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.

Introduction

One quarter of randomized clinical 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 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.

Methods

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/ non-inferiority/ 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.

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 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 1017 RCT protocols approved between 2000 and 2003 by one of 6 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 (**Figure 1**).

Data extraction

We designed and piloted data extraction forms using an electronic data extraction tool (<http://www.squiek.io/>). 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.

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.

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.

We stratified RCT characteristics and reasons for poor recruitment by funding source (industry-funded versus not).

We used a three-step-approach to develop our classification of reasons for poor recruitment: In an initial step, we created a preliminary, non-hierarchical list of potential reasons for trial discontinuation due to poor recruitment based on prior collections of reasons for poor recruitment (which were not necessarily reasons leading to trial discontinuation),[2,13-17] discussions with experts, and our own experience with discontinued trials.[1] This list provided the basis for the first version of the data extraction form but adding additional reasons was also possible. Two pairs of reviewers extracted the first half of the eligible studies (published up to 2012) and resolved discrepancies by discussion. In a second step, three investigators (MB, KKO, and SS) adapted the list of individual reasons by adding new and modifying existing reasons. They achieved consensus by discussion and implemented the second version of the list in the data extraction form. Then, two pairs of reviewers extracted the second part of studies (published between 2013 and 2014). We did not update the electronic search because no new individual reasons had emerged during the second part suggesting saturation.[19] In a third step, five investigators (MB, KKO, SS, BK and EvE) drafted and iteratively discussed the initial versions of the classification, developed superordinate categories, and merged and split categories where needed. In addition, they discussed whether individual reasons could have been prevented at the planning stage of RCTs. We presented the preliminary classification at an internal meeting to colleagues, at a workshop for clinical investigators, and at two scientific meetings [20,21] which led to additional changes. Finally, we considered the suggestions of three independent referees.

Results

RCT characteristics

We identified a total of 172 eligible RCTs (148 through electronic search and 24 through the RCT cohort) that explicitly reported discontinuation due to poor recruitment in their abstract (**Figure 1**). General characteristics of industry and non-industry funded trials were very similar (**Table 1**).

Reporting quality

Of the 172 RCT publications, 76% reported one or more specific reasons for trial discontinuation due to poor recruitment. Most reports (83%) focused on results which were in 77% presented in sufficient detail for inclusion in meta-analyses while only 17% of RCTs mentioned the objective to discuss recruitment failure in the abstract (**Table 2**). Most RCTs (91%) reported both the planned and achieved sample size. Included RCTs recruited a median of 33% (IQR, 19%-50%) of the planned target. Few RCTs provided detailed information on recruitment such as how eligible participants were identified (32%), how many participants were assessed for eligibility (45%), who recruited trial participants (27%), whether there were incentives for eligible patients (2%) or recruiters/ recruiting centers (4%), or employed strategies to monitor or support recruitment (8%).

Reasons for recruitment failure

In total, we identified 28 different reasons for recruitment failure that we classified in 4 categories as funding-, design-, recruiter-, or participant-related (**Table 3**). The most frequently reported reasons were overestimated prevalence of eligible patients

(n=71, in 51 reports described as overly restrictive eligibility criteria), prejudiced views of recruiters (n=34) or participants (n=33) on the effectiveness of trial interventions, new evidence from another study that led to prejudiced views of recruiters on the effectiveness of trial interventions (n=28), and high burden for patients (n=20) and recruiters (n=14).

We estimated that most (25/28, 89%) of the reported reasons could have been addressed at the planning stage of the trial, e.g., by conducting a feasibility study that piloted the informed consent procedure (Table 3).

Discussion

We reviewed a total of 172 RCTs reporting trial discontinuation due to poor recruitment in their abstract. We identified a total of 28 different reasons for recruitment failure and categorized these in a way to provide orientation for trial investigators about common pitfalls. Investigators most frequently mentioned lack of eligible patients due to overestimated prevalence followed by prejudiced views of recruiters and participants on trial interventions; most reported reasons appeared preventable. Although many RCT publications reported planned and actual achieved sample size, duration of enrolment, a reason for recruitment failure, and trial results in sufficient detail to contribute to meta-analyses, few RCTs reported the number of patients assessed for eligibility, how eligible participants were identified, and who actually recruited participants.

Our systematic review has several limitations and strengths. Our search strategy and trial selection was tailored to identify the spectrum of reported reasons for recruitment failure. The relative frequency of reported reasons may, therefore, differ from the true distribution of underlying reasons for poor recruitment due to our eligibility criteria for this review. We performed the last search update in April 2014, so we might have missed several recent publications of RCTs discontinued due to poor recruitment. However, when classifying reasons for recruitment failure from the 50 most recent RCTs in our sample, we hardly encountered any new individual reasons for recruitment failure suggesting saturation [19]. Although we discussed our checklist of reasons for recruitment failure with several trialists, we did not perform formal user testing. An exploration of reasons for recruitment failure in unpublished RCTs would require a different approach (e.g., interviews with trialists). A strength of our review is

that we included published RCTs from a vast range of clinical settings and medical specialties, thereby enhancing the generalizability of our results;

Recruitment difficulties of RCTs have already been emphasized by numerous studies [8,17,22,23]. Other systematic reviews or surveys on barriers and facilitators for recruitment focused on patient perspectives [10,11] often in specific contexts such as HIV [13], cancer [14], genetics [5], or surgery [15], or on recruiter/physicians' perspectives [3,7,24], or on both [2,6,17]. Some studies used quantitative methods to explore risk factors for poor recruitment with the limitation that analyses included only a small number of variables entailing a narrow and superficial view [1,8]. The present systematic review is to our knowledge the first that takes an angle from investigators of discontinued trials, the worst consequence of recruitment problems. In our study, the by far most frequently reported individual reason was lack of eligible participants, which many investigators reported as a problem of overestimated prevalence and overly strict eligibility criteria. This suggests that many investigators did not test their eligibility criteria. Another frequent category was poor motivation of eligible participants. Investigators rarely mentioned their estimated proportion of consenting participants out of eligible patients, which had been criticized before in a review on critical care research [25]. In our sample, only 1% of RCT reports mentioned a pilot or feasibility phase which would be the ultimate test of both the number of eligible and the number of consenting patients. The current Consolidated Standards of Reporting Trials (CONSORT) statement [26] explicitly recommends reporting the number of patients assessed for eligibility, number of eligible patients, and number of consenting patients. This was rarely the case in our trial sample. Previous studies focusing on breast cancer trials [27] or trials published in six major journals [9] had already found that recruitment information, that is how participants entered the trial, is

often poorly reported. This makes it difficult for readers to judge if the encountered recruitment difficulties apply to their own setting or not, and how they can prevent recruitment failure. Thus, in the context of trial discontinuation due to recruitment failure, an updated version or extension of the CONSORT statement should ask for a description how investigators projected the number of eligible and consenting participants, whether a pilot study including an informed consent procedure was done, how recruiters were trained, whether recruitment was closely monitored, and which measures were undertaken to improve recruitment.

In our view, most (89%) reasons for poor recruitment that led to trial discontinuation could be anticipated in the planning phase of an RCT. Investigators could use Table 3 as a checklist to ensure that they have taken appropriate precautions and to efficiently identify lever points for improvement measures. For instance, interventions to train recruiters and enhance their motivation and knowledge about the trial (and to promptly follow-up with them after the initial training [28]), as well as considerations of how the burden for participants could be minimized, are likely worthwhile investments. Piloting the final strategies for patient screening and consent procedures should reveal lurking problems early on and enable trialists to adapt their protocol.[29,30] In addition, sufficient funding and professional planning and conduct of RCTs (a typical feature of industry-funded trials) may help protect against recruitment failure.[1]

Although numerous researchers have recommended the adoption of multiple recruitment strategies to enhance participant enrollment into RCTs [15,16,31,32], evidence on what actually works to improve recruitment to clinical trials is sparse and high-quality intervention studies are urgently needed [33-35]. The most appropriate

and efficient way to test promising recruitment interventions may be to incorporate them with a randomized design in a host trial as promoted by the Systematic Techniques for Assisting Recruitment to Trials (START) program [36]. Initiatives to improve trial efficiency (including recruitment) should ideally be coordinated and efforts undertaken in a collaborative way; the recently founded Trial Forge platform could be instrumental for such trial methods research [37].

Conclusion

We identified 28 different reasons for poor recruitment leading to RCT discontinuation, most of which could be prevented. Our classification may serve as a checklist to remind investigators of crucial aspects. Detailed reporting of recruitment strategies, actual recruitment and retention rates, and publication of encountered recruitment difficulties would go a long way in helping other investigators in the planning of future RCTs and preventing the repetition of mistakes.

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Ethical approval

For this type of study formal consent is not required.

Author contributions

MB, KKO, and SS conceived of the study, wrote the protocol, helped design the search strategy, collected data from included publications, conducted statistical analyses, interpreted the results, and wrote the manuscript. EVE and BK helped design the study, collected data from included publications, and critically revised the manuscript. NB designed and conducted the literature search and critically revised the manuscript. RA and AA collected data from included publications, helped with

interpretation of results, and critically revised the manuscript. All authors approved the final version before submission.

Figures

Figure 1. Trial flow

Abbreviations: RCT, randomized controlled trial; REC, research ethics committee

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Tables

Table 1: RCT characteristics

	Total N = 172	Not industry funded N = 109	Industry-funded N = 63
Publication type			
Journal article	146 (85%)	93 (85%)	53 (84%)
Abstract / Letter / brief report	26 (15%)	16 (15%)	10 (16%)
Trial registration reported	106 (61%)	72 (66%)	34 (54%)
Trial design			
Parallel	162 (94%)	103 (95%)	59 (94%)
Factorial	7 (4%)	4 (4%)	3 (5%)
Cross-over	3 (2%)	2 (2%)	1 (2%)
Unit of randomization			
Individuals	168 (98%)	107 (98%)	61 (97%)
Body parts	2 (1%)	1 (1%)	1 (2%)
Clusters	2 (1%)	1 (1%)	1 (2%)
Multiple centers			
Multicenter, national	85 (49%)	56 (51%)	29 (46%)
Multicenter, international	59 (34%)	28 (26%)	31 (49%)
Single center	28 (16%)	25 (23%)	3 (5%)
Study purpose			
Superiority	138 (80%)	87 (80%)	51 (81%)
Non-inferiority / equivalence	20 (12%)	14 (13%)	6 (10%)
Unclear	14 (8%)	8 (7%)	6 (10%)
Clinical area			
Adult medical	119 (69%)	68 (62%)	51 (81%)
Adult surgical	37 (22%)	26 (24%)	11 (18%)
Pediatrics	16 (9%)	15 (14%)	1 (2%)
Control intervention			
Active (drug/other treatment)	86 (50%)	53 (49%)	33 (52%)
Placebo/sham procedure	36 (21%)	20 (18%)	16 (25%)
No active /standard care	50 (29%)	36 (33%)	14 (22%)
Planned sample size			
Planned sample size reported	157 (91%)	100 (92%)	57 (90%)
If reported, planned sample size, median (IQR)	232 (120,566)	229 (118,536)	240 (120,566)
Duration of follow up in months, median (IQR)	6.0 (1.8, 13.6)	6.0 (1.8, 16.8)	6.0 (1.6, 12.1)

Abbreviations: RCT, randomized controlled trial, IQR, inter-quartile range

Table 2: Content of RCT reports

	Total N=172	Non- industry N=109	Industry N=63
Report included one or more reasons for recruitment failure	131 (76%)	89 (82%)	42 (67%)
Main objective(s) of report(s)			
Trial results	143 (83%)	85 (78%)	58 (92%)
Reasons for recruitment failure	15 (9%)	14 (13%)	1 (2%)
Both	14 (8%)	10 (9%)	4 (6%)
Reporting of results			
Sufficiently detailed for inclusion in meta-analysis	132 (77%)	79 (73%)	53 (84%)
Effect on primary outcome was significant	23 (14%)	14 (14%)	9 (15%)
Actual recruitment			
Number of patients assessed for eligibility reported	77 (45%)	54 (50%)	23 (37%)
Achieved sample size reported	170 (99%)	107 (98%)	63 (100%)
Planned and achieved sample size reported	156 (91%)	99 (91%)	57 (91%)
If reported, actual sample size relative to planned sample size, median (IQR)	33% (19%, 50%)	33% (18%, 48%)	36% (20%, 53%)
Actual duration of enrolment reported	142 (83%)	93 (85%)	49 (78%)
Planned and actual duration of enrolment reported	32 (19%)	24 (22%)	8 (13%)
Projection of recruitment			
Projected rate of eligible patients reported	16 (9%)	13 (12%)	3 (5%)
Method of projection of eligible patients reported*			
<i>retrospective check at participating centers</i>	14 (8%)	12 (11%)	2 (3%)
<i>literature / patient registry / national statistics</i>	12 (7%)	11 (10%)	1 (2%)
<i>pilot / feasibility phase</i>	6 (3%)	5 (5%)	1 (2%)
<i>pilot / feasibility phase</i>	2 (1%)	2 (2%)	0
Projected rate of consenting patients reported	35 (20%)	27 (25%)	8 (13%)
Method of projection of consenting patients reported			
<i>pilot / feasibility phase with informed consent</i>	2 (1%)	2 (2%)	0
<i>pilot / feasibility phase with informed consent</i>	2 (1%)	2 (2%)	0
Recruitment process			
Strategies to identify eligible patients reported*			
<i>at consultation / hospitalization</i>	55 (32%)	44 (40%)	11 (17%)
<i>Advertisement (newspaper, leaflet in clinics and wards)</i>	45 (26%)	36 (33%)	9 (14%)
<i>Review of patient records</i>	13 (8%)	12 (11%)	1 (2%)
<i>Briefing of multidisciplinary teams (e.g. tumor boards) or advocacy groups</i>	2 (1%)	2 (2%)	0
<i>Briefing of multidisciplinary teams (e.g. tumor boards) or advocacy groups</i>	4 (2%)	4 (4%)	0
Incentive for patients reported	4 (2%)	3 (4%)	1 (2%)
Incentive for recruiting centers/ recruiters reported	7 (4%)	6 (5%)	1 (2%)
Recruiters described (e.g. treating physicians/study personnel)	46 (27%)	37 (34%)	9 (14%)
Study-specific training for recruiters reported	4 (2%)	4 (4%)	0
Strategies to monitor or support recruitment (e.g. regular progress reports, study visits, screening logs) reported	13 (8%)	13 (12%)	0
Protocol amendments to improve recruitment reported	23 (13%)	20 (18%)	3 (5%)
Changes in planned sample size reported	10 (6%)	6 (6%)	4 (6%)

Abbreviations: RCT, randomized controlled trial; IQR, inter-quartile range

* More than one category possible

Table 3: Reasons for recruitment failure

Reported reasons	Frequency (total n=131) ^a	Preventable? ^b
Funding-related		
Initial funding insufficient to reimburse recruiting staff/ sites	15	Yes
Additional funding for recruitment escalation/ prolongation unavailable	6	Yes
Initial funding withdrawn when slow recruitment became apparent	4	No
Design-related^c		
Context specific logistic obstacles (e.g. urgent transfers from intensive care, different treatment availabilities at different centres or on weekends)	11	Yes
Lack of methodological/ logistical support (e.g. from contract research organisation or clinical trial unit)	7	Yes
Unclear/ complex trial design (e.g. complex interventions, factorial design)	4	Yes
Unclear eligibility criteria	3	Yes
Unclear enrolment process (e.g. regarding timing of randomization or responsibilities of involved investigators/ personnel)	3	Yes
Recruiter-related		
<i>Lack of recruiters</i>		
Delay in opening recruitment sites (e.g. delayed ethical approval, new regulatory acts)	7	No
Potential recruiters (e.g. practising clinicians) unaware of trial	2	Yes
<i>Motivation/ performance</i>		
Prejudice against effectiveness of trial interventions ^d	34	Yes
New evidence from other study about effectiveness of trial interventions ^e	28	No ^f
Administrative burden/ time constraints	14	Yes
Lack of financial incentive/ reimbursement/ recognition	4	Yes
General mistrust in research	2	Yes
Lack of engagement (e.g. recruiters were not part of the study team)	2	Yes
Financial conflict of interest (e.g. trial results favouring conservative treatment over surgery may lead to less earnings)	1	Yes
Participant-related		
<i>Lack of eligible participants</i>		
Overestimated prevalence (mostly reported as overly narrow eligibility criteria)	71	Yes
Concurrent competing trials	11	No ^f
Ineffective screening/ advertising strategy (e.g. email instead of phone call, newspaper campaign only)	5	Yes
<i>Motivation</i>		
Prejudice against effectiveness of trial interventions ^g	33	Yes
High burden (e.g. many visits, invasive procedure, questionnaires, costs)	20	Yes
Concerns regarding side effects or potential diagnosis	7	Yes
Language or cultural barriers	4	Yes
Approached in inconvenient situation (e.g. women in labor)	5	Yes
General mistrust in research	2	Yes
Lack of financial incentive	2	Yes
Lack of encouragement from patient support organizations	1	Yes

^a Most reports mentioned more than one reason

^b Assuming the ideal situation that the trial is preceded by a pilot including application of informed consent in at least some participating centers.

^c Complex features making recruitment in daily practice difficult, or recruiters did not understand/ could not explain trial to patients. Need for simpler/ more pragmatic design or adapt/ intensify training of recruiters.

^d Reported as: lack of equipoise, concerns about disadvantages for patients, trial questioning current practice, loss of professional autonomy, concerns regarding randomization to unwanted intervention, worry about doctor-patient relationship, recommendations from opinion leaders, media information favoring a particular treatment, inadvertent use of unbalanced terminology such as gold standard.

^e May also affect the motivation of participants (mentioned in two reports)

^f Although these reasons for recruitment failure may ultimately not be preventable or modifiable, investigators could carefully search for ongoing trials and try to estimate/ clarify potential risks.

^g Reported as: influenced by next of kin or caring physician, concerns regarding randomization to unwanted intervention, unwillingness to receive placebo or no treatment, loss of personal autonomy/ reluctance to become a "guinea pig", worry about doctor-patient relationship, media information favoring a particular treatment.

**Source 1: systematic search
of MEDLINE and EMBASE**

**Source 2: international
cohort of 1017 RCTs**