Premature Discontinuation of Pediatric Randomized Controlled Trials: A Retrospective Cohort Study

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Objectives To determine the proportion of pediatric randomized controlled trials (RCTs) that are prematurely discontinued, examine the reasons for discontinuation, and compare the risk for recruitment failure in pediatric and adult RCTs.

Study design A retrospective cohort study of RCTs approved by 1 of 6 Research Ethics Committees (RECs) in Switzerland, Germany, and Canada between 2000 and 2003. We recorded trial characteristics, trial discontinuation, and reasons for discontinuation from protocols, corresponding publications, REC files, and a survey of trialists.

Results We included 894 RCTs, of which 86 enrolled children and 808 enrolled adults. Forty percent of the pediatric RCTs and 29% of the adult RCTs were discontinued. Slow recruitment accounted for 56% of pediatric RCT discontinuations and 43% of adult RCT discontinuations. Multivariable logistic regression analyses suggested that pediatric RCT was not an independent risk factor for recruitment failure after adjustment for other potential risk factors (aOR, 1.22; 95% CI, 0.57-2.63). Independent risk factors were acute care setting (aOR, 4.00; 95% CI, 1.72-9.31), nonindustry sponsorship (aOR, 4.45; 95% CI, 2.59-7.65), and smaller planned sample size (aOR, 1.05; 95% CI 1.01-1.09, in decrements of 100 participants).

Conclusion Forty percent of pediatric RCTs were discontinued prematurely, owing predominately to slow recruitment. Enrollment of children was not an independent risk factor for recruitment failure. *(J Pediatr 2017;184:209-14).*

RCT	Randomized controlled trial
REC	Research Ethics Committee

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Randomized controlled trials (RCTs) involving children are rare compared with trials of adults,[1-5] owing in part to lack of funding.[4,6] In addition, pediatric trials may be at particularly high risk for premature trial discontinuation, for several reasons. First, recruitment of children involves specific challenges;[7-9] the informed consent process is more complex[7] and may be affected by the reservations and skepticism of parents (who usually must provide consent for their children) or pediatricians.[10-15] Second, compared with adult trials, rules for stopping a pediatric trial for benefit, harm, or futility may be stricter, further increasing the risk for early discontinuation.

On the other hand, a report of the United Kingdom Children's Cancer Study Group has suggested that pediatric trials recruit more successfully than adult trials,[16] possibly owing to the nation's highly collaborative network of pediatric oncology centers.[17] Other qualitative studies have found that parents are less skeptical about having their child participate in clinical trials than was anticipated.[14,18] Therefore, recruitment failure may be no higher—or perhaps even lower—for pediatric trials compared with adult trials.

Little empirical data exist about the actual risk of premature trial discontinuation in pediatrics. In a survey of 110 published pediatric RCTs, 32 were discontinued overall, including 8 for slow recruitment, 7 for futility, 6 for efficacy, 6 for harm, and 5 for other reasons.[19,20] Another survey of cardiovascular studies registered at ClinicalTrials.gov suggested that 65 of 782 pediatric studies (8%) were discontinued prematurely. However, the foregoing data originate from published or registered trials and might not be representative of all initiated trials; many discontinued trials remain unpublished[21] or fail to acknowledge discontinuation in trial registries.[22]

We analyzed an international cohort of RCTs approved by 6 Research Ethics Committees (RECs) in 3 countries to determine the risk of trial discontinuation in pediatric trials and to compare the risk for trial discontinuation specifically due to slow recruitment between pediatric and adult trials.

Methods

Previous publications have described the rationale and design of this international cohort study,[21,23] and we have presented parts of the regression analysis previously in the context of acute care RCTs.[24] In brief, we included RCTs approved between 2000 and 2003 by 6 RECs in Switzerland (Basel, Lucerne, Zurich, and Lausanne), Germany (Freiburg), and Canada (Hamilton). Each REC was responsible for human research in large university centers and hospitals in its respective catchment area. Every REC had pediatric units in its catchment area and approved pediatric trials. We approached the RECs through existing contacts and, to minimize the number of ongoing or unpublished RCTs, focused on protocols that had been approved more than 10 years earlier.

For this analysis, we excluded protocols of RCTs that involved only healthy volunteers, were never initiated, or were reported as ongoing as of April 2013 (**Figure**). The participating RECs either approved the study or explicitly stated that no formal ethical approval was necessary.

Definitions

We classified an RCT as pediatric if more than 50% of the enrolled patients were younger than 18 years of age. The rationale for this inclusive threshold was that trials with more than 50% children are likely to be affected by pediatric-specific challenges.

We considered an RCT discontinued if the investigators indicated trial discontinuation in correspondence with an REC, in a journal publication, or in their response to our survey (see below). If still unclear, we compared the final sample size with the planned sample size. We classified a trial as discontinued if the final sample size was ≤90% of the planned sample size.[23] If the planned or final sample size was unclear, we classified the trial status as unclear. In addition, we recorded reasons for trial discontinuation.

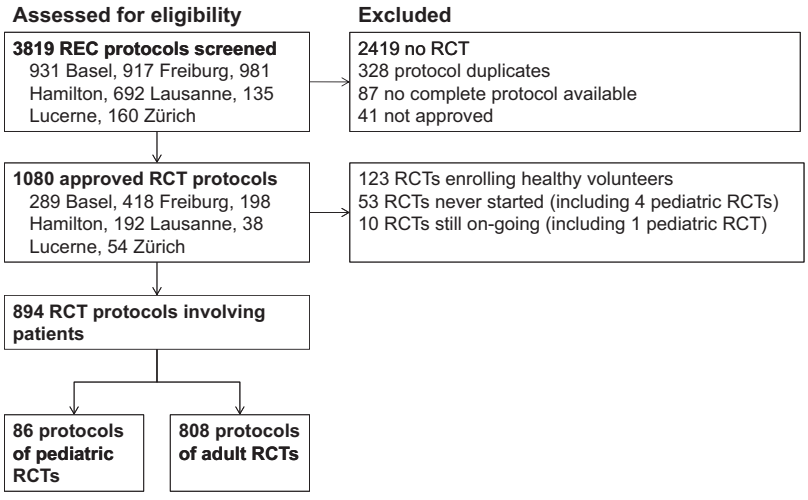

Figure. Study selection.

Data Sources and Abstraction

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 the RCTs as of April 27, 2013, using information from REC files and conducting comprehensive searches for corresponding publications in electronic databases and trial registries.[23] If trial completion or publication status remained unclear, we surveyed the investigator by sending a standardized questionnaire through the overseeing REC. We extracted data from all corresponding publications independently and in duplicate and resolved disagreements by consensus or third-party adjudication.

Statistical Analyses

We present trial characteristics, discontinuation, and publication status as frequencies and percentages stratified by pediatric/adult. To determine the prevalence of pediatric trials in the overall cohort, we excluded RCTs that were approved in Zurich, where we had selective access to pediatric and surgical trials only. To determine the proportion of discontinued pediatric trials, we considered RCTs from all centers and excluded RCTs with unclear completion status, assuming that these RCTs were missing at random.

We used complete-case multivariable logistic regression analysis to investigate the association between enrollment of pediatric vs adult patients (independent variable) and trial discontinuation due to slow recruitment.[23] We limited our regression analysis to trials that were either completed or discontinued due to slow recruitment. We also excluded pilot trials (4 pediatric, 47 adult) and cluster trials (2 pediatric, 6 adult) for which we expected different recruitment mechanisms. Independent variables were pediatric (vs adult) patients, investigator sponsorship (vs industry), sample size (as planned, continuous variable), multicenter (vs single-center), cross-over design (vs parallel), active control (vs placebo or nonactive intervention), reported method to predict recruitment rate (vs no method reported), logistical support from a contract research organization or clinical trial unit (vs no support reported), and acute care (including emergency and intensive care vs nonacute care). The study protocol provides rationales for the chosen variables.[23] The event-to-variable ratio was 10 (90 trials discontinued due to slow recruitment and 9 explanatory variables). We conducted sensitivity analyses using multiple imputations for missing information about trial discontinuation.[15] A 2-tailed P value $\leq .05$ was considered to indicate statistical significance.

Motivated by reports that pediatric oncology RCTs may be at lower risk for early stopping compared with adult RCTs,[16,17,25] we further explored whether pediatric oncology RCTs differed from other pediatric RCTs in terms of their rate of premature discontinuation. For this analysis, we did not adjust for other potential risk factors owing to the limited power.

Results

Classification and Prevalence of Pediatric Trials

We included 894 RCTs, of which we classified 86 (10%) as pediatric RCTs and 808 (90%) as adult RCTs (**Figure**). Thirty-three trials included a mixed-age population, of which we classified 9 as pediatric because the proportion of children younger than 18 years was >50%. All 9 trials focused on conditions that typically manifest in childhood (ie, 4 on pediatric tumors, 2 on cerebral palsy, 2 on cystic fibrosis, 1 on type 1 diabetes). After excluding the 43 trials approved in Zürich, the proportion of pediatric trials in the remaining 5 RECs was 6% (53 of 851) (**Table I**; available at www.jpeds.com).

Trial Characteristics

Most of the pediatric RCTs were multicenter, investigator-initiated trials and enrolled children of various age groups (**Table II**). Compared with the adult trials, pediatric trials were more frequently conducted in the acute care setting (15% vs 6%), were less frequently sponsored by industry (44% vs 63%), and more frequently piloted their informed consent process (7% vs 1%).

Trial Discontinuation

We determined trial discontinuation from the publication alone (61 of 249; 25%), the survey alone (69 of 249; 28%; response rate, 80%), REC files alone (67 of 249; 27%), combined sources (27 of 249; 11%), or recruiting <90% of the target sample (25 of 249; 10%; including 5 pediatric trials).[23] Of the 894 included RCTs, 575 (64%) were completed, 249 (28%) were discontinued before enrollment of target sample size, and completion status was unclear for 70 RCTs (8%) (**Table III**).

Of the 80 pediatric RCTs with known status, 32 (40%) were discontinued. Of the 744 adult RCTs with known recruitment status, 217 (29%) were discontinued. Slow recruitment was the most frequent reason for discontinuation in both the pediatric (15 of 27; 56%) and adult (85 of 197; 43%) RCTs (**Table III**). The difference was significant in the unadjusted logistic regression model (OR, 1.95; 95% CI, 1.00-3.81), but not after adjustment for other potential risk factors (OR, 1.22; 95% CI, 0.57-2.63). Independent risk factors for trial discontinuation due to slow recruitment were investigator (nonindustry) sponsorship (aOR, 4.45; 95% CI, 2.59-7.65), acute care setting (aOR, 4.00; 95% CI, 1.72-9.31), and smaller planned sample size (aOR, 1.05; 95% CI, 1.01-1.09, in decrements of 100) (**Table IV**). The results were robust to sensitivity analyses using multiple imputations for missing data.[24]

None of 9 pediatric cancer trials was discontinued due to slow recruitment (**Table V**; available at www.jpeds.com).

Trial Publication and Reporting of Discontinuation

After a median follow-up of 11.6 years from REC approval, 46 of the 86 pediatric trials (53%) were published as a

Table II. Characteristics of included trials

Characteristics	Pediatric RCTs (n = 86)	Adult RCTs (n = 808)
Age group, n (%)		
Unborn/preterm/newborn (0 y)	15 (17)	
Infant/toddler (eg, 0-3 y)	10 (12)	
Primary school (eg, 4-11 y)	2 (2)	
Adolescent (eg, 12-17 y)	8 (9)	
Mix, primary school/adolescent (eg, 6-17 y)	12 (14)	
Broad mix (eg, 1-21 years)	39 (45)	
Research ethics committee, n (%)		
Basel	5 (6)	216 (27)
Hamilton	15 (17)	163 (20)
Freiburg	23 (27)	249 (31)
Lausanne	5 (6)	144 (18)
Zürich*	33 (38)	10 (1)
Lucerne	5 (6)	26 (3)
Acute care (emergency or intensive care), n (%)	13 (15)	51 (6)
Oncology, n (%)	10 (12)	171 (21)
Industry sponsorship, n (%)	38 (44)	513 (63)
Drug intervention (in 1 or more arms), n (%)	70 (81)	676 (84)
Planned target sample size, median (IQR)	200 (80-447)	275 (103-630)
Planned centers, n (%)		
Multiple	67 (78)	674 (83)
Single	18 (21)	131 (16)
Unclear	1 (1)	3 (0)
Unit of randomization, n (%)		
Individuals	84 (98)	795 (98)
Clusters	2 (2)	10 (1)
Body parts	0 (0)	30 (4)
Study design, n (%)		
Parallel	81 (94)	755 (93)
Cross-over	4 (5)	37 (5)
Factorial	1 (1)	14 (2)
Unclear	0 (0)	2 (0)
Study purpose, n (%)		
Superiority	57 (66)	595 (74)
Noninferiority	19 (22)	120 (15)
Unclear	10 (12)	93 (12)
Labeled as pilot RCT, n (%)	5 (6)	64 (8)
Comparison group(s), n (%)		
Included placebo or no treatment (often add-on RCTs)	50 (58)	483 (60)
Active comparator(s) only	36 (42)	325 (40)
Data Safety and Monitoring Board mentioned, n (%)	18 (21)	239 (30)
Method for predicting recruitment rate mentioned, n (%)	21 (24)	60 (7)
Pilot study including informed consent, n (%)	6 (7)	5 (1)
Reported methodological/logistical support, n (%)	31 (36)	355 (44)

*In Zurich, we selectively included pediatric and surgical trials only.

peer-reviewed journal article (14 in pediatric journals, 23 in other specialty journals, and 9 in general medical or surgical journals), and another 8 (9%) were published as abstracts only. We could not identify any publications corresponding to the remaining 32 (37%) REC-approved trial protocols. The respective proportions in the 808 adult RCTs were 484 (60%) published in a peer-reviewed journal, 48 (6%) published as abstracts, and 276 (34%) not published (**Table VI**; available at www.jpeds.com).

Of the 32 discontinued pediatric trials, 12 (38%) were published as a peer-reviewed journal article, of which 5 explicitly reported that the trial had stopped early.

Table III. Prevalence of trial discontinuation and reported reasons for discontinuation

	Pediatric RCTs (n = 86)	Adult RCTs (n = 808)
Completion status, n (%)		
Completed	48 (56)	527 (65)
Discontinued	32 (37)	217 (27)
Unclear	6 (7)	64 (8)
Reason for discontinuation, n (%)		
Slow recruitment	15 (19)	85 (11)
Futility	4 (5)	33 (4)
Benefit/harm	5 (6)	28 (4)
Other*	3 (3)	51 (6)
Unknown reason	5 (6)	20 (2)

*Such as administrative, strategic, or financial.

Discussion

In an international cohort of 894 RCTs, 86 enrolled 50% or more children. Of these, 40% were discontinued prematurely. The main reason for trial discontinuation was slow recruitment. Overall, the risk for discontinuation due to slow recruitment was higher in pediatric RCTs than in adult RCTs; however, multivariable logistic regression analysis suggested that the pediatric setting is not an independent risk factor. Instead, an elevated risk for discontinuation due to slow recruitment was associated with investigator sponsorship (nonindustry), acute care setting (eg, newborn intensive care), and smaller planned sample size of RCTs.

Strengths of our study include collaboration with 6 RECs from 3 countries to document the history of 894 RCTs that received REC approval during a 3-year period. We had full access to all REC files and successfully contacted 80% of the authors to clarify whether their trial was stopped early and if so, why. We involved trained methodologists to identify eligible studies and to collect data. To minimize associations due to chance alone, 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 report information regarding trial discontinuation. We used single data extraction for almost 70% of the 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 excellent, with only 2 discrepancies in answers to 30 main questions of the extraction form among 270 protocols extracted in duplicate. In addition, a second investigator verified all outcome data on discontinuation and publication of RCTs.

Our findings are based on protocols that were approved more than 10 years ago. Data from more recently initiated trials are not available but might differ. Advances in standards for RCT planning[26] and understanding of the recruitment process[27] might help reduce the high proportion of discontinued

Table IV. Risk factors for discontinuation due to slow recruitment, multivariable logistic regression

Protocol characteristics	Discontinued due to slow recruitment (n = 90)*	Completed (n = 526)*	Univariable effect		Multivariable effect	
			OR (95% CI)	*P*	aOR (95% CI)	*P*
Pediatric RCT (vs adult), n (%)	13 (14)	44 (8)	1.95 (1.00-3.81)	.049	1.22 (0.57-2.63)	.61
Acute care RCT (vs nonacute care), n (%)	12 (13)	27 (5)	2.97 (1.44-6.14)	.003	4.00 (1.72-9.31)	.002
Investigator sponsorship (vs industry), n (%)	59 (66)	158 (30)	4.43 (2.76-7.12)	<.001	4.45 (2.59-7.65)	<.001
Smaller planned sample size, median (IQR)	180 (80-320)	364 (155-800)	1.06 (1.01-1.11)†	.010	1.05 (1.01-1.09)†	<.001
Multicenter status (vs single-center), n (%)	71 (79)	470 (89)	0.46 (0.26-0.84)	.011	1.80 (0.85-3.82)	.12
Methodological/logistical not supported (vs reported), n (%)	62 (69)	279 (53)	1.94 (1.2-3.14)	.007	1.49 (0.86-2.56)	.088
Active control (vs placebo/no active control), n (%)	37 (41)	204 (39)	1.14 (0.72-1.79)	.58	1.37 (0.83-2.24)	.22
Cross-over design (vs parallel), n (%)	8 (9)	21 (4)	2.61 (1.11-6.17)	.028	2.18 (0.82-5.79)	.13
Method to predict recruitment not reported (vs reported), n (%)	78 (87)	486 (92)	0.53 (0.27-1.06)	.073	1.15 (0.52-2.54)	.74

*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 for rationale). We excluded 71 RCTs with missing discontinuation information, 25 RCTs with missing reasons for discontinuation, and 12 RCTs with missing sample size information.
†In decrements of 100 patients.

pediatric trials. It is unlikely that the main risk factors for recruitment failure have changed substantially over time, however. Although our collaboration with 6 RECs in 3 countries increases the generalizability of our results, our findings may not be transferable to RCTs performed in other jurisdictions, such as in developing countries, where unique trial completion challenges exist.

A previous analysis of reasons for discontinuation of pediatric RCTs attributed only 25% (8 of 32) to slow recruitment.[19,20] In our sample, slow recruitment was the main cause of early discontinuation in 56% (15 of 32). The difference may stem from the fact that the previous analysis was based on published RCTs only. However, many discontinued RCTs are never published or, if published, fail to acknowledge slow recruitment.[21] We addressed this limitation by evaluating REC files and directly surveying trialists.

Our findings suggest that pediatric trials are at particularly high risk for recruitment failure (40%), which is concerning, especially because there are already many fewer pediatric trials with major gaps in the RCT-informed clinical evidence base.[1] Nonetheless, our risk factor analysis should prove encouraging to pediatric trialists, in that enrollment of children is not an independent risk factor for slow recruitment. Rather, recruitment in pediatric trials was associated with the same risk factors as RCTs in adults. Nonindustry sponsorship may represent insufficient funding and lack of professional planning and conduct, and acute care settings often imply that substitute decision makers and caregivers are reluctant to make decisions about trial participation under time pressure. The link between small sample size and recruitment failure is less clear. Larger sample size might be a marker for RCTs conducted in research networks or in more prevalent diseases. Those RCTs might be better organized from the outset, and established networks around experienced investigators might be better able to respond to recruitment challenges. Diseases in children often have a low prevalence and thus may implicitly constitute a particular recruitment challenge.

Our results support previous observations that pediatric cancer trials seem to be less affected by recruitment problems.[16] None of the 9 pediatric cancer trials in our sample was discontinued due to slow recruitment. The apparent success of pediatric oncology trials may be the result of well-established national and international networks, and integration of the trial protocols into routine clinical care. Thus, investigators designing trials for adult patients may consider the cooperative research culture in pediatric oncology as a model.[17,25] The next step may be careful estimation of the expected recruitment performance, which is often overestimated.[27,28] Unless reliable and easily applicable prediction models are available,[29] pilot trials that apply the full recruitment protocol are critical to test recruitment performance and identify important barriers, such as lack of eligible patients, doubt among recruiting physicians regarding equipoise, or complex protocols.[27] In our sample, only 7% of pediatric trial protocols mentioned a feasibility study. Finally, active monitoring of recruitment and proactive implementation of strategies to bolster recruitment when necessary might be crucial once RCTs are underway.[30,31]

More than one-third of pediatric RCTs were discontinued prematurely, due primarily to slow recruitment. Investigators who plan to enroll children in an RCT should consider measures to mitigate slow recruitment, especially if the trial is conducted in the acute care setting, lacks industry partnership, and has a small sample size. ■

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Table I. Proportion of pediatric trials by REC

	Zürich (n = 43)*	Not Zürich (n = 851)	Basel (n = 221)	Freiburg (n = 272)	Lausanne (n = 149)	Lucerne (n = 31)	Hamilton (n = 178)
Pediatric, n (%)	33 (78)	53 (6)	5 (2)	23 (8)	5 (3)	5 (16)	15 (8)
Adult, n (%)	10 (22)	798 (94)	216 (97)	249 (92)	144 (97)	26 (84)	163 (92)

*In Zurich, we selectively included pediatric and surgical trials only.

Table V. Comparison of pediatric cancer trials with non-cancer trials and adult trials

	Pediatric cancer trials* (n = 9)	Pediatric non-cancer trials* (n = 48)	Adult cancer trials* (n = 117)
Completed, n (%)	9 (100)	35 (73)	98 (84)
Discontinued due to slow recruitment, n (%)	0	13 (27)	19 (16)

*Same sample as used for multivariable regression; see **Table IV**.

Table VI. Publication of included trials

Publication type	Pediatric RCTs (n = 86)	Adult RCTs (n = 808)
Peer-reviewed journal, n (%)	46 (53)	484 (60)
Abstract/letter/other, n (%)	8 (9)	48 (6)
Not published, n (%)	32 (37)	276 (34)