Factors Influencing the Enrollment of Eligible Individuals in Orthopedic Randomized Controlled Trials

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Purpose: Low rates of subject enrollment are a threat to the external validity of clinical trials, which are necessary to confirm or contradict basic assumptions about clinical management. Our goal was to examine the association of subject enrollment rates in orthopedic randomized controlled trials (RCTs) with characteristics of the interventions being studied, the investigators of the studies, and the publications in which the RCTs are reported.

Methods: We performed a search in PubMed/MEDLINE for RCTs involving an orthopedic surgical procedure, comparing different intraoperative interventions, published in English in a peer-reviewed journal during 2003 to 2014, and reporting both the numbers of enrolled and eligible subjects. The primary outcome variable was the enrollment rate, calculated as the number of enrolled subjects divided by the number of eligible subjects. We collected and analyzed data from papers meeting inclusion criteria.

Results: The average enrollment rate across all 393 studies meeting inclusion criteria was 84.5% (standard deviation (SD) 16.6%). Trials in the United States and Canada had significantly lower enrollment rates when compared to trials in the rest of the world (72.9% vs. 87.6%, $p<0.0001$), and trials comparing an operative arm to a non-operative arm had significantly lower enrollment rates than trials comparing two different operative arms (73.1% vs. 86.3%, $p<0.0001$). The national differences were observed primarily in trials comparing operative and non-operative interventions, in which the average North American enrollment rate was 47.9% (SD 25.9%) and the average enrollment rate elsewhere was 81.1% (SD 15.8%).

Conclusions: Trials may have variable rates of success recruiting subjects depending on their location and the difference between the interventions being studied, with North American trials and trials comparing operative and non-operative interventions having lower enrollment rates.

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Section 1: Introduction

Low rates of subject enrollment undermine the success of clinical trials. The percentage of eligible individuals consenting 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 underpowered or require additional time and funding to complete.[2,3] Even for adequately powered trials, low enrollment rates pose a threat to external validity.[4]

As suggested by several recent trials of common orthopedic procedures, RCTs are necessary to confirm or contradict basic assumptions about clinical management in surgery.[5-7] It may be challenging to enroll subjects into surgical RCTs because 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 if he or she has a preference for one form of therapy over another, has difficulty understanding the concept of an RCT, or is uncomfortable with the idea of being randomized.[1,10-13] For investigators leading surgical RCTs, it may be helpful to know not only why prospective subjects decline to participate in an RCT but also what factors are associated with lower enrollment rates.

The existing literature on clinical trial enrollment rates can be divided into two categories. First, analyses of the enrollment experiences of individual trials typically examine survey data from participants and eligible non-participants to identify participant characteristics associated with RCT enrollment, such as age, gender, marital status, language fluency, ethnicity, vocation, and socioeconomic status.[10,12,14-16] However, reported associations between these characteristics and the likelihood of participation are not consistent across studies.[3,11,15,17]

Second, studies have evaluated enrollment rates across multiple trials.[12,18] One showed that enrollment rate in the first two months of a trial was predictive of its overall enrollment rate,[3] and another showed that patient enrollment per month per study site was lower for trials comparing surgical and non-surgical interventions than other types of surgical or medical trials.[19] However, there has been no comprehensive study of trials' enrollment rates and associations with a wide range of trial characteristics.

In this study, we calculate the enrollment rates reported in publications of orthopedic RCTs over a 12-year period and assess for associations between enrollment rate and various trial characteristics, namely characteristics of (a) the interventions being studied, (b) the investigators of the studies, and (c) the publications in which the RCTs are reported. In addition, we examine

the proportion of papers reporting orthopedic RCTs in which subject enrollment rate is reported. We hypothesized that trials with a greater degree of difference between the interventions being compared would have lower enrollment rates, and that trials comparing operative and non-operative interventions would have the lowest enrollment rates. Our study is the first of which we are aware to compare enrollment rate across a sample of trials within a single surgical specialty and the first to investigate associations of enrollment rate with intervention-related, investigator-related, and publication-related characteristics.

Section 2: Student Role

As the first author on this study, I:

- Performed a literature review
- Refined the search process, with advice from other authors (H.J.R., J.N.K.), and collected a set of published papers from 2003-2014 reporting orthopedic RCT results to be screened for inclusion
- Proposed data categories and created a data collection tool in Microsoft Excel
- Performed the screening of papers and extracted data from those included (in conjunction with H.J.R.)
- Performed data analysis

Section 3: Methods

We used PubMed/MEDLINE to search for orthopedic RCTs whose results were published in the twelve-year period from 2003 to 2014. We used the following search term to identify 6757 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 included if they met following inclusion criteria: publication in a peer-reviewed journal between January 2003 and December 2014, English language, reporting of an RCT with at least one arm examining an intraoperative intervention during an orthopedic surgical procedure, living human subjects over the age of 18, and reporting of both the number of eligible subjects and the number of enrolled subjects. Exclusion criteria included the following: comparison of interventions only involving injections (e.g. corticosteroids), comparison of anesthesiology interventions, manuscript retraction, and lack of journal access. Access to papers was attempted in the library systems of Harvard University and two major academic hospitals (Brigham and Women's Hospital and Massachusetts General Hospital). Trials comparing intraoperative interventions such as tourniquets, drainage, and antimicrobials were included if otherwise meeting criteria.

Two investigators (C.T.L. and H.J.R.) performed the screening and data collection process. To ensure concordance in this process, they each independently screened the same initial set of 200 papers and collected data from papers meeting inclusion criteria, and compared findings. Thereafter, remaining papers were divided for screening and data collection by the two investigators. Any cases of uncertainty were discussed during serial meetings and resolved by consensus.

For papers meeting inclusion criteria, we abstracted the following data elements.

Primary outcome data: number of enrolled subjects; number of eligible subjects

Enrollment rate = number of enrolled subjects divided by number of eligible subjects

Other enrollment-related data: number of screened subjects

Screening yield = number of enrolled subjects divided by number of screened subjects

Intervention-related data: characterization of difference between interventions (seven categories: surgery versus non-surgery, different procedures, different approaches or techniques for the same procedure, same procedure with versus without additional procedure, different materials, different use of surgical

technology, other); orthopedic subspecialty (eight categories: trauma, sports, reconstructive, spine, oncology, hand, foot/ankle, other); months of follow-up; inpatient versus outpatient follow-up

Investigator-related data: single-site versus multi-site trial; number of study sites; nationality of first author's primary institution (by continent: USA/Canada, Europe, Asia/Middle East, Australia/New Zealand, Mexico/Central America/South America, other); funding sources (public, foundation, and/or industry); months of recruitment

Publication-related data: year of publication

Statistical Analysis

The range of enrollment rate was characterized across all trials included in our study, and factors associated with higher or lower enrollment rate were identified. T-test and linear regression were used to examine factors independently associated with the enrollment rate. We examined the joint effects of nationality and difference between interventions using a stratified analysis. Analysis was performed using Microsoft Excel (2011).

Ethical approval was not required for our study, as there were no humans subjects. All data were extracted from papers published in peer-reviewed journals.

Section 4: Results

6727 papers were screened for inclusion (Figure 1). 150 papers were duplicate studies, and 6184 were excluded for not meeting the inclusion and exclusion criteria: 1778 papers did not report the number of eligible subjects but met all other criteria, and 4406 failed to meet at least one of the other criteria. 393 papers met all inclusion criteria, including the reporting of both the numbers of eligible and enrolled subjects, and were thus included in this study. The proportion included studies to studies excluded for failing to report the number of eligible subjects increased over the twelve-year study period (r^2=0.932, Figure 2). Characteristics of the included papers are shown in Table 1.

The mean enrollment rate of the 393 included papers was 84.5% (SD 16.6%). Of the 393 included papers, 330 (84.0%) reported the number of patients screened for eligibility. The mean screening yield was 61.6% (SD 25.3%).

Intervention-related factors: Studies in which subjects were randomized to either an operative or a non-operative intervention had a significantly lower enrollment rate than studies in which subjects were randomized to one of two or more operative arms (73.1% vs. 86.3%, $p<0.0001$, Table 2). A significant difference was also observed for screening yield (47.0% vs. 64.1%, $p<0.0001$, Table 2). No significant difference in enrollment rate was observed by orthopedic subspecialty, inpatient versus outpatient follow-up, or duration of follow-up.

Investigator-related factors: Studies in which the first author was primarily affiliated with an institution in the United States or Canada, used as a proxy for studies performed in those countries, had significantly lower enrollment rates than studies in which the first author was primarily affiliated with an institution in another country (72.9% vs. 87.6%, $p<0.0001$, Table 2). A significant difference was also observed for screening yield (46.7% vs. 65.3%, $p<0.0001$, Table 2). We performed a stratified analysis of the simultaneous effects of nationality and intervention difference on enrollment rate. There was a marked difference in average enrollment rate between trials comparing operative and non-operative interventions in the US or Canada and such trials in other countries (47.9% vs. 81.1%, $p<0.0001$, Table 3). There was a smaller though still significant geographic difference in enrollment rate for other trials (Table 3). In addition, studies that were performed at a single site had a significantly higher average enrollment rate than studies performed at multiple sites (86.2% vs. 78.3%, $p=0.0001$, Table 2). No significant difference in enrollment rate was observed by funding source or duration of subject recruitment.

Publication-related factors: No significant difference in enrollment rate was observed by year of publication.

Section 5: Discussion, Limitations, Conclusions, Suggestions for Future Work

Low rates of patient enrollment in RCTs threaten their successful completion and the generalizability of study results. Previous studies have described the characteristics of and reasons stated by subjects who refuse to enroll in clinical trials, but no study has quantitatively examined the association between enrollment rates and intervention-, investigator-, and publication-related factors. In this analysis of 393 orthopedic RCTs, enrollment rate varied significantly with the degree of difference between treatment arms, region of the world in which the study was conducted, and number of sites at which the study was conducted.

As we had hypothesized, patients were less likely to enroll in studies that compared an operative to a non-operative intervention than studies that compared two or more operative interventions, regardless of the country in which the trial was performed. This may be because patients have strong preferences surrounding the irrevocable decision to undergo surgery, and are reluctant to leave their treatment type to chance.[1,9] Our finding is consistent with a prior study of 114 publicly funded RCTs in the United Kingdom, which also found lower rates of patients recruited per month per trial site among trials comparing operative and non-operative interventions.[19] Furthermore, we observed a significant difference in overall screening yield between these two trial types.

Our finding that orthopedic RCTs in the US and Canada have lower enrollment rates than those across the rest of the world is less easily explained. North American patients may be less willing to consent to clinical trials, perhaps because they have stronger treatment preferences or feel more authorized than their counterparts in other countries to express these preferences. It is also possible that North American investigators provide a fairer consent process or are more willing to offer the opportunity to refuse participation. It has been posited that single-payer health systems incentivize physicians to recruit more patients to clinical trials.[20] Indeed, we performed a post-hoc analysis comparing enrollment rates of RCTs in Canada to those of US trials, which also showed significantly lower enrollment rates in US trials. Our initial stratification of countries was by continent and had not taken into account national health systems. Although international differences in patient recruitment have been noted in prior studies,[21] further investigation into this hypothesis is warranted.

In the past two decades, an increasing emphasis on full transparency of methodology has been standardized through the Consolidated Standards of Reporting Trials (CONSORT) statements, first published in 1996 and subsequently updated in 2001 and 2010.[22-24] Among the items the CONSORT statement recommends reporting is a diagram of the recruitment process that includes the numbers of screened, eligible, and enrolled subjects. In this study, we note that the proportion of papers excluded solely on the basis of not reporting the number of eligible subjects decreased over the 12-year period, which may be in response to implementation of the CONSORT statements.

The scope of this study was limited to orthopedic RCTs; thus, the findings must be generalized cautiously to other fields. As a future direction, studying the factors that are

associated with enrollment rate in RCTs within other specialties may help to generalize our findings and identify other key factors that influence enrollment rates. In addition, we gathered data on the journal in which each paper was published, and journal and journal impact factor are two other potential avenues of investigation. Lastly, this study did not report on subject-related characteristics, as demographic statistics about the population of eligible individuals who declined participation in a study are seldom included in papers.

Our results show that the country in which a trial is performed may influence its enrollment rate, especially for trials comparing operative and non-operative interventions. This finding has implications beyond orthopedics that warrant further investigation. Underlying the geographic differences in enrollment rates may be cultural and economic differences pertaining to the relationship between patients and medical professionals as well as incentives to conduct or enroll in trials. Although lower enrollment rates undermine external validity, we hesitate to argue that nationality and complexity of design should disadvantage trials. In particular, trials comparing operative and non-operative interventions may have the most important implications for clinical practice.

Section 6: Acknowledgements

No outside funding was obtained for completion of this study.

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Figures and Tables

Figure 1. Flow chart of paper screening process

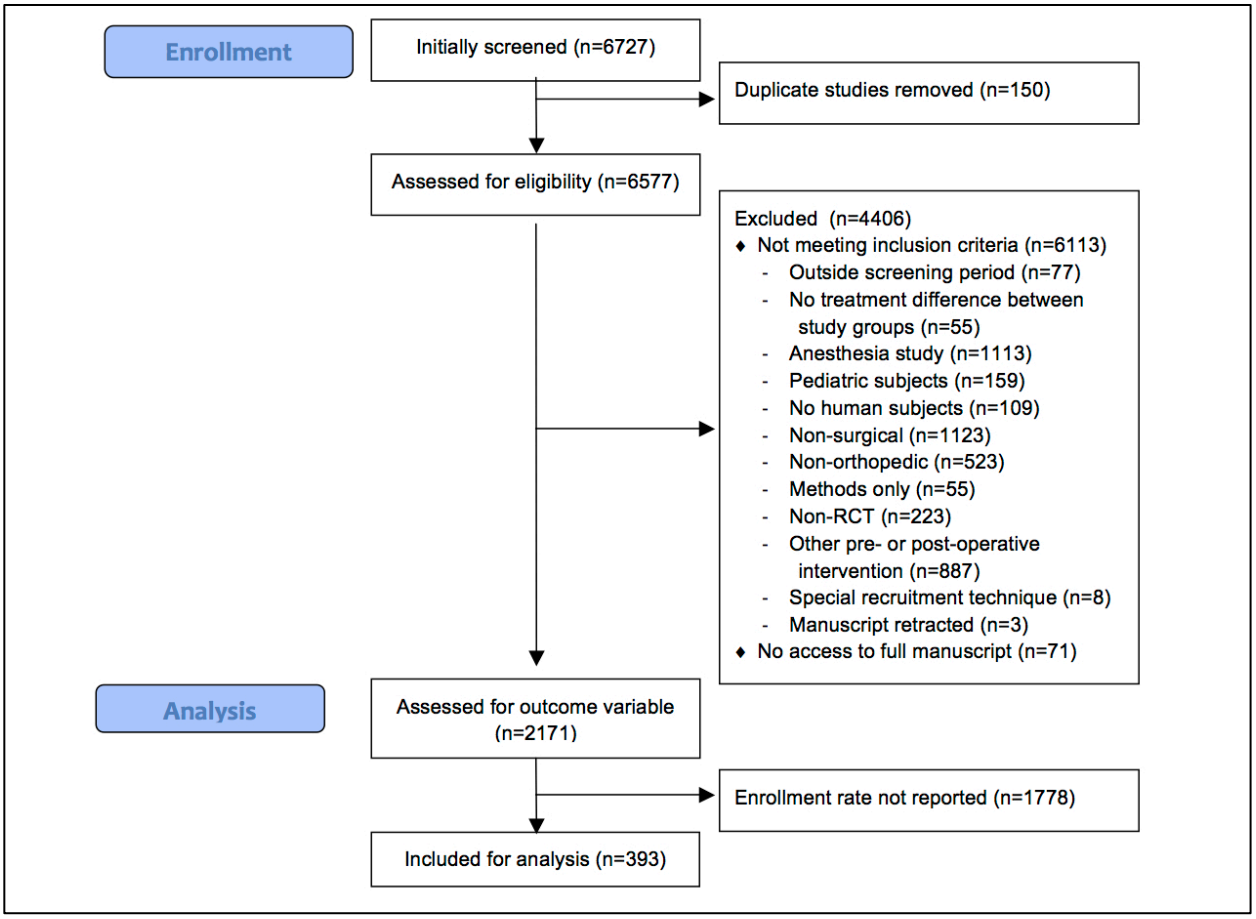

Figure 2. Proportion of included papers (i.e. meeting all inclusion criteria) to papers meeting all inclusion criteria except reporting of number of eligible subjects, by publication year (r^2=0.932, p<0.0001)

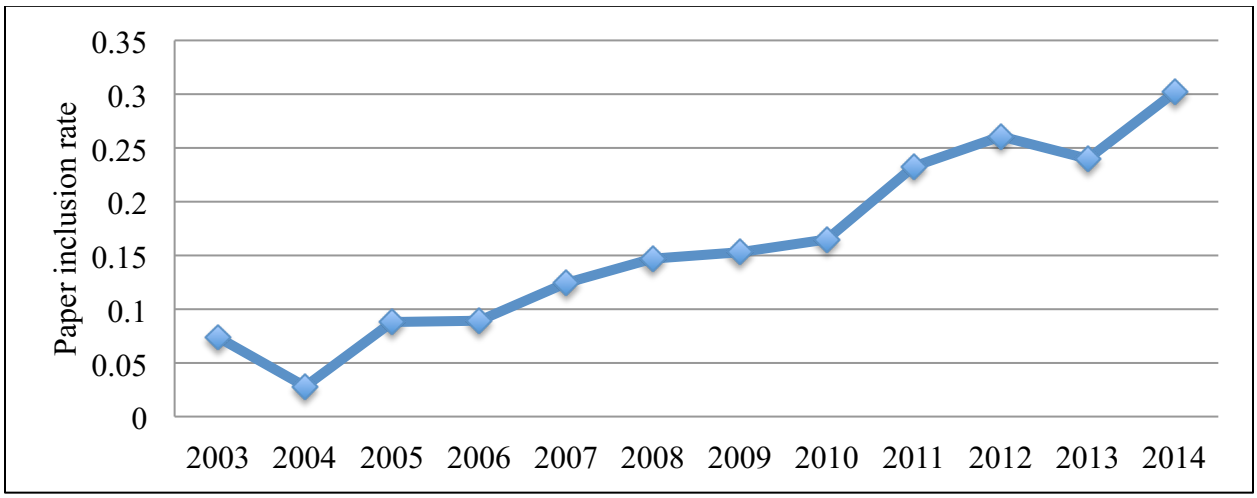

Table 1. Characteristics of included papers/trials

Paper/trial characteristics	**Number of papers/trials**
Orthopedic subspecialty	
Trauma	68
Sports	75
Reconstructive	184
Spine	42
Oncology	
Foot and ankle	6
Hand	15
Other	3
Degree of difference between interventions	
Operative vs. non-operative	54
Different procedures	50
Different approaches or techniques, same procedure	80
Same procedure with or without additional procedure	32
Different materials, same procedure	79
Different use of intraoperative technology, same procedure	32
Other	66
Inpatient only vs. outpatient follow-up	
Inpatient only	30
Outpatient follow-up	361
Not reported	2
Duration of follow-up	
1 month or less	42
>1 month, up to 3 months	43
>3 months, up to 6 months	25
>6 months, up to 12 months	115
>12 months, up to 24 months	103
>24 months, up to 36 months	12
>36 months, up to 60 months	32

>60 months	19
Not reported	2
Single-center vs. multi-center	
Single-center	309
Multi-center	80
Not reported	4
Nationality of first author's institution	
USA or Canada	83
Europe	204
Asia or Middle East	75
Australia or New Zealand	24
Mexico, Central America, or South America	4
Other	3
Funding source (Not mutually exclusive categories)	
Public funding	64
Foundation funding	61
Industry funding	71
Duration of subject enrollment	
0 to 6 months	14
7 to 12 months	40
13 to 18 months	55
19 to 24 months	61
25 to 30 months	27
31 to 36 months	38
37 to 48 months	50
48 to 60 months	25
61 to 90 months	18
>90 months	6
Not reported	59
Year of publication	
2003	7

2004	3
2005	12
2006	14
2007	18
2008	27
2009	30
2010	31
2011	50
2012	67
2013	57
2014	77

Table 2. Average trial enrollment rate (with 95% confidence interval), average screening yield (with 95% confidence interval) and number of trials by degree of intervention difference, author nationality, and number of sites

		Average enrollment rate	Average screening yield	Number of trials
Degree of difference	Surgery vs. non-surgery	73.1% (66.7-79.4%)	47.0% (39.6-54.4%)	54
	Other	86.3% (84.7-87.9%)	64.1% (61.5-66.8%)	339
Author nationality	USA and Canada	72.9% (67.6-78.1%)	46.7% (40.7-52.6%)	83
	Other	87.6% (86.2-89.0%)	65.3% (62.6-67.9%)	310
Number of sites	Single-center	86.2% (84.6-87.9%)	64.4% (61.7-67.1%)	309
	Multi-center	78.3% (73.5-83.1%)	51.0% (44.8-57.2%)	80

Table 3. 2x2 contingency table of average trial enrollment rate (with 95% confidence interval) and number of trials by degree of intervention difference and author nationality

		Nationality	
		USA and Canada	Other
Degree of difference	Surgery vs. non-surgery	47.9% (33.5-62.2%)	81.1% (76.1-86.0%)
		13 trials	40 trials
	Other	77.5% (72.6-82.4%)	88.6% (87.2-90.0%)
		70 trials	269 trials