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REVIEWS

A systematic review of discontinued trials suggested that most reasons for recruitment failure were preventable

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Abstract

Objective: To collect and classify reported reasons for recruitment failure in discontinued randomized controlled trials (RCTs) and to assess reporting quality.

Methods: We systematically searched MEDLINE and EMBASE (2010−2014) and a previous cohort of RCTs for published RCTs reporting trial discontinuation due to poor recruitment. Teams of two investigators selected eligible RCTs working independently and extracted information using standardized forms. We used an iterative approach to classify reasons for poor recruitment.

Results: We included 172 RCTs discontinued due to poor recruitment (including 26 conference abstracts and 63 industry-funded RCTs). Of those, 131 (76%) reported one or more reasons for discontinuation due to poor recruitment. We identified 28 different reasons for recruitment failure; most frequently mentioned were overestimation of prevalence of eligible participants and prejudiced views of recruiters and participants on trial interventions. Few RCTs reported relevant details about the recruitment process such as how eligible participants were identified, the number of patients assessed for eligibility, and who actually recruited participants.

Conclusion: Our classification could serve as a checklist to assist investigators in the planning of RCTs. Most reasons for recruitment failure seem preventable with a pilot study that applies the planned informed consent procedure.

Keywords: Randomized controlled trials as topic; Early termination of clinical trials; Poor recruitment; Reasons for recruitment failure; Reporting quality; Systematic review

1. Introduction

One quarter of randomized controlled trials (RCTs) are prematurely discontinued [1]. RCT discontinuation represents a considerable waste of scarce research resources, in particular when the results and reasons for discontinuation are not published. The most common reason for RCT discontinuation is poor recruitment of participants [1]. Sharing the encountered recruitment difficulties with the scientific community is an important contribution to overcome similar problems in the future [2].

Qualitative and quantitative studies have already suggested various barriers and facilitators of recruitment [2−17]. However, these studies were mostly restricted to specific countries or contexts; a current and comprehensive collection of recruitment barriers that led to the discontinuation of RCTs is still missing.

We conducted a qualitative systematic review of published RCTs discontinued due to poor recruitment to collect underlying reasons for recruitment failure as reported by trial investigators. We developed a comprehensive classification

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What is new?

Key finding

- Common reasons for recruitment failure were overestimation of the number of eligible participants, prejudices against effectiveness of trial interventions, and high burden for recruiters and participants.
- Investigators of discontinued trials rarely reported how and by whom patients were recruited which makes it difficult for readers to apply the findings to their own context, also when planning future trials.

What this adds to what was known?

- Many surveys and interview studies with patients or physicians identified numerous barriers and facilitators of recruitment to trials; this study summarized and classified empirical reasons for recruitment failure from the perspective of investigators of discontinued trials which may help to clarify the importance of specific recruitment aspects on trial discontinuation.

What is the implication and what should change now?

- Investigators planning new trials should carefully check and take into account the empirically collected reasons in order to minimize their risk for recruitment failure; Table 3 could be used as a checklist.
- Authors should report the recruitment process of their trial in sufficient detail, in particular when recruitment failed, to help avoiding repetition of mistakes.

of reasons as orientation for investigators planning RCTs. A secondary objective of our study was to assess the reporting of recruitment in included RCT publications.

2. Methods

2.1. Eligibility criteria

We included RCT publications explicitly stating in their abstract that trials were discontinued due to poor recruitment of participants (i.e., the target sample size was not achieved). We did not impose any restrictions in terms of language of publications, RCT design, trial purpose (superiority/noninferiority/equivalence), or sample size. We did not consider interview studies, focus group studies, or surveys of trial participants or recruiting physicians independent of an actual RCT report.

2.2. Study selection

We used two systematic approaches to identify eligible RCT reports. First, we systematically searched MEDLINE and EMBASE using the OVID interface. We limited the search to the period after January 2010 when the Medical Subject Heading (MeSH) *Early Termination of Clinical Trials* was introduced. We performed the last search update in April 2014. An experienced research librarian (N.B.) developed the search algorithm based on the MeSH term and text words such as *patient recruitment, enrolment*, or *sample* in combination with *slow, poor, suboptimal, inadequate, low, difficulty, failure,* or *challenge* (see Supplement/Appendix at www.jclinepi.com for detailed search strategy). Two investigators working independently and in duplicate screened titles and abstracts and assessed full texts for final eligibility. Second, we searched our own database of 101 RCTs discontinued due to poor recruitment that we identified through a cohort of 1,017 RCT protocols approved between 2000 and 2003 by one of six research ethics committees in Switzerland, Germany, and Canada [1,18]. The cohort included 101 RCTs discontinued due to slow recruitment of which two investigators independently assessed the eligibility of the 40 RCTs that were published (Fig. 1).

2.3. Data extraction

We designed and piloted data extraction forms using an electronic data extraction tool (http://www.squiekero.org). Two investigators independently extracted data from all available publications (including conference abstracts) about RCT characteristics, reporting of trial results, details about the recruitment process, and reported reasons for poor recruitment. Disagreements were resolved through discussion and consensus.

2.4. Definitions

We defined trials as ‘‘industry funded’’ when explicitly stated or if any authors were employees of a pharmaceutical company. We deemed ‘‘results sufficiently detailed for inclusion in a meta-analysis’’ if a publication reported the primary outcome for each trial arm separately (numbers of events for dichotomous outcomes or average and dispersion for continuous outcomes) or a measure of effect plus confidence interval. We considered a report’s ‘‘main objectives’’ being results or reasons for recruitment failure if explicitly mentioned as such in the title or abstract.

2.5. Data analysis

We described RCT characteristics and reasons for discontinuation due to poor recruitment using frequencies for categorical data, and measures of average and dispersion for continuous data. Data analysis was carried out using R version 3.1.0 (https://www.r-project.org). We stratified RCT characteristics and reasons for poor recruitment by funding source (industry funded vs. not).

We used a three-step approach to develop our classification of reasons for poor recruitment: In an initial step, we