The harms of early cessation of trials on systematic reviews

Citation for published version:

Digital Object Identifier (DOI):
10.1016/S2468-1253(19)30192-X
10.1016/S2468-1253(19)30192-X

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Peer reviewed version

Published in:
Lancet Gastroenterology and Hepatology

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Download date: 06. Mar. 2021
Title: Influence of early cessation of clinical trials in surgery for harm on subsequent systematic reviews and meta-analyses

Article Type: Correspondence

Corresponding Author: Professor Stephen J. Wigmore,

Corresponding Author's Institution:

First Author: Cameron J Fairfield, MBBS

Order of Authors: Cameron J Fairfield, MBBS; Saxon Connor, MBChB FRACS; Ewen M Harrison, MB ChB PhD FRCSEd; Stephen J. Wigmore

Manuscript Region of Origin: UNITED KINGDOM
Influence of early cessation of clinical trials in surgery for harm on subsequent systematic reviews and meta-analyses

Cameron J Fairfield¹, Saxon Connor², Ewen M Harrison¹, Stephen J Wigmore¹

¹Department of Clinical Surgery University of Edinburgh, Royal Infirmary of Edinburgh EH16 4SA
²Department of Surgery, Christchurch Hospital, Christchurch, Canterbury, New Zealand

Randomised controlled trials form an important part of the evidence supporting surgical innovation. The Leopard-2 trial of laparoscopic versus open pancreateoduodenectomy for pancreatic or periampullary cancer was stopped early due to safety concerns when it became clear that after randomisation of 99 patients proceeding to surgery there was a 5 fold increase in 90 day mortality in the laparoscopic surgery arm¹. We are interested in the consequences of the early termination of clinical trials for subsequent systematic reviews and meta-analyses. Clearly the early cessation of a trial on safety grounds is justifiable, however, it creates an interesting problem in interpretation. It could be presumed that had the Leopard 2 trial been allowed to continue it might have shown an adverse effect of laparoscopic pancreateoduodenectomy that would have had statistical power. Clearly this would have been at a human cost and so is unacceptable.
Researchers studying the question of equivalence or superiority of laparoscopic or open pancreatoduodenectomy are likely to pool data from the Leopard 2 trial into meta-analyses and there is no specific guidance about how to handle such data. The PRISMA statement\textsuperscript{2} describes the need to describe sources of potential bias in the methodology or results presentation of clinical trials but does not specifically comment on the issue of early cessation of clinical trials due to adverse or unfavourable outcomes.

Trials which are stopped early following analysis of interim data are likely to show more extreme intervention effects than those which enroll their intended sample size particularly in trials with rare events\textsuperscript{3,4}. Further trials investigating the same hypothesis are unlikely to replicate the extreme point estimate obtained in the truncated trial, a feature known as “regression to the truth”. Whilst much of the existing debate over the influence of truncated trials has focused on inappropriate adoption of novel treatments following truncated trials demonstrating benefit\textsuperscript{5}, trials stopped early for harm are subject to the same biases. Researchers, clinicians and policy-makers will undoubtedly make decisions, which incorporate evidence from truncated trials, such as the Leopard 2 trial, which raise ethical and practical concerns about how such trials are interpreted. Potential implications of decisions made on the basis of results from the Leopard 2 trial include misleading summary effects from meta-analyses, a potential “freezing” effect on the conduct of similar trials and interpretation of the large effect size as irrefutable evidence of harm despite a lack of statistical significance or data available from other trials.
References


