# 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).*

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| 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.

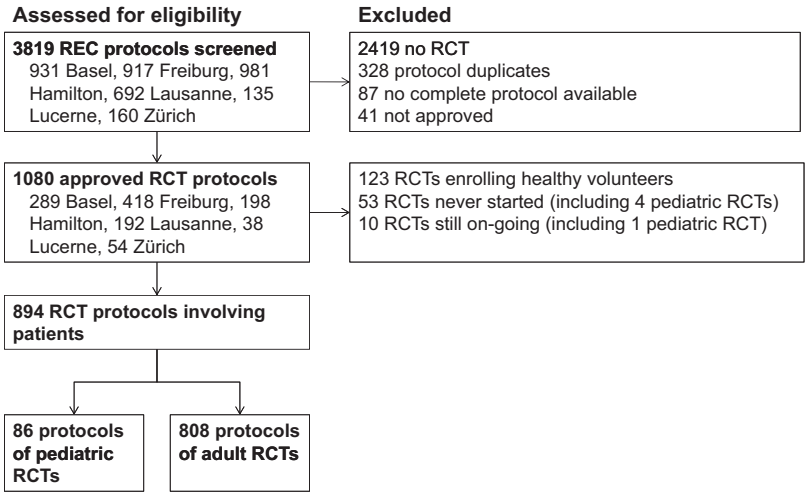


**Figure.** Study selection.