Journal of Pediatric Surgery 53 (2018) 879–884

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Review Articles

Enrollment and reporting practices in pediatric general surgical randomized clinical trials: A systematic review and observational analysis☆,☆☆

Etienne St-Louis [a,b,*], Marcus Oosenbrug [c], Tara Landry [d], Robert Baird [e]

[a] Division of General Surgery, McGill University, Montréal, Quebec, H3G 2M1, Canada
[b] Division of Pediatric General and Thoracic Surgery, McGill University Health Centre, Montreal, Quebec, H4A 3J1, Canada
[c] Faculty of Medicine, McGill University, Montréal, Quebec, H3G 2M1, Canada
[d] Medical Library, Montreal General Hospital, McGill University Health Centre, Montreal, Quebec, H4A 3J1, Canada
[e] Department of Pediatric General and Thoracic Surgery, British Columbia Children's Hospital, Rm K0-134, 4480 Oak Street, Vancouver, BC, V6H 3V4, Canada

ARTICLE INFO

Article history:
Received 16 January 2018
Accepted 1 February 2018

Key words:
Recruitment
Clinical trials
Pediatric general surgery
Systematic review
Quality of reporting

ABSTRACT

Background: Pediatric surgical randomized clinical trials (RCTs) are labor-intensive and costly. This systematic review investigated patient accrual and estimates of study duration in RCTs by interrogating enrollment and registration practices.
Methods: We performed a peer-review search of multiple databases from 2000 to 2016 evaluating RCTs salient to the field with inclusion mandated that a self-identified pediatric surgeon be listed as an author. Trial registries were also searched. RCTs were appraised, and predictors of success were evaluated using multivariate logistic regression, with success defined as achievement of recruitment objectives.
Results: After screening, 137 RCTs were analyzed. Mean Jadad score was 1.80 (median = 2). CONSORT scores ranged between 17% and 97% (median = 58%). Sixty-seven studies described sample-size determination, 49 reported projected enrollment, and 26 were successful. Among 26 registered RCTs, 15 disclosed their expected completion date, which was achieved by 8. On average, protocols underwent 3.42 iterations. 9% of trials were terminated before completion, most commonly owing to poor recruitment. Trial registration and urgent cases significantly predicted success on multivariable analysis ($p < 0.05$).
Conclusion: Overall quality of reporting in pediatric surgical trials is poor. Sample-size calculation and patient accrual are frequently poorly performed or underestimated, resulting in trial overrun and/or premature termination. These data may help inform subsequent study design and facilitate successful completion.
Level of Evidence: Level III—Systematic Review and Observational (Case–Control) Analysis.

Evidence-based medicine is the gold standard of sound clinical care. The well-executed randomized controlled trial (RCT) is widely regarded as the highest quality study design available to investigate the efficacy of treatment or screening interventions. However, RCTs are challenging to conduct, being both time-consuming and costly. Funding is almost universally required to launch and sustain a rigorous trial. Consequently, investigators must be able to reliably estimate the number of patients needed in the trial to demonstrate significant effects as well as to anticipate the timeframe and resources needed to recruit enough patients, thereby justifying the sums requested in grant applications. There is a substantial body of literature investigating the various factors that impact recruitment in adult clinical trials [1–4]. However, the problem is altogether different in the pediatric population; trials involving children can be challenging owing to the necessity of obtaining consent by proxy from parents and an overall smaller pool of available patients [5,6]. Pediatric surgical trials may present additional challenges owing to the frequently urgent nature of surgical conditions and surgeons' preconceived notions about which technique is superior in their hands.

There are, as of yet, no systematic data examining the various predictors of successful trial completion in the pediatric surgery literature. One retrospective study looking at discontinuation and nonpublication of RCTs conducted in children found that trials were more likely to be completed if they were funded by industry [7]. There is a paucity of well-conducted clinical trials for many pediatric surgical conditions

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; cOR, crude odds ratio; CONSORT, consolidated standards of reporting trials; FAST, focused assessment with sonography in trauma; PRISMA, preferred reporting items for systematic reviews and meta-analyses; RCT, randomized clinical trial; VATS, video assisted thoracoscopic surgery.

☆ All authors declare no conflicts of interest.

☆☆ No external funding was received to support this work.

* Corresponding author at: McGill University Health Centre, 1001 Décarie Boulevard, Montreal, QC, Canada. Tel.: +1 514 6773761.
E-mail address: etienne.st-louis@mail.mcgill.ca (E. St-Louis).

https://doi.org/10.1016/j.jpedsurg.2018.02.009
0022-3468/

[8]. Moreover, many pediatric surgical trials are stopped before reaching the required sample size owing to poor recruitment rates [9,10]. We hypothesize that there are significant differences in basic characteristics between successful and unsuccessful pediatric surgical RCTs.

The primary objective of this investigation was to determine which factors have the greatest impact on the success of pediatric surgical RCTs and to assess whether these factors can be modified or optimized by investigators prior to launching a trial. Our secondary objective was to assess the quality of reporting in pediatric surgical RCTs using a standardized checklist. Our downstream aim is to inform prospective investigators about strategies for improving recruitment rates in pediatric general surgery RCTs and in turn assist in better anticipating the timeframe and resources needed for successful completion.

1. Methods

We performed a systematic review of the literature to retrieve reports of pediatric general surgery clinical trials. This systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The study protocol was not registered with the International Prospective Register of Systematic Reviews (PROSPERO) because only protocols that review clinical interventions are accepted in that registry.

1.1. Search strategy

A peer-reviewed search strategy was developed in collaboration with a senior hospital librarian at our institution (TL) in Montreal, Canada. The following databases were searched for relevant studies: MEDLINE (via Ovid 2000 to 08/July/2016; via PubMed 2000 to 08/July/2016); Embase Classic + Embase (via Ovid 2000 to 08/July/2016); BIOSIS Previews (via Ovid 2000 to 2016 Week 32); The CENTRAL Registry of Controlled Trials (via the Cochrane Library to issue 6 of 12, June 2016) and Global Health (via Ovid 2000 to 2016 Week 26). The search strategy used text words and relevant indexing to retrieve reports of pediatric surgery clinical trials. The full MEDLINE strategy is appended (Appendix 1) and was modified for each database as necessary. National Institutes of Health (NIH) Clinical Trials Registry (www.clinicaltrials.gov/) and the International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/) were also searched (on 21/04/2016) to identify recruiting, completed or terminated pediatric surgery RCTs.

We established a sample of 51 surgically-correctable conditions that are representative of the pediatric general surgery practice at a quaternary-care Canadian institution through review of textbooks and in consultation with senior members of the department (Appendix 2).

1.2. Selection criteria

To be included in our systematic review, studies had to meet the following criteria: involve patients whose age ranges from twenty weeks of gestation up to eighteen years undergoing a procedure or treatment for one of the 51 surgically-correctable conditions in our representative sample list (Appendix 2). One of the listed authors of the study had to self-identify as a pediatric general surgeon. The status of included studies had to be either published, or listed as “completed” or “terminated” on a clinical trial registry.

Exclusion criteria included the following: studies published before the year 2000, owing to the lack of clinical trial registry data prior to this date. Non-RCTs and studies involving adult patients over eighteen or fetuses under 20 weeks of gestation were excluded. Any registered clinical trial whose status is “ongoing” at the time of the search was not considered for review. Any study lacking recruitment data was excluded.

1.3. Study selection

In accordance with PRISMA guidelines, a first screen of articles was performed by two independent reviewers (ESL and MO) on the basis of title and abstract only. After preliminary selection was completed, a second and final selection was made by the same two independent reviewers (ESL and MO) based on full-text review. Disagreements failing resolution by discussion between reviewers were arbitrated by the principal investigator (RB).

1.4. Data extraction

An electronic data extraction sheet (Appendix 3) with agreed-upon definitions was developed and piloted in the first 10 articles then performed independently in the remaining articles by both reviewers (ESL and MO). Data on various characteristics of included studies were extracted, including details on the setting, the participants, the intervention, the control, the recruitment process, the consent process, the randomization, the blinding, the timeframe and the outcomes of the study.

A successful trial was defined as one that was completed in the expected timeframe and recruited a large enough sample to reach required power. Trials that were arrested owing to the results of interim analysis were not considered unsuccessful but were excluded from quantitative analysis. Other cases of early trial termination owing to lack of funding or poor compliance from subjects, parents or staff, were labeled unsuccessful.

We assessed the quality of reporting for each clinical trial using two indices: the Jadad score and the Consolidated Standards of Reporting Trials (CONSORT) checklist [11,12]. Trials were assigned 1 point for each criterion in the Jadad scale, up to a maximum score of 5. For the CONSORT checklist, a single point was allotted for each item if reporting was considered adequate and no points if inadequate, up to a maximum score of 37. Not all criteria were applicable to each study; therefore, the overall scores were reported as a percentage of applicable items.

1.5. Data analysis

Articles being analyzed included those identified through the database and registry search. When possible, published studies were linked to their registry information, allowing us to assess whether a published study was successful or not according to definitions above. The registry search also identified unsuccessful studies and allowed us to gather information regarding reason for failure for those that remain unpublished. Characteristics of both successful and unsuccessful studies were described with summary statistics. Groups were evaluated using the nonparametric Fisher's exact test for comparison of proportions as well as the two-sample two-sided Student t-test for comparison of means.

Univariate logistic regression was performed for each variable, identifying potential predictors of “success”. Variables having achieved a p-value <0.25 were included in a multivariable logistic regression model to determine which study characteristics were independent predictors of successful clinical trial completion. Additional variables which have been reported in the literature to be correlated with discontinuation owing to poor recruitment, such as industry-funding, were also included in the model. A p-value <0.05 was considered statistically significant in the multivariable logistic regression model.

2. Results

2.1. Search results

After full-text manuscript review, 137 RCTs met our eligibility criteria and were included for qualitative analysis. The PRISMA Flow Diagram for our review is depicted in Fig. 1.