Osteoarthritis and Cartilage 23 (2015) 798–802

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Review

OARSI Clinical Trials Recommendations: Design and conduct of clinical trials of surgical interventions for osteoarthritis

J.N. Katz † *, E. Losina †, L.S. Lohmander ‡ § ||

† *Department of Orthopedic Surgery and Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital and Harvard Medical School, USA*
‡ *Department of Orthopedic Surgery, Clinical Sciences Lund, Lund University, Sweden*
§ *Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Denmark*
|| *Department of Orthopedics and Traumatology, University of Southern Denmark, Denmark*

ARTICLE INFO

Article history:
Received 23 November 2014
Received in revised form
17 February 2015
Accepted 20 February 2015

Keywords:
Surgery
Randomized trial
Blinding
Sham
Cross-over

SUMMARY

To highlight methodological challenges in the design and conduct of randomized trials of surgical interventions and to propose strategies for addressing these challenges. This paper focuses on three broad areas: enrollment; intervention; and assessment including implications for analysis. For each challenge raised in the paper, we propose potential solutions. *Enrollment* poses challenges in maintaining investigator equipoise, managing conflict of interest and anticipating that patient preferences for specific treatments may reduce enrollment. *Intervention design and implementation* pose challenges relating to obsolescence, fidelity of intervention delivery, and adherence and crossover. Assessment and analysis raise questions regarding blinding and clustering of observations. This paper describes methodological problems in the design and conduct of surgical randomized trials and proposes strategies for addressing these challenges.

This paper focuses on several methodological issues that are especially important in the context of surgical randomized controlled trials. This is a broad category of trials that includes comparisons of two (or more) distinct surgical procedures (e.g., open vs arthroscopic); comparisons of distinct technical features (e.g., different types of implants or screws); comparisons of surgical vs nonoperative treatments for a given condition (e.g., arthroscopy vs physical therapy) and still others. The authors include two clinician investigators (a rheumatologist and an orthopedic surgeon) and a biostatistician. Each of us has experience in the design and conduct of surgical trials. We planned the content of this paper via email conversations and resolved any differences in opinion through iterative comments on working drafts, emails and occasional face to face discussions. We focus our recommendations around three broad aspects of surgical randomized trials: enrollment; intervention; and assessment including implications for analysis.

Enrollment

This section focuses on three related issues: investigator equipoise; conflict of interest; and patient preference.

Investigator equipoise

As the term suggests, 'equipoise' refers to indifference (or equal position) between two alternatives. In the context of an RCT, equipoise refers to acceptance by members of the research team that each of the arms under study offers a reasonable treatment[1–3]. This is especially important for research team members engaged in enrolling patients. If the enrolling investigator believes that one of the treatments under study is superior, he or she may subtly steer eligible patients away from enrollment in the trial and toward that treatment[4,5]. There is no straightforward way to estimate and remedy biases in enrollment that may arise because investigators lack equipoise[6,7].

* Address correspondence and reprint requests to: J.N. Katz, Orthopedic and Arthritis Center for Outcomes Research, Brigham and Women's Hospital, 75 Francis Street, Boston, MA, 02115, USA.
E-mail address: jnkatz@partners.org (J.N. Katz).

http://dx.doi.org/10.1016/j.joca.2015.02.024
1063-4584/

Table I
Challenges arising in surgical randomized trials and suggested approaches

Challenge	Description	Potential approaches
Investigator equipoise	Surgeon investigator may believe one treatment is superior, leading to selective enrollment and potential bias.	- Standardized enrollment scripts delivered by research staff, not the treating surgeon. - Screen potential surgical investigators carefully - Role-playing to help investigators present the trial in an unbiased fashion. - Monitoring to detect biased enrollment.
Patient preference	Patients must assess their preferences for surgical vs nonoperative therapy to ascertain whether they are indifferent to the options under study.	- Standardized enrollment script delivered by unbiased research staff. - Media presentations (e.g., DVDs) providing unbiased, standardized information on risks and benefits in each arm.
Intervention obsolescence	The interventions under study may already be obsolete by the time the study is reported.	- Choose fundamental principles as study questions rather than very specific technologies.
Intervention fidelity	The surgical intervention must be delivered in a standard fashion, despite inherent variability in the procedure depending on surgical findings.	- Meetings among surgical investigators prior to study launch to establish protocol for intraoperative decision points. - Ensure that all surgeons are experienced with the interventions under study to avoid learning curve effects.
Crossover and adherence	Subjects may cross over from nonoperative to surgical therapy and may choose not to undergo the assigned surgery; these phenomena make interpretation of the intention-to-treat analyses challenging.	- Explain clearly to subjects and investigators that subjects should adhere to assigned treatment at least until the first assessment. - Capture reasons for crossover when they occur. - Specify secondary analyses *a priori* that include crossover as failures.
Blinding and controls	Mounting evidence points to the potency of the surgical placebo effect, creating a rationale for sham interventions. Sham procedures present ethical, logistical and interpretative challenges.	- Research funding bodies must be persuaded that sham procedures are worth paying for, as many insurers will refuse to do so. - Investigators should consider an additional 'no treatment' group to quantify the sham effect. - Research is needed to harness sham effects at lowest possible cost and risk.

There are practical and conceptual consequences of departure from investigator equipoise. If investigators surgeons choose not to present the trial to certain eligible patients, because they feel these patients would benefit more with one treatment than the other, the selective enrollment can introduce bias. This is especially problematic if it turns out that particular subgroups of subjects have a higher likelihood of successful outcome if they receive one treatment than if they receive the comparator[5]. For example, if an investigator selectively enrolls patients with more severe symptoms, and if treatment A turns out to be more efficacious than treatment B in those with more severe symptoms than it is in those with less severe symptoms, then treatment A may have spuriously favorable results.

Several approaches have been developed to address the need for the research team to maintain equipoise. Perhaps the most important is that the trial should be presented to the potential subject by a member of the research team who is not involved in the patient's care. While clinicians may identify potentially eligible patients in their practices, they should refer these patients to members of the research staff who present the trial in a standardized, neutral fashion. These presentations should follow scripts developed by the research team to convey the treatment arms neutrally. Members of the research team who present the study to patients can engage in role-playing prior to launching the trial in order to gain comfort with presenting the treatment arms in an unbiased fashion. Finally, as the trial progresses the research team can assess patterns of enrollment to discern whether particular investigators are referring selectively. The PI and team can try to work with such investigators and, if that is not effective, can resort to replacing the investigators with others better able to approach enrollment with equipoise (Table I).

Conflicts of interest

Commercial bias and conflict of interest are additional reasons for the erosion of equipoise in RCTs[8]. Investigators who stand to benefit financially if the treatment under study is successful may be especially likely to steer toward the trial those patients whom they suspect will benefit from that treatment and less likely to refer to the trial those patients who they suspect may not benefit from the treatment[9–13]. In these circumstances, it is particularly critical for the trial to be presented to potential subjects by dispassionate research staff using standardized scripts. Clinician-investigators with a financial interest in one of the treatments under study should not participate as investigators in trials that assess the efficacy of that treatment.

Patient preference

Patients with a strong preference for one treatment typically decline enrollment in a trial of that treatment, knowing that they have just a 50% chance of receiving their treatment of choice (assuming a two-arm trial). If such patients enroll in trials they may be less likely to adhere if they are assigned to the comparator arm[14]. Thus, it is important to provide patients with detailed, comprehensible information on short- and long-term benefits of each treatment under study so that they can determine whether they have a preference for one of the treatments. Several groups of investigators have used videotaped presentations of the options, presented in a neutral fashion that highlights the benefits and drawbacks of each intervention[15–19]. These programs permit potential subjects to learn about risks, benefits and alternatives in their own homes, providing them with an opportunity to develop preferences that are informed by the best evidence in the field. Investigators should be careful not to describe the treatment arms in a way that subtly fosters a preference for one treatment over the other. For example, the term 'watchful waiting' may suggest to patients a weak treatment, whereas the term 'active, individualized monitoring,' used to describe the same regimen, may seem more appealing.

Enrollment in surgical trials is often slower than the investigators anticipate. This observation underscores the importance of performing a pilot recruitment so that the research team can appreciate the number of patients that will need to be approached to yield the desired sample. Recruitment in multiple centers adds complexity but may permit enrollment goals to be