

ORIGINAL ARTICLES

# Departures from community equipoise may lead to incorrect inference in randomized trials

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## Abstract

**Objective:** To assess the impact of selective enrollment on the results of randomized controlled trials (RCTs).

**Study Design and Setting:** We simulated an RCT of arthroscopic partial meniscectomy vs. nonoperative therapy in patients with meniscal tear and osteoarthritis (OA). We estimated efficacy with the risk ratio (RR) comparing the likelihood of clinically important improvement after surgery with that after nonoperative therapy. We assumed that efficacy differs by extent of OA. We simulated four scenarios: (1) nonselective enrollment; (2) higher likelihood of enrolling subjects with mild OA; (3) higher likelihood of enrolling subjects with severe OA; (4) much higher likelihood of enrolling subjects with severe OA. For each scenario, we simulated 100 trials with sample size 340.

**Results:** With nonselective enrollment, reflecting community equipoise, the results in 100 trials were consistent with those in the underlying population (mean RR: 1.87; 95% confidence interval [95% CI]: 1.57, 2.14). Selective enrollment of subjects with much higher likelihood of severe OA resulted in 28% lower efficacy of surgery (mean RR: 1.34; 95% CI: 0.93, 2.15), with 95% CI containing the true efficacy in just 25% of trials and empirical power of 44%.

**Conclusion:** Selective enrollment with respect to factors associated with efficacy may affect trial results and lead to inaccurate conclusions. © 2011 Elsevier Inc. All rights reserved.

**Keywords:** Equipoise; Randomized controlled trial; Meniscectomy; Selection bias; Simulation; Generalizability; Arthroscopy

## 1. Introduction

The randomized controlled trial (RCT) is widely recognized as the most rigorous method for establishing the efficacy of health care interventions. Problems may arise, however, if certain patients are reluctant to enroll in a trial, or if physicians are reluctant to recommend patients for a trial, based on specific clinical characteristics.

Clinicians' beliefs about the optimal management of individual patients may create a dilemma when clinicians enroll patients into an RCT. On the one hand, if suitably planned, the

trial's entry and exclusion criteria reflect "community equipoise"—defined as the set of circumstances in which the community of clinicians and other scientists who designed the trial are comfortable with either treatment option [1–3]. On the other hand, the individual clinician may have strong beliefs about the optimal management for a particular patient, although the patient meets eligibility criteria. In these circumstances, individual equipoise—defined as the individual clinician's comfort with both options under study—may not be congruent with community equipoise [1–5].

When a clinician investigator endorses the eligibility criteria for a trial and yet is reluctant to randomize specific patients who meet these criteria, the clinician's preferences and community equipoise come into tension. Should the standard for physician conduct in randomized trials be community equipoise (clinician offers randomization to all eligible patients) or individual equipoise (clinician only offers randomization when he or she feels comfortable recommending both options)?

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**What is new?**

**Key points**

Departures from community equipoise leading to selective enrollment in randomized trials with respect to factors associated with the efficacy of the intervention may distort trial results. Such departures from community equipoise may lead to inaccurate conclusions and incorrect inferences regarding efficacy.

What this adds to what was known?

This is the first study we are aware of to quantify the effects of departures from community equipoise on bias and power of randomized trials.

What is the implication? What should change now?

Trial investigators should take steps to prevent departures from community equipoise in trial enrollment and should quantify the extent of selective enrollment to estimate the likelihood and magnitude of selection bias.

We do not intend to resolve this ethical debate but rather to quantify what is at stake. We seek to determine whether deviations from community equipoise have implications for the findings and interpretation of randomized trials. We perform a simulation study based on a common clinical dilemma, the use of arthroscopic partial meniscectomy (APM) vs. nonoperative therapy in subjects with symptomatic meniscal tear and underlying osteoarthritis (OA). This is the focus of an ongoing RCT, the Meniscal Tear in Osteoarthritis Research (MeTeOR) Trial ([Clinicaltrials.gov](http://Clinicaltrials.gov) NCT00597012). The efficacy of surgery in this setting is uncertain [6,7]. Our specific concern is whether selective enrollment with respect to the extent of underlying OA would affect trial results. Observational cohort studies have shown that patients with more severe underlying OA tend to have more pain and functional loss than patients with less severe underlying arthritis if they are managed surgically [8]. However, patients with more severe OA also may have a worse outcome after nonoperative therapy; this question has not been examined rigorously.

We simulate several alternative enrollment scenarios ranging from community equipoise (all eligible patients enrolled) to selective enrollment with respect to knee OA severity; a factor that may be related to treatment outcomes. The question we address is whether randomization of certain subgroups of eligible patients, and failure to randomize other eligible patients, affects trial results.

**2. Methods**

*2.1. Overview*

We simulated trials of the same size as MeTeOR under alternative subject enrollment criteria reflecting selective surgeon enrollment preferences that deviate from community equipoise. The enrollment preferences are based on a clinical factor—radiographic severity of underlying OA—that, for the sake of this simulation, we assume to be associated with the efficacy of surgery. To quantify the consequences of selective enrollment, we estimated bias, empirical power, and “coverage” of 95% confidence intervals (95% CIs).

*2.2. Design of the simulated trial*

*2.2.1. Underlying assumptions*

We assumed that surgery is considerably more effective than nonoperative therapy in patients with minimal OA and symptomatic tear (improvement in Western Ontario McMaster Osteoarthritis Index [WOMAC] score of 20 points with surgery and 8 points with nonoperative therapy; Table 1), whereas surgery is just slightly more effective than nonoperative therapy in patients with moderate OA and symptomatic meniscal tear (improvement in WOMAC of three points with surgery and zero with nonoperative therapy). This reflects the clinical observation that meniscal surgery is most effective in reducing mechanical symptoms and less effective in reducing symptoms resulting from OA [8]. Whether evidence of effect modification is in fact demonstrated awaits larger trials with prespecified subgroup analyses.

*2.2.2. Details of the simulated trials*

The sample consisted of patients with OA of the knee and symptomatic meniscal tear. The extent of underlying OA was reflected in the Kellgren–Lawrence (KL) radiographic scale, which rates radiographic OA as: 0 = none; 1 = questionable osteophytes; 2 = definite osteophytes; 3 = definite joint space narrowing with loss of up to 50% of the joint space; and 4 = >50% joint space narrowing [9]. Subjects with K–L grade 4 OA were excluded from

Table 1  
Distribution of clinical characteristics based on KL radiographic grade

KL grade	0	1	2	3
Correlation between pre- and postoperative WOMAC pain score	0.5	0.5	0.5	0.4
Baseline WOMAC pain score	65	65	65	60
Improvement in WOMAC pain score for surgically treated subjects	20	15	5	3
Improvement in WOMAC pain score for nonoperatively treated subjects	8	5	3	0

*Abbreviations:* KL, Kellgren–Lawrence; WOMAC, Western Ontario McMaster Osteoarthritis Index.

WOMAC pain score has theoretical range from 0 (worst pain) and 100 (no pain).

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