Journal of Clinical Epidemiology 81 (2017) 56−63

Premature trial discontinuation often not accurately reflected in registries: comparison of registry records with publications

Reem Alturki[a,b,1], Stefan Schandelmaier[a,c,*,1], Kelechi Kalu Olu[a], Belinda von Niederhäusern[d], Arnav Agarwal[d], Roy Frei[a], Neera Bhatnagar[d], Lotty Hooft[e], Erik von Elm[f], Matthias Briel[a,d]

[a]*Department of Clinical Research, Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Spitalstrasse 12, 4031 Basel, Switzerland*

[b]*Multi Organ Transplant Center, King Fahad Specialist Hospital−Dammam, P.O. Box 15215, Dammam 31444, Saudi Arabia*

[c]*Department of Clinical Epidemiology and Biostatistics, McMaster University, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada*

[d]*Clinical Trial Unit, Department of Clinical Research, University Hospital Basel, Schanzenstrasse 55, Basel 4031, Switzerland*

[e]*Cochrane Netherlands, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, University of Utrecht, P.O. Box 85500, 3508 GA Utrecht, The Netherlands*

[f]*Cochrane Switzerland, Institute of Social and Preventive Medicine (IUMSP), Lausanne University Hospital, Route de la Corniche 10, 1010, Lausanne, Switzerland*

Accepted 26 August 2016; Published online 8 September 2016

Abstract

Background: One quarter of randomized clinical trials (RCTs) are prematurely discontinued and frequently remain unpublished. Trial registries can document whether a trial is ongoing, suspended, discontinued, or completed and therefore represent an important source for trial status information. The accuracy of this information is unclear.

Objective: To examine the accuracy of completion status and reasons for discontinuation documented in trial registries as compared to corresponding publications of discontinued RCTs and to investigate potential predictors for accurate trial status information in registries.

Methods: We conducted a cross-sectional study comparing information provided in publications (reference standard) to corresponding registry entries. First, we reviewed publications of RCTs providing information on both discontinuation and registration. We identified eligible publications through systematic searches of MEDLINE and EMBASE (2010−2014) and an international cohort of 1,017 RCTs initiated between 2000 and 2003. Second, pairs of investigators independently and in duplicate extracted data from publications and corresponding registry records. Third, for each discontinued RCT, we compared publication information to registry information. We used multivariable regression to examine whether accurate labeling of trials as discontinued (vs. other status) in the registry was associated with recent initiation of RCT, industry sponsorship, multicenter design, or larger sample size.

Results: We identified 173 publications of RCTs that were discontinued due to slow recruitment (55%), harm (16%), futility (11%), benefit (5%), other reasons (3%), or multiple reasons (9%). Trials were registered with clinicaltrials.gov (77%), isrctn.com (14%), or other registries (8%). Of the 173 corresponding registry records, 77 (45%) trials were labeled as discontinued and 57 (33%) provided a reason for discontinuation (of which 53, 93%, provided the same reason as in the publication). Labeling of discontinued trials as discontinued (vs. other label) in corresponding trial registry records improved over time (adjusted odds ratio 1.16 per year, confidence interval 1.04−1.30) and was possibly associated with industry sponsorship (2.01, 0.99−4.07) but unlikely with multicenter status (0.81, 0.32−2.04) or sample size (1.07, 0.89−1.29).

Conclusions: Less than half of published discontinued RCTs were accurately labelled as discontinued in corresponding registry records. One-third of registry records provided a reason for discontinuation. Current trial status information in registries should be viewed with caution.

Keywords: Randomized controlled trial as topic (MeSH); Early termination of clinical trials (MeSH); Trial registration; Reporting quality

Funding: None.

Conflict of interest: None.

[1] Shared first authorship.

* Corresponding author. Tel.: +41-(0)61-23-85410; fax: +41-(0)61-265-3109.

E-mail address: stefan.schandelmaier@usb.ch (S. Schandelmaier).

http://dx.doi.org/10.1016/j.jclinepi.2016.08.011

0895-4356/

What is new?

Key findings

- Less than half of trial registry records accurately labelled RCTs as 'discontinued' when compared to information in peer-reviewed publications.

What this adds to what was known?

- The ethical problem of masking premature trial discontinuation affects not only journal publications but also trial registry information.
- Information about trial status—one of the key items of trial registries—is often misleading; many discontinued RCTs are just labelled 'completed'.
- Different trial registries use different definitions and labels for trial status categories.

What is the implication and what should change now?

- Trial registries need to harmonize their labels and definitions and improve the accuracy of trial status information.

1. Introduction

One quarter of randomized clinical trials (RCTs) are not completed as originally planned [1]. Typical reasons for discontinuation include poor recruitment, harm, futility, or benefit. About 55% of discontinued RCTs remain unpublished [1] although their outcome data—conclusive or not—could contribute to meta-analysis. Moreover, it is unethical to withhold reasons for discontinuation thereby risking that future trials fail for the same reason.

Prospective trial registries are electronic databases that allow trial investigators or sponsors to document their RCTs from inception to reporting of final results. One advantage of trial registries is that they can be used to regularly update the recruitment status of a trial. The records of the most common registries, clinicaltrials.gov and isrctn.com, include specific fields for recruitment/completion status and reasons for trial discontinuation (in case of such) and place this information very prominently on their web sites. Therefore, trial registries theoretically represent an ideal source of information about trial status for patients, physicians, those who plan a new trial, and systematic reviewers.

The proportion of registered RCTs increased substantially after 2004 when the International Committee of Medical Journal Editors recommended to publish RCT reports only if the RCT was registered [2]. More recently, the World Medical Association included a statement in the Declaration of Helsinki that "every research study involving human subjects must be registered" which will likely further increase the proportion of registered trials [3]. However, there is no comparable incentive to ensure completeness, accuracy, and topicality of information provided in trial registries. Previous studies criticized the unsatisfactory accuracy of trial registry information with respect to trial methodology [4,5] or outcome reporting [6,7]. Accurate trial status information is crucial to help patients to find ongoing trials and hence improve recruitment, guide researchers in the development of new trials, or inform systematic reviewers; however, the accuracy of trial status information in registries remains unknown.

We systematically compared RCT publications that explicitly mentioned trial discontinuation to corresponding registry records for information on trial status and reasons for discontinuation. In addition, we examined four prespecified candidate predictors for accurate trial status information in registries.

2. Methods

2.1. Eligibility criteria

We included RCTs that (1) were published, (2) reported trial discontinuation in the title or abstract of the publication, and (3) provided a registration number in the full text irrespective of the reason for discontinuation, type of trial registry, or language of publication.

2.2. Search strategy

We systematically searched MEDLINE and EMBASE for eligible RCTs published between January 2010 (date of introduction of the Medical Subject Heading *Early Termination of Clinical Trials*) and March 2014. The search strategy was designed with the help of an experienced research librarian (N.B.) and included the Medical Subject Heading and combinations of text words (Table S1 in the Supplement at www.jclinepi.com). Two investigators independently screened records and potential full texts for eligibility and resolved disagreements by discussion or arbitration with a third investigator. In addition, they screened 113 publications of discontinued studies that were identified through archived documents from research ethics committees, a survey of principal investigators, author surveys, or literature searches in a retrospective cohort study of 1,017 RCTs (the DISCO study). These RCTs were approved between 2000 and 2003 by one of six research ethics committees in Switzerland, Germany, and Canada and published between 2002 and 2013 [1,8].

2.3. Data extraction

We designed and piloted two data extraction forms for publications and registry records using an electronic data extraction tool (http://www.squiek.org/). The forms were accompanied by detailed manuals instructing about definitions and other peculiarities of the trial registries. Pairs of investigators independently and in duplicate extracted data about completion status, reasons for discontinuation, and other trial characteristics relevant for trial discontinuation