Contemporary Clinical Trials Communications 8 (2017) 203–208

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

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

Factors influencing the enrollment in randomized controlled trials in orthopedics

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ARTICLE INFO

Keywords:
Orthopedics
Randomized controlled trials
Recruitment

ABSTRACT

Background: Low enrollment rates are a threat to the external validity of clinical trials. The purpose of this study was to identify factors associated with lower enrollment rates in randomized controlled trials (RCTs) involving orthopedic procedures.

Methods: We performed a search in PubMed/MEDLINE for RCTs that involved any orthopedic surgical procedure, compared different intraoperative interventions, were published in English in a peer-reviewed journal between 2003 and 2014, and reported the numbers of both enrolled and eligible subjects. The primary outcome was the enrollment rate, defined as the number of enrolled subjects divided by the number of eligible subjects. We used a meta-regression to identify factors associated with lower enrollment rates.

Results: The combined estimate of enrollment rate across all 393 studies meeting inclusion criteria was 90% (95% CI: 89–92%). Trials in North America had significantly lower enrollment rates compared to trials in the rest of the world (80% vs. 92%, $p < 0.0001$). Trials comparing operative and non-operative treatments had significantly lower enrollment rates than trials comparing two different operative interventions (80% vs. 91%, $p < 0.0001$). Among trials comparing operative and non-operative interventions, there was a marked difference in enrollment rate by region: 49% in North America and 86% elsewhere ($p < 0.0001$).

Conclusions: RCTs investigating orthopedic procedures have variable enrollment rates depending on their location and the difference between the interventions being studied. North American trials that compare operative and non-operative interventions have the lowest enrollment rates. Investigators planning RCTs would be well advised to consider these data in planning recruitment efforts.

1. Introduction

Low enrollment rates can compromise clinical trials. The percentage of eligible individuals who consent to participate in a given randomized controlled trial (RCT) has been reported to be as low as 4% [1]. As a result, trials may be inconclusive or require additional time and funding to complete [2,3]. In addition, even for adequately powered trials, low enrollment rates pose a threat to external validity [4].

As suggested by several recent trials that have helped shape treatment recommendations for common orthopedic procedures, RCTs are pivotal for investigating the efficacy of surgical procedures or their components [5–7]. It may be challenging to enroll subjects into RCTs that randomly allocate subjects to different types of procedures, since surgery is irrevocable [8,9]. Previous studies have identified a number of reasons why an eligible individual may decline to participate in an RCT, such as a preference for one form of therapy over another, difficulty understanding the concept of an RCT, or discomfort with the idea of being randomized [1,10–13].

Investigators have examined the patient characteristics associated with whether an eligible patient enrolls or refuses to enroll in a

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http://dx.doi.org/10.1016/j.conctc.2017.10.005
Received 5 April 2017; Received in revised form 6 October 2017; Accepted 13 October 2017
Available online 16 October 2017

particular trial. Factors associated with refusal to enroll have included older age, gender, marital status, language fluency, ethnicity, vocation, and socioeconomic status [10,12,14–16]. To our knowledge there has been no comprehensive study carried out at the trial (not subject) level that examines enrollment rates of trials and trial characteristics associated with enrollment rates.

In this study, we calculated the enrollment rates reported in publications of orthopedic RCTs over a 12-year period and assessed for associations between enrollment rate and various trial characteristics, including features of the interventions being studied, the investigators of the studies, and the publications in which the RCTs were reported. We hypothesized that trials in which the treatment arms offer similar patient experiences (e.g., two different screws for fracture fixation) would have higher enrollment, on average, than trials that randomized patients to very different experiences (e.g., surgical operation versus physical therapy). Accordingly, we hypothesized that trials comparing operative and non-operative interventions would have the lowest enrollment rates.

2. Materials and methods

1. Paper selection: Papers were included if they were written in English, were published in a peer-reviewed journal between January 2003 and December 2014, reported an RCT of living human subjects over the age of 18, and reported both the number of eligible subjects and the number of enrolled subjects. To be included, RCTs were required to have at least one arm that involved an orthopedic surgical procedure, and the arms were required to compare different intraoperative interventions. Reports of trials comparing preoperative or postoperative interventions, such as rehabilitation protocols, were not included.

Because we wished to focus on orthopedic aspects of management, we excluded studies that compared interventions involving only injections (e.g., corticosteroid vs. saline injections). Similarly, we excluded studies of different types of anesthetics. We included trials comparing intraoperative interventions such as tourniquets, drainage, and antimicrobials if they otherwise met criteria. Manuscripts that had been retracted were excluded. We selected a 12-year period in order to adequately power our findings and minimize the risk of secular trends—that is, major shifts in subject or investigator approaches to RCTs over time.

We used PubMed/MEDLINE to search for publications of orthopedic RCT results. The search was last performed on November 4, 2015. We used the following search term to identify 6727 papers for initial screening for inclusion in our study:

> “(((((“2003/1”[Date - Publication]: “2014/12”[Date - Publication])) AND English[Language]) AND Randomized Controlled Trial [Publication Type]) AND (orthoped* OR orthopaed* OR arthroplast* OR arthroscop* OR meniscect* OR “cruciate ligament” OR “rotator cuff” OR laminect* OR “spinal fusion” OR “carpal tunnel release” OR “open reduction” OR “internal fixation” OR “external fixation” OR osteotom* OR “bone grafting” OR arthrodesis OR patellect* OR capsulot* OR synovect* OR syndesmot* OR “tendon repair” OR tenodesis OR “trigger finger release” OR fasciect* OR laminect* OR discect*)) AND (humans[MeSH Terms])”.

Papers were accessed through the library systems of Harvard University and two major academic hospitals (Brigham and Women's Hospital and Massachusetts General Hospital). We excluded papers if they were not available through these three library systems.

2. Abstraction of data: Two investigators (C.T.L. and H.J.R.) performed the screening of papers and data abstraction. They each independently screened the same initial set of 200 papers and abstracted data from papers that met inclusion criteria, and then met to resolve discrepancies and ensure a uniform approach to excluding and including papers. Thereafter, they divided all remaining papers for screening and data collection. Any papers raising uncertainty were set aside to be resolved by the team.

For each paper that met inclusion criteria, we performed a manual data extraction to obtain the following data elements. We extracted the number of subjects screened for the trial, the number of eligible subjects, and the number enrolled. We characterized the difference between study interventions; each study was categorized as either a comparison of operative and non-operative management or as one of various comparisons of operative techniques or strategies (as shown in Appendix 1). We extracted the orthopedic subspecialty area of the clinical problem addressed by the RCT, the number of months of follow-up, and whether there was inpatient follow-up only or outpatient follow-up. In terms of investigator-related data, we extracted the number of study sites for the trial, the nationality of the first author's primary institution (by region: USA/Canada, Europe, Asia/Middle East, Australia/New Zealand, Mexico/Central America/South America, other), reported external funding sources (public, foundation, and/or industry), and the number of months of recruitment. Lastly, we extracted the year of paper publication.

3. Characterization of included and excluded papers: We gathered data on our screening process by recording the total number of papers screened, the number of papers excluded for each inclusion/exclusion criterion, and the number of papers included in the study. Many papers were excluded based on more than one criterion, and if so they were categorized by the most salient exclusion criterion, with two exceptions. First, papers were only categorized as “not accessible” if they otherwise met criteria for inclusion. Second, among papers that met criteria for inclusion and whose full manuscripts were accessible, papers were excluded if they did not report the number of eligible subjects.

4. Statistical analysis: The primary outcome variable was enrollment rate, which was calculated as the number of enrolled subjects divided by the number of eligible subjects. The secondary outcome variable was screening yield, which was calculated as the number of enrolled subjects divided by the number of screened subjects. We employed a logistic random-effects model, which incorporates properties of the logistic and binomial distributions, to model the number enrolled and thus obtain an estimate for enrollment rate. The logistic random-effects model uses the exact binomial likelihood to estimate the within-study variability. Random-effects estimated by maximum likelihood were used to account for between-study variability. We used the model to calculate within-study variability, to calculate an overall combined estimate for enrollment rate and to evaluate the effect of study-level characteristics on enrollment rate [20,21]. This allowed us to include studies with zero cells (i.e., 100% enrollment) without requiring an ad-hoc adjustment. In our model, enrollment rate and screening rate were the dependent variables, and all other variables gathered (as described in “Abstraction of data” above) were predictor variables: orthopedic subspecialty, degree of intervention difference, inpatient only vs. outpatient follow-up, duration of follow-up, single-center vs. multi-center, nationality of first author's institution, external funding source (if reported), duration of subject enrollment, and year of publication.

Study-level variables found to be significantly associated with enrollment rate differences in bivariate analysis were examined further for interactions. Given our hypothesis that studies with patient-relevant differences in intervention would have lower enrollment rates, we planned to perform interaction analyses between intervention difference and other significant predictors.

For each year of publication, we calculated the proportion of included papers (i.e., those meeting all inclusion criteria) to papers meeting all inclusion criteria except the reporting of number of eligible subjects. We termed this result the paper inclusion rate, as a proxy for the proportion of investigators reporting enrollment rates for their RCTs. We chose to examine this result rather than the proportion of included papers to all papers screened, because other RCT characteristics (e.g., the number of trials studying anesthetic use) could affect the