

Clinical Equipoise and the Surgical Randomized Controlled Trial

It is generally agreed that randomized controlled trials (RCTs) are the “gold standard” for determining whether one intervention is better than an alternative, yet surgical RCTs are relatively infrequent. It is estimated that less than 1% of published papers in leading neurosurgical journals are RCTs (*J Neurosurg* 103:439–443, 2005). Perhaps we should ask: why are so few RCTs mounted? And why do so many RCTs fail to reach a satisfactory conclusion?

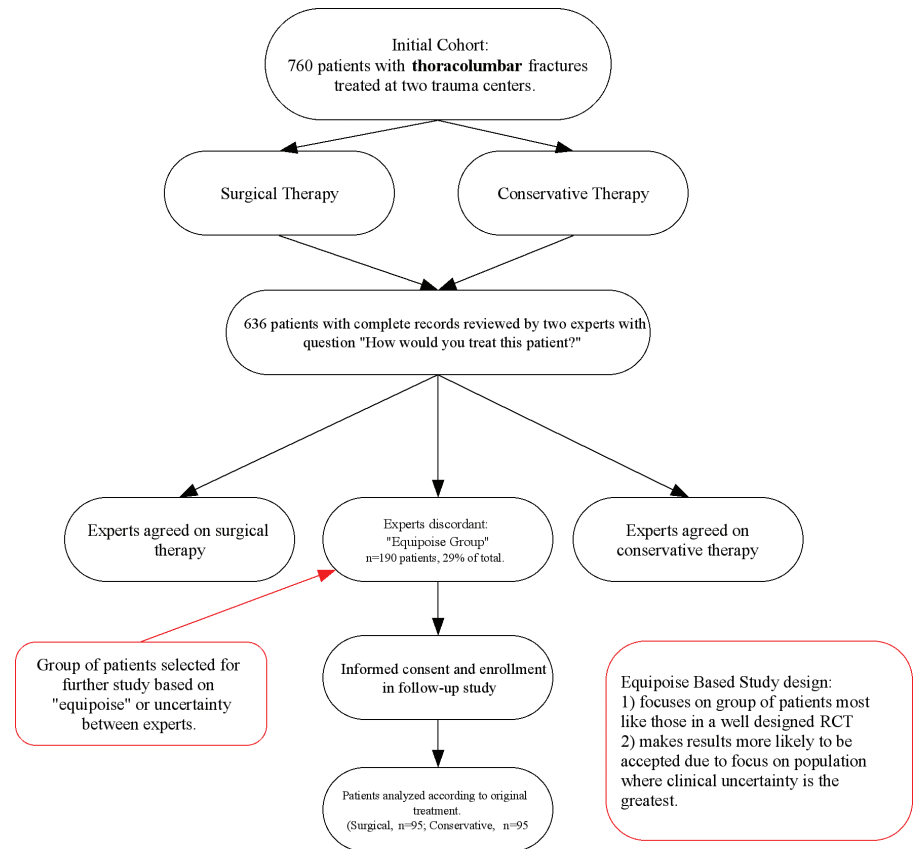
There are many barriers to performing high-quality RCTs in surgery. RCTs require a complex organization involving numerous personnel at multiple centers and specialists in data management and analysis. They must meet the requirements of multiple regulatory investigational review boards. Once designed and organized, they must be funded, and multicenter trials typically cost millions of dollars. Finally, once funded, accrual can be a significant challenge (e.g., the National Institute of Neurological Disorders and Stroke-funded Carotid Occlusion Surgery Study trial). One of the major factors limiting patient accrual in many studies is the lack of sufficient *equipoise* on the part of both the treating clinician as well as the patient.

What is clinical equipoise? This term, introduced by Freedman in a classic 1987 paper (*N Engl J Med* 317:141–145, 1987), means “genuine uncertainty within the expert medical community” on the optimal approach for a certain medical condition. A necessary condition for an RCT to be ethical and feasible is clinical equipoise between the treatment arms of any trial.

Lack of equipoise affected the National Institutes of Health-sponsored SPORT trial (*JAMA* 296: 2441–2450, 2006), an RCT that compared surgery versus conservative management for symptomatic lumbar disc herniation. Few practicing spinal surgeons are uncertain whether surgery relieves painful lumbar radiculopathy when conservative management has failed (*Neurosurgery* 60:N6–N7, 2007). The high crossover rate (30% from the nonoperative cohort to the operative cohort within 3 mo) was a telling indication that clinicians, patients, or both wanted surgical relief and limited the ability of the study to detect better outcomes from surgery. In retrospect, randomization of such patients to either surgery or further conservative care was not adequately justified.

An understanding of equipoise is vital in designing clinically meaningful trials. Two recent articles show how we may use equipoise to better define target populations for clinical outcomes studies. Stadhouders et al. (*Spine J* [in press]) from the University Medical Center in Utrecht discuss the use of surgeon equipoise in comparing two prospectively applied treatment algorithms for thoracolumbar fractures.

The heterogeneity of thoracolumbar fractures is cited as a major barrier to performing an RCT and



Use of equipoise as an inclusion criterion for a prospective follow-up study of thoracolumbar fractures. Adapted from *Spine J* [in press].

in interpreting the results of published prospective trials. To address this problem, the authors used a unique observational study design based on equipoise (Fig. 1). The authors submitted the records of 636 patients with complete records (treated from 1991 to 2005 at two trauma centers) to retrospective review by two spinal experts (one orthopedic surgeon from each of the two hospitals). For 190 patients (29%), there was disagreement as to the optimal treatment strategy, operative versus conservative. Among these 190 patients, baseline clinical characteristics were similar between those who went on to have either operative or conservative treatment. This approach is potentially valuable in two ways. First, it identifies the proportion of patients (~25% in this study) who may be eligible for an RCT. Second, it suggests that it may be possible to compare the outcomes of surgical versus nonsurgical treatment for a complex problem short of conducting an RCT. The concept here is that a comparative analysis of this more select cohort for which true equipoise exists may be more valid (and

later accepted by practicing physicians) than an outcome study of the larger, unselected cohort.

Although the majority of patients were neurologically intact on admission (American Spinal Injury Association Scale E), there was a greater percentage of patients with more significant spinal cord injuries in the operative group, highlighting the fact that this approach does not fully equalize the distribution of known and unknown prognostic factors in the way the RCT randomization process does. However, the authors found that the use of equipoise as an inclusion criterion greatly limited the unbalanced distribution of prognostic variables, focusing the clinical question on the patient population in whom most of the clinical uncertainty lies and most like the population one would find in a well-designed RCT. This type of approach may become a promising technique for evaluating spinal outcomes without having to perform RCTs.

Cervical spondylotic myelopathy (CSM) is another heterogeneous disorder whose treatment challenges spinal surgeons. Here, the dilemma is not surgery



A typical patient with CSM for whom there is clinical equipoise between ventral and dorsal surgical approaches is shown. This patient is eligible for an RCT.

Clinical Equipoise Case

- 57 year-old female
- Myelopathy
- 3 levels of cord compression

What Operative Approach*?

- Ventral 50%
- Dorsal 35%
- Both 15%

*Cervical Spine Research Society Survey Respondents

versus no surgery, but the type of surgical approach, i.e., front versus back. Ghogawala et al. (*Spine* 32:429-436, 2007) presented brief clinical and radiological vignettes on 20 consecutively treated patients with CSM who underwent surgery for review by attendees at the Cervical Spine Research Society Annual Meeting. Two-thirds of the surgeon respondents were orthopedic surgeons and one-third were neurosurgeons. Eligibility for randomization ranged from 23% to 78% for individual patients. In *Figure 2*, a typical patient with CSM (eligible for randomization) is shown. Investigators defined specific objective factors (e.g., segmental kyphotic deformity) that would classify a patient as being ineligible for randomization, as a critical step in designing an RCT comparing ventral and dorsal sur-

gery. With the use of these criteria, most patients (12 of 20) were judged to be eligible for randomization. Orthopedic and neurological surgeons reached similar conclusions about eligibility for randomization.

In summary, this work suggests that a scientific survey of experts may be helpful for complex heterogeneous spinal problems to determine for which patients clinical equipoise exists. This particular study demonstrated that greater than 50% of patients with CSM from a general spine practice might be eligible for randomization. It further suggested that objective eligibility criteria for an RCT could be derived scientifically by making clinical equipoise the central focus.

Many clinical dilemmas in neurosurgery (e.g., clip versus coil, gamma knife versus open surgery, and fusion versus no fusion) are, at first, daunting from the perspective of designing effective clinical trials. However, the systematic determination of equipoise for specific cohorts of patients within heterogeneous groups is a promising strategy for future trials and may identify the most relevant questions, which are also most amenable to RCTs.

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Increasing Health Care Expenditures on Back and Neck Problems

Neck and back symptoms are among the most common chief complaints and reasons for outpatient primary care office visits in the United States. The past decade has seen an increase in the consumption of health care resources for these complaints, including a proliferation in the use of imaging, medications, physical therapy, chiropractic modalities, and surgery for these patients. A recent paper published in *JAMA* (299:656-664, 2008) examined the national trends for health care spending and the health status of adults with neck and back problems.

The investigators, including Richard Deyo from the University of Washington, examined the health care expenditures in the United States related to back and neck problems yearly from 1997 to 2005 using the nationally representative Medical Expenditure Panel Survey. The Medical Expenditure Panel Survey is a sex- and age-matched household survey of greater than 20,000 persons annually that is considered a comprehensive source of data for estimates of United States health care utilization and spending. Data from this survey were used to estimate trends of expenditures in patients with neck and back problems. The study in *JAMA* found that, in 1997, the mean age- and sex-adjusted medical costs for persons with spine complaints were \$4695 compared with \$2557 for those without spine complaints (infla-



tion adjusted to 2005 dollars). In 2005, expenditures increased to \$6096 and \$3516, respectively. This is a 65% increase in inflation-adjusted national spending on patients with spine problems between 1997 and 2005. In addition, spending in this category is rising more rapidly than overall health care expenditures. The greatest differences in expenditures between those with and without spine problems were in outpatient services, which accounted for the largest proportion of total cost, followed by inpatient services, and, finally, by prescription medications, which increased 188% over the period examined. The prescription medication expenditures increased greatly after 2003 when the use of cyclooxygenase 2 inhibitors declined and there was a dramatic increase in spending on

narcotic analgesics (423%). From the Medical Expenditure Panel Survey data, the investigators calculated the 2005 national expenditure on spine complaints to be 85.9 billion, second only to stroke and heart disease and equivalent to diabetes. Investigators also examined the overall health status of patients with spine complaints between 1997 and 2005 and found that despite rising spending on spine-related problems, the overall health and functional capacity of this population did not improve.

The authors of this study concluded that from 1997 to 2005 there was a significant increase in spending on spine problems without associated improvement in self-assessed health or functional status. Therefore, they also concluded that this area may offer opportunities to reduce medical expenditures without associated worsening of clinical outcomes. Because of the prevalence and rising medical expense of persons with neck and back complaints as well as the aging population of the United States, this issue will probably continue to be at the forefront of the medical spending debate and possible discussions for reform.

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