Premature Discontinuation of Randomized Trials in Critical and Emergency Care: A Retrospective Cohort Study

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Objectives: Randomized clinical trials that enroll patients in critical or emergency care (acute care) setting are challenging because of narrow time windows for recruitment and the inability of many patients to provide informed consent. To assess the extent that recruitment challenges lead to randomized clinical trial discontinuation, we compared the discontinuation of acute care and nonacute care randomized clinical trials.

Design: Retrospective cohort of 894 randomized clinical trials approved by six institutional review boards in Switzerland, Germany, and Canada between 2000 and 2003.

Setting: Randomized clinical trials involving patients in an acute or nonacute care setting.

Subjects and Interventions: We recorded trial characteristics, self-reported trial discontinuation, and self-reported reasons for discontinuation from protocols, corresponding publications, institutional review board files, and a survey of investigators.

Measurements and Main Results: Of 894 randomized clinical trials, 64 (7%) were acute care randomized clinical trials (29 critical care and 35 emergency care). Compared with the 830 nonacute care randomized clinical trials, acute care randomized clinical trials were more frequently discontinued (28 of 64, 44% vs 221 of 830, 27%; $p = 0.004$). Slow recruitment was the most frequent reason for discontinuation, both in acute care (13 of 64, 20%) and in nonacute care randomized clinical trials (7 of 64, 11%). Logistic regression analyses suggested the acute care setting as an independent risk factor for randomized clinical trial discontinuation specifically as a result of slow recruitment (odds ratio, 4.00; 95% CI, 1.72–9.31) after adjusting for other established risk factors, including nonindustry sponsorship and small sample size.

Conclusions: Acute care randomized clinical trials are more vulnerable to premature discontinuation than nonacute care randomized clinical trials and have an approximately four-fold higher risk of discontinuation due to slow recruitment. These results highlight the need for strategies to reliably prevent and resolve slow patient recruitment in randomized clinical trials conducted in the critical and emergency care setting. (*Crit Care Med* 2016; 44:130–137)

Key Words: critical care; early termination of clinical trials; emergency medicine; ethics committees; randomized controlled trials

Randomized clinical trials (RCTs) enrolling patients who are acutely ill in the critical care or emergency care (acute care) setting are particularly challenging. One difficulty concerns the informed consent that is typically sought from substitute decision makers who are not always available or are difficult to identify (1). When substitute decision makers are available, they are often overwhelmed and under stress because of the need to decide rapidly on potentially life-saving interventions (1). Narrow time windows also challenge the recruiting staff who must quickly identify eligible patients and initiate study procedures (2). Another barrier to efficient recruitment can be the prohibition of coenrollment of patients into more than one RCT by protocols, physicians, or institutional review boards (IRBs) (1). Finally, decision making in multidisciplinary settings such as critical or emergency care is typically a shared process and thus more individuals might decline to proceed or continue with the research.

A prospective study of critically ill adults in 23 Canadian ICUs found that 57% of opportunities to recruit eligible patients into studies (mostly RCTs) are either missed or infeasible (1). In two U.S. studies, the proportion of missed opportunities was 69% (94 of 136) in an ICU (3) and 47% (563 of 1,202) in a trauma center (4). Others have described lessons learned from acute care RCTs that were discontinued due to slow recruitment (5–10). Lack of substitute decision makers was the most common reason for slow recruitment in a trial

of acute lung injury (5), and inability to complete the recruitment interview was the most common reason for slow recruitment in a trial enrolling patients with palliative care needs in an emergency department (9). However, the frequency with which recruitment challenges actually lead to premature discontinuation of acute care RCTs in comparison to nonacute care RCTs is unknown.

The objective of this study was to compare the risk for trial discontinuation, in particular due to slow recruitment, in a large sample of acute and nonacute care RCTs approved by IRBs.

METHODS

Study Design and Sample

We conducted a retrospective cohort study using RCTs approved between 2000 and 2003 by six IRBs in Switzerland (Basel, Lucerne, Zurich, and Lausanne), Germany (Freiburg), and Canada (Hamilton). The IRBs were responsible for human research in large university centers and additional hospitals in their respective catchment areas. We approached the IRBs through existing contacts in order to acquire our convenience sample. To minimize the number of ongoing or unpublished RCTs, we focused on protocols that had been approved more than 10 years ago. For this analysis, we excluded protocols of RCTs that involved only healthy volunteers, RCTs that were never started, and RCTs that investigators reported as ongoing in our survey as of April 2013 (see below). The participating IRBs approved this study or explicitly stated that no formal ethical approval was necessary. A detailed study protocol (11), an analysis of the dataset describing the prevalence of discontinued trials across medical specialties (12), and two ancillary analyses of the dataset (13, 14) are published elsewhere.

Definitions

Two researchers independently classified RCTs as acute care if they enrolled 1) patients receiving critical care irrespective of when acute symptoms occurred (critical care) or 2) emergency patients who received the study intervention within 24 hours of presentation with acute symptoms (emergency care). Disagreements were resolved by discussion or consultation with a clinician who was familiar with the RCT topic. We did not consider an RCT as acute care if patients consented to surgical intensive care before they received elective surgery—that is, if the recruitment took place in a nonacute situation.

We considered an RCT discontinued if the investigators indicated trial discontinuation in correspondence with IRBs, in journal publications, or in their response to our survey (see below). If still unclear, we additionally classified trials as discontinued if the actual sample size was less than a prespecified threshold of 90% of the target sample size (for studies with known achieved and target sample size). Accordingly, we considered an RCT completed if at least 90% of the targeted sample size was recruited and the investigators did not indicate discontinuation. We recorded all reasons for trial discontinuation. If we could not elucidate the reason for RCT discontinuation, we classified the trial as discontinued due to unknown causes (11, 12).

Data Sources and Extraction

Reviewers trained in trial methodology abstracted 30% of RCT protocols independently and in duplicate using pretested forms with detailed written instructions and following formal calibration exercises with all data abstractors. Disagreements arising in duplicate review were resolved by discussion. Single investigators abstracted the remaining RCT protocols, with periodic duplicate agreement checks from a random sample of protocols at several points during the process.

We followed-up on the completion status and publication history of RCTs as of April 27, 2013 by using information from IRB files and by conducting comprehensive searches for corresponding publications in electronic databases and trial registries. If trial completion or publication status remained unclear, we surveyed the investigator by sending them a standardized questionnaire through the overseeing IRB. All corresponding publications were abstracted independently and in duplicate; disagreements were resolved by consensus or by third-party adjudication.

Statistical Analyses

We present trial discontinuation, reported reasons, and publication status as frequencies and percentages, stratified by acute care and nonacute care RCTs. We explored differences between acute and nonacute care RCTs by using chi-square or Fisher exact tests for proportions, *t* tests for normally distributed, and rank sum tests for non-normally distributed continuous variables. We considered two-tailed *p* value less than or equal to 0.05 statistically significant and did not correct for multiple testing.

We investigated possible factors associated with RCT discontinuation due to slow recruitment by using multivariable logistic regression. As prespecified (11, 12), we limited our regression analysis to completed RCTs and RCTs discontinued due to slow recruitment and excluded RCTs with other reasons for discontinuation. Assuming different recruitment and discontinuation patterns, we additionally excluded RCTs that were explicitly labeled as pilot RCTs (5 acute care and 46 nonacute care) and RCTs that randomized clusters such as hospitals or families (0 acute care and 8 nonacute care RCTs) from our regression model. We investigate the incremental risk associated with acute care (vs nonacute care) after adjustment for previously examined prespecified protocol-level variables (11, 12): investigator sponsorship (vs industry), planned sample size (in decrements of 100), center status (multicenter vs single center), crossover design (vs parallel), type of control intervention (active control vs placebo or nonactive intervention), any reported method to predict recruitment rate (vs no method reported), and methodologic or logistic support from a contract research organization or clinical trial unit (vs no support reported). In addition, we adjusted for pediatric RCTs (vs adult), another setting-specific potential risk factor for slow recruitment (11). The event-to-variable ratio was 10 (90 discontinuations due to slow recruitment and 9 explanatory variables). We conducted a complete case analysis and sensitivity analyses by using multiple imputations for missing

information about trial discontinuation (missing in 5 acute and 66 nonacute care RCTs), reasons for discontinuation (missing in 1 acute and 24 nonacute care RCTs), and sample size (missing in 1 acute and 11 nonacute care RCTs) (15).

RESULTS

RCT Characteristics

We included 894 RCTs in the analysis (**Fig. 1**). Of those, 64 (7%) recruited patients in an acute care setting and 830 recruited patients in a nonacute care setting. The 64 acute care RCTs included 29 critical care RCTs (17 adult and 12 pediatric) and 35 emergency care RCTs (14 stroke trials, 13 acute coronary syndrome trials, and 8 others). Nonacute RCTs included four postsurgical critical care trials for which patients consented preoperatively and three RCTs that recruited emergency care patients but started the intervention not within 24 hours (all 48 hr or later).

Most characteristics of critical and emergency care RCTs were similar (**Table 1**). Critical care RCTs had on average a shorter follow-up (median 0.9 vs 3.0 mo; $p = 0.032$), were less frequently labeled as pilot trial (0% vs 17%; $p = 0.028$), were less frequently sponsored by industry (41% vs 71%; $p = 0.030$), and more frequently enrolled children (41% vs 3%; $p < 0.001$) than emergency care RCTs.

Acute care RCTs as compared with nonacute care RCTs had a slightly larger planned sample size (median 300 vs 260; $p = 0.023$), a shorter planned follow-up (median 2.8 vs 6 mo; $p < 0.001$), were more frequently overseen by a data safety and monitoring board (DSMB) (56% vs 27%; $p < 0.001$), more frequently had planned interim analyses (47% vs 31%; $p = 0.015$), more frequently included a placebo or no-treatment arm (78% vs 58%; $p = 0.003$), more frequently enrolled children (20% vs 9%; $p = 0.005$), and less frequently reported quality of life as predefined outcome (11% vs 38%; $p < 0.001$). The remaining characteristics did not differ significantly between acute and nonacute care RCTs (Table 1).

Of the 64 acute care RCTs, 37 (58%) were published as a peer-reviewed journal article, 6 (9%) in abstract format only, and 21 (33%) were not published at a median follow-up of 11.6 years from IRB approval. The respective publication rates in the 830 nonacute care RCTs were similar: 493 (59%) peer-reviewed journal articles, 50 (6%) abstracts, and 286 (35%) not published (difference not formally tested, see *Discussion* section). The year of publication ranged from 2001 to 2013, with a median in 2006. Confidentiality agreements with collaborating IRBs do not allow us to provide a list of references of all included RCT publications.

Discontinuation

Of the 894 RCTs, 575 (64%) were completed and 249 (28%) were discontinued prior to enrolling the target sample, and the completion status remained unclear in 71 RCTs (8%) (**Table 2**). We determined RCT discontinuation from the publication alone (61 of 249, 25%), the survey alone (69 of 249, 28%; response rate 80%), IRB file alone (67 of 249, 27%), combined sources (27 of 249, 11%), or because the actual sample size was less than 90% of the target sample size (25 of 249, 10%, including one acute care trial).

Acute care RCTs were more frequently discontinued (28 of 64, 44%) than nonacute care RCTs (221 of 830, 27%; $p = 0.004$). Unknown completion status was balanced between settings. Slow recruitment was the most frequent reason for discontinuation, both in acute care (13 of 64, 20%) and nonacute care RCTs (87 of 830, 11%) (Table 2). Multivariable logistic regression identified acute care RCTs as an independent incremental risk factor for discontinuation due to slow recruitment (adjusted odds ratio [OR], 4.00; 95% CI, 1.72–9.31). Investigator sponsorship (OR, 4.45; 95% CI, 2.59–7.65) and small planned sample size (OR, 1.05; 95% CI, 1.01–1.09, in decrements of 100) were also significantly associated with discontinuation due to slow recruitment (**Table 3**). Multiple imputations for missing information regarding trial discontinuation and sample

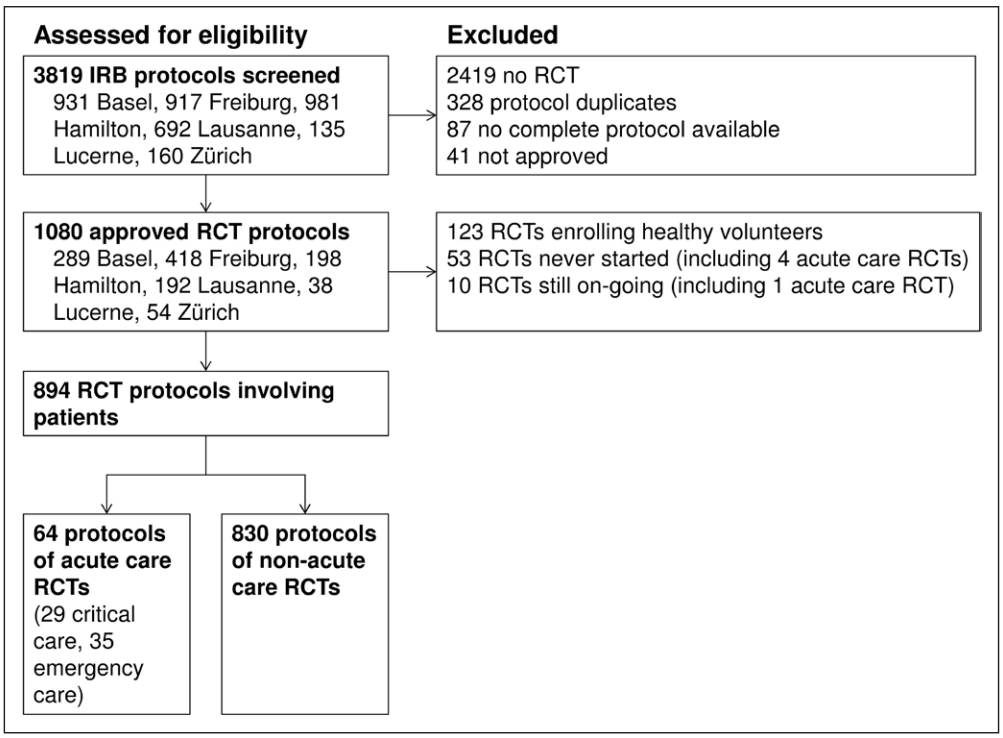

Figure 1. Trial flow diagram illustrating sample generation. IRB = institutional review board, RCT = randomized clinical trial.

TABLE 1. Characteristics of Acute Care and Nonacute Care Randomized Clinical Trials

RCT Characteristics	Critical Care (*n* = 29)	Emergency Care (*n* = 35)	Total Acute Care (*n* = 64)	Total Nonacute Care (*n* = 830)
Planned target sample size, median (IQR)	235 (175–680)	400 (153–2,080)	300 (158–1,200)	260 (100–600)
Planned centers (%)				
Multiple	23 (79)	30 (86)	53 (83)	688 (83)
Single	6 (21)	5 (14)	11 (17)	138 (17)
Unclear	0	0	0	4 (0.5)
Unit of randomization (%)				
Individuals	29 (100)	35 (100)	64 (100)	815 (98)
Clusters	0	0	0	12 (1)
Body parts	0	0	0	3 (0.4)
Pediatric trial (%)	12 (41)	1 (3)	13 (20)	73 (9)
Study design (%)				
Parallel	26 (90)	34 (97)	60 (94)	776 (94)
Crossover	2 (7)	0	2 (3)	39 (5)
Factorial	1 (3)	1 (3)	2 (3)	13 (2)
Unclear	0	0	0	2 (0.2)
Study purpose (%)				
Superiority	25 (86)	30 (86)	55 (86)	597 (72)
Noninferiority	3 (10)	3 (7)	6 (9)	133 (16)
Unclear	1 (3)	2 (6)	3 (5)	100 (12)
Research ethics committee (%)				
Basel	3 (10)	11 (31)	14 (22)	207 (25)
Hamilton	9 (31)	10 (29)	19 (30)	159 (19)
Freiburg	6 (21)	7 (20)	13 (20)	259 (31)
Lausanne	6 (21)	5 (14)	11 (17)	138 (17)
Zürich	5 (17)	1 (3)	6 (9)	37 (5)
Lucerne	0	1 (3)	1 (2)	30 (4)
Labeled as pilot RCT	0	6 (17)	6 (9)	63 (8)
Industry sponsorship	12 (41)	25 (71)	37 (58)	514 (62)
Comparison group(s) (%)				
Included placebo or no treatment (often add-on RCTs)	24 (83)	26 (74)	50 (78)	483 (58)
Active comparator(s) only	5 (17)	9 (26)	14 (22)	347 (42)
Data safety and monitoring board mentioned (%)	12 (41)	24 (69)	36 (56)	221 (27)
Stopping rule mentioned (%)	5 (17)	9 (26)	14 (22)	141 (17)
Interim analysis mentioned (%)	14 (48)	16 (46)	30 (47)	259 (31)
Follow-up, months from randomization, median (IQR)	0.9 (0.9–5.9)	3.0 (1.0–12.0)	2.8 (0.9–6.0)	6.0 (2.5–13.0)
Method to predict recruitment rate mentioned (%)	7 (24)	2 (6)	9 (14)	72 (9%)
Pilot study including informed consent (%)	3 (10)	0	3 (5)	8 (1)
Reported methodologic/logistic support (%)	11 (38)	18 (51)	29 (45)	357 (43)
Primary outcome specified (%)	24 (83)	31 (89)	55 (86)	778 (94)
Quality of life outcome planned (%)	3 (10)	4 (11)	7 (11)	312 (38)

RCT = randomized clinical trial, IQR = interquartile range.

TABLE 2. Completion Status and Reasons of Discontinuation of Acute and Nonacute Care Randomized Clinical Trials

Completion Status and Reasons For Discontinuation	Critical Care (*n* = 29)	Emergency Care (*n* = 35)	Total Acute Care (*n* = 64)	Total Nonacute Care (*n* = 830)
Completion status (%)				
Completed	12 (41)	19 (54)	31 (48)	544 (66)
Discontinued	14 (48)	14 (40)	28 (44)	221 (27)
Unclear	3 (10)	2 (6)	5 (8)	66 (8)
Reason for discontinuation (%)				
Slow recruitment	6 (21)	7 (20)	13 (20)	87 (11)
Futility	3 (10)	4 (11)	7 (11)	30 (4)
Benefit/harm	2 (7)	0	2 (3)	31 (4)
Other[a]	2 (7)	3 (9)	5 (8)	49 (6)
Unknown reason	1 (3)	0	1 (2)	24 (3)

[a]Included other reasons such as administrative, strategic, or financial.

size did not alter the results (Supplemental Digital Content 1, http://links.lww.com/CCM/B501).

Of the 31 completed acute care RCTs, 27 (87%) were published as peer-reviewed journal articles or abstracts, and the primary outcome was statistically significant in 13 of 27 (41%) publications. Of the 28 discontinued acute care RCTs, 15 (54%) were published as peer-reviewed journal articles or abstracts, and all reported that the primary outcome was not statistically significant. Of the five RCTs with unclear completion status, one was published with a nonsignificant result for the primary outcome.

Of the 15 acute care RCTs discontinued due to slow recruitment, 7 were subsequently published (in peer-reviewed journals) and 3 reported causes for slow recruitment. In the first trial, unforeseeable changes in the regulatory environment

TABLE 3. Risk Factors for Discontinuation Due to Slow Recruitment

Protocol Characteristics	Discontinued Due to Slow Recruitment (*n* = 90)[a]	Completed (*n* = 526)[a]	Univariable Effect		Multivariable Effect	
			OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Acute care RCT (vs nonacute care) (%)	12 (13)	27 (5)	2.97 (1.44–6.14)	0.003	4.00 (1.72–9.31)	0.002
Investigator sponsorship (vs industry) (%)	59 (66)	158 (30)	4.43 (2.76–7.12)	< 0.001	4.45 (2.59–7.65)	< 0.001
Smaller sample size, median (interquartile range)	180 (80–320)	364 (155–800)	1.06 (1.01–1.11)[b]	0.010	1.05 (1.01–1.09)[b]	< 0.001
Multicenter status (vs single center) (%)	71 (79)	470 (89)	0.46 (0.26–0.84)	0.011	1.80 (0.85–3.82)	0.12
No methodologic/logistic support reported (vs reported) (%)	62 (69)	279 (53)	1.94 (1.2–3.14)	0.007	1.49 (0.86–2.56)	0.088
Active control (vs placebo/no active control) (%)	37 (41)	204 (39)	1.14 (0.72–1.79)	0.58	1.37 (0.83–2.24)	0.22
Crossover design (vs parallel) (%)	8 (9)	21 (4)	2.61 (1.11–6.17)	0.028	2.18 (0.82–5.79)	0.13
No method to predict recruitment reported (vs reported) (%)	78 (87)	486 (92)	0.53 (0.27–1.06)	0.073	1.15 (0.52–2.54)	0.74
Pediatric RCT (vs adult) (%)	13 (14)	44 (8)	1.95 (1.00–3.81)	0.049	1.22 (0.57–2.63)	0.61

OR = odds ratio, RCT = randomized clinical trial.

[a]We limited the analysis to RCTs discontinued for slow recruitment and completed RCTs and excluded 51 pilot RCTs and 8 RCTs that randomized clusters (see *Methods* section for a rationale). We excluded 71 RCTs with missing discontinuation information, 25 RCTs with missing reasons for discontinuation, and 12 RCTs with missing sample size information.

[b]In decrements of 100.

precluded the participation of several countries. In the second trial, the doubt among recruiting physicians regarding clinical equipoise of the treatment arms and their discomfort in approaching substitute decision makers caused the slow recruitment. In the third trial, slow recruitment was a result of the complex study protocol—specifically, logistic challenges related to patient transfer and lack of eligible patients due to overly strict inclusion criteria—and poor motivation of recruiting physicians who perceived a conflict of interest.

DISCUSSION

In a sample of 894 RCT protocols approved by one of the six IRBs from Switzerland, Germany, and Canada, 64 studies (7%) enrolled patients in an acute care setting. Investigators of almost half (28 of 64, 44%) of the acute care RCTs indicated early discontinuation, and the most commonly reported reason for discontinuation (20%) was slow recruitment. The risk for discontinuation due to slow recruitment was approximately four-fold higher in acute than in nonacute care RCTs.

This increased risk may result from recruitment challenges that are specific to the acute care setting (e.g., narrow time windows or unavailability of substitute decision makers), a higher frequency of general recruitment challenges that are not specific to the acute care setting (e.g., untested eligibility criteria, lack of equipoise for the research, or overly complex study protocol) (16), or a combination of both setting-specific and nonspecific challenges. However, publications rarely reported causes for slow recruitment, and we were therefore unable to determine the relative impact of specific and nonspecific causes on the increased risk of trial discontinuation due to slow recruitment in acute care RCTs.

Only a minority of RCT protocols specified strategies to mitigate recruitment challenges such as support by a clinical trial unit and measures to sustain recruitment. Furthermore, only 14% of acute and 9% of nonacute care RCT protocols specified a method to predict patient recruitment over time. Of those, very few based their prediction on data from a pilot study that included an informed consent process. The remainder predicted recruitment using retrospective or prospective screening for eligible patients, which are unreliable methods (16, 17). Rare specification of recruitment strategies (since these are often documented in internal trial documents such as operation manuals and likely underreported in trial protocols) and use of unreliable methods to predict recruitment may explain why our regression model did not identify a protective effect of explicit recruitment prediction on the prevention of slow recruitment.

Apart from the acute care setting, significant risk factors for trial discontinuation due to slow recruitment were small sample size and nonindustry sponsorship, which were factors we identified in a previous analysis (12). Larger RCTs may be better organized (e.g., conduct by established research networks engaging multiple centers and collaboration among experienced investigators), and industry-funded RCTs may be better resourced to address the problem of slow recruitment versus investigator-initiated trials.

Investigators of acute care RCTs more frequently reported a DSMB and more frequently specified interim analyses in the protocol than investigators of nonacute care trials. This could suggest that trialists in the acute care setting were more sensitized to monitor early evidence of benefit, harm, or futility in vulnerable populations or simply reflect the tradition of DSMB oversight in trials of acute care interventions.

Strengths of our study include collaboration with six IRBs from three countries to document the history of 894 planned RCTs. We had full access to the files of all RCTs approved during a 3-year period, which provides additional safeguards against selection bias. We systematically searched all documents and contacted the authors to capture any relevant information about the course of the RCT. We involved trained methodologists to identify eligible studies and abstract data, following pretesting and calibration exercises (11). To minimize chance associations, we considered only a limited number of variables in our statistical model and conducted sensitivity analyses using multiple imputations for missing data.

Our study is limited by the reporting quality of the original RCT protocols and reports, which did not always transparently indicate factors that can predispose to trial discontinuation due to slow recruitment (e.g., the extent of preparatory or pilot work, logistic barriers, financial, or nonfinancial incentives). We used single data extraction for almost 70% of protocols, thereby potentially increasing extraction errors. However, we used prepiloted extraction forms with detailed written instructions, conducted formal calibration exercises with all data extractors, and checked extractions from a random sample of protocols at several points during the process. Agreement was good with no more than two discrepancies in answers to 30 main questions of the extraction form. All outcome data on discontinuation and publication of RCTs were verified by a second investigator. Our comparison of acute care versus nonacute care RCTs is based on protocols that were approved by IRBs more than 10 years ago. Results might differ if more recent trials were analyzed. However, discontinuation due to recruitment challenges for RCTs in acute care is likely to remain. Collaborating with six IRBs in three countries increases the generalizability of our results, but findings may differ among RCTs performed in other jurisdictions where unique trial completion challenges exist, such as developing countries. Furthermore, although we reported risk factors for nonpublication in our analysis of the full RCT cohort (12), namely early trial discontinuation, industry sponsorship, single-center trial, and small sample size, we did not test whether risk factors differ between acute and nonacute care RCTs; appropriate tests for interaction would have low power to either identify or exclude such differences. However, we do not expect risk factors for nonpublication to differ substantially between acute and nonacute care RCTs.

Our work provides the basis to test interventions aimed at limiting early discontinuation of acute care trials. We believe that interventions should primarily focus on the prevention of slow recruitment because it was the most frequent reason for discontinuation. Multicenter pilot randomized trials that

apply the full recruitment protocol could be part of the solution—they represent an opportunity to identify important barriers for recruitment such as lack of eligible patients, difficulties obtaining informed consent, doubt among recruiting physicians regarding clinical equipoise of the treatment arms, or prohibitively complex protocols. A necessary feature of such pilot trials would be to include the same screening and informed consent processes as in the main trial. Further research is necessary to estimate the optimal size and duration of such pilot trials and the number and type of centers in which the pilot trial should be conducted to obtain the most stable recruitment estimates. Another possible solution would be to develop reliable prediction models for recruitment performance (18). In addition, ongoing attention to recruitment trends, and introduction of strategies to sustain, bolster, or accelerate recruitment when necessary (19), is also imperative for acute care trialists once RCTs are underway.

CONCLUSIONS

Acute care RCTs are more vulnerable to premature discontinuation than nonacute care RCTs and have an approximately four-fold higher risk of discontinuation specifically due to slow recruitment. These results highlight the need to develop strategies to reliably prevent and resolve slow patient recruitment in RCTs conducted in the critical and emergency care setting.

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