abstract

Objective: We explored how investigators of ongoing or planned trials respond to the publication of a trial stopped early for benefit addressing a similar question.

Study Design and Setting: We searched multiple databases from the date of publication of the truncated trial through August, 2015. Independent reviewers selected trials and extracted data.

Results: We identified 207 trials truncated for early benefit; of which 102 (49%) were followed by subsequent trials (262 subsequent trials, median 2 per truncated trial, range 1−13). Only 99 (38%) provided a rationale justifying conducting a trial despite prior stopping. The top reasons were to address different population or setting (33%), skepticism of truncated trials findings because of small sample size (12%), inconsistency with other evidence (11%), or increased risk of bias (7%). We did not identify significant associations between subsequent trials and characteristics of truncated ones (risk of bias, precision, funding, or rigor of stopping decision).

Transparency declaration: M.H.M. affirms that the article is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Conflict of interest: None.

Ethical approval: Not required.

Funding: None.

[1] Equal contributions to this work.

* Corresponding author. Tel.: 507-284-2560.
E-mail address: murad.mohammad@mayo.edu (M.H. Murad).

http://dx.doi.org/10.1016/j.jclinepi.2016.10.006

Conclusion: About half of the trials stopped early for benefit were followed by subsequent trials addressing a similar question. This suggests that future trialists may have been skeptic about the decision to stop prior trials. A more rigorous threshold for stopping early for benefit is needed.

Keywords: Randomized controlled trials; Trials stopped early for benefit; Early termination of trials; Systematic review; Methodology; Trial design

1. Introduction

Randomized controlled trials are sometimes stopped early by trialists if one of the interventions appears to be associated with a large benefit. Investigators may halt their trial to avoid depriving participants in the comparison group of a beneficial treatment and to ensure rapid dissemination of the intervention [1]. Trials stopped early for benefit (truncated trials) are usually published in high-impact journals, receive considerable attention, and are likely to influence practice [2]. However, truncated trials tend to overestimate the magnitude of benefit by approximately up to one-third, and overestimates can be much greater when sample sizes and number of events are modest [3].

Further, most published truncated trials fail to adequately report at least one important factor regarding the decision to stop early; such as the planned sample size, details of interim analyses, whether a stopping rule informed the decision to stop, or whether the analysis was adjusted to account for interim monitoring and truncation [2]. Misleading overestimates from truncated trials seriously threaten the integrity of decisions made by patients and clinicians when they trade off the benefits and harms of interventions. Unfortunately, most (71%) systematic reviews that included truncated trials did not comment or recognize this possible bias [4]. Simulation studies have shown that when trials stopped early for benefit are included in a meta-analysis, the pooled effect size and heterogeneity parameters become distorted [5]. Therefore, this issue affects the synthesis of evidence and subsequent decision making that depends on systematic reviews, such as guidelines. For example, a trial evaluated the efficacy of bisoprolol in patients with a positive dobutamine echocardiography undergoing elective vascular surgery. It showed that bisoprolol significantly reduced the risk of perioperative myocardial infarction and cardiac death. The trial was stopped early because of this large effect [6]. Guidelines in Europe and the U.S. recommended this intervention; which was implemented on a large scale [7]. Subsequent trials showed markedly different results and demonstrated that the reduction in myocardial infarction was not as large as originally demonstrated and that the intervention increased the risk of stroke, hypotension, and may increase mortality [7].

The motivation to stop a trial early for benefit should be balanced against the risk of disseminating overestimated treatment effect. It should also be balanced against the loss of the opportunity to generate more precise evidence and opportunity to capture the effect of treatment on secondary outcomes and outcomes that require longer follow-up (particularly adverse effects). If stopping a trial early for benefit was the correct decision (i.e., it would be unethical to continue the trial); then the conduct of subsequent trials addressing the same question (subsequent trials) would also be unethical.

Several justifiable reasons for launching subsequent trials are plausible. First, researchers may want to test the intervention in a population or setting that is somewhat different from that of a truncated trial. Second, researchers may be skeptic about the results of the truncated trials (because the trial was small or at high risk of bias). Third, researchers may be interested in knowing the effect of the treatment on other outcomes.

If investigators, the clinical community, and ethics committees sanction subsequent trials, it raises serious questions regarding the initial decision to truncate the original trials for benefit. To explore the incidence of and rationale for subsequent trials, we conducted a meta-epidemiological study addressing how often subsequent trials were launched or continued after the publication of a truncated trial asking the same or similar research question.

2. Methods/design

The protocol of this study has been published and provides further details [8]. In brief, we identified a cohort of 207 truncated trials (published 1970–2007) [2,3] through systematic searches of electronic databases (including MEDLINE, EMBASE, and Cochrane), communication with content experts, and manual review of journals [3]. We then identified published subsequent trials for each truncated trial. We defined a subsequent trial as a subsequent RCT that was launched (i.e., started enrollment) or continued enrollment after the truncated trial publication date and addressed a similar question (similar population, intervention, comparison, and outcome). We only included subsequent trials with parallel design that continued follow-up or patient enrollment for at least 6 months after truncated trial publication.

We hypothesized three possible reactions of researchers (scenarios) to the publication of a truncated trial (Fig. 1). Researchers may stop conducting future similar trials (i.e., truncated trial caused a freezing effect on future research): (1) launch a new trial or continue ongoing trials