

PRACTICAL TIPS FOR SURGICAL RESEARCH

Ethical issues in surgical research

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One may question the moral or ethical right to continue with casual or unplanned new surgical procedures — procedures which may encompass no more than a placebo effect — when these procedures are costly of time and money, and dangerous to health or life.

Harry Beecher 1961¹

INTRODUCTION

Although codes of ethics date back millennia to the Hippocratic Oath and the Prayer of Maimonides, modern medical ethics, especially as it relates to research involving humans, began with the Nuremberg Code, a series of principles articulated by jurists at the trial of Nazi physicians responsible for atrocities against prisoners during the Second World War. The core principles of the 10-point Nuremberg Code include voluntary informed consent, lack of coercion, properly formulated experiments and beneficence toward participants.² The Nuremberg Code has been largely superseded by the World Medical Association's Declaration of Helsinki,³ last revised in 2008. Western biomedical ethics, including research ethics, are guided by 4 over-reaching principles:

1. Respect for autonomy: the human capacity and the right to self-determination and decision making.
2. Nonmaleficence: avoiding the causation of harm or *primum non nocere*.
3. Beneficence: acting in a way that benefits the patient after balancing the potential risks and harms.
4. Justice: treating patients in similar positions in a similar manner by distributing risks and costs fairly.⁴

The need for surgical research is not in doubt. Well-designed research studies have led to the near disappearance of previously common surgical procedures such as extracranial–intracranial bypass for stroke prevention,⁵ internal mammary artery ligation for heart disease⁶ and, to some extent, arthroscopy for osteoarthritis of the knee.⁷ Conversely, surgical research has led to the continued widespread use of some procedures whose efficacy had been questioned, such as carotid endarterectomy for symptomatic carotid stenosis.⁸

There is a perception, however, that surgical procedures, both well-established and novel, are held to a less-rigorous standard than are medical treatments,⁹ both ethically and methodologically, resulting in procedures being “smuggled” into practice without proper review.¹⁰ As the need for more rigorous evaluation of surgical research is recognized, so too is the need for proper application of ethical principles and oversight to that research.

In the following sections, we provide a brief review of some of the more pressing ethical issues encountered in surgical research. Although not meant to be a comprehensive review, this will hopefully act as a starting point for awareness and further discussion of ethical issues in surgical research. By the end of this article, the reader will appreciate the significance of ethics in conducting research involving surgical patients.

PRINCIPLES OF ETHICAL CLINICAL RESEARCH

Emanuel and colleagues¹¹ have proposed 7 requirements for the ethical conduct of research involving humans. Although not specific to surgery, these requirements are considered necessary for research involving humans:

1. The research must have value; that is, it must have the potential to enhance health or knowledge.
2. It must have sufficient methodologic rigor to make the results of the research scientifically valid.
3. Research participants should be selected in a way such that the risks of participation in research studies and the potential benefits of the knowledge gained from the research are distributed fairly among groups.
4. The potential benefit of the research results to society outweigh the risks, and risks to the individual are minimized.
5. The research is reviewed and approved by an independent body.
6. Consent is informed and voluntary and can be withdrawn at any time.
7. The privacy of participants is protected and their well being is monitored.

CLINICAL EQUIPOISE

The gold standard for clinical research remains the randomized clinical trial (RCT). With the call for more methodologically rigorous evaluation of both novel and well-established surgical procedures and their outcomes also comes a call for more RCTs in surgical research.⁹ A surgical RCT may compare 2 different surgical procedures or it may compare surgery with nonsurgical management or with the natural history of the illness being studied. For a surgeon–researcher to enroll patients in an RCT, it is widely accepted that a state of “clinical equipoise” must exist.

Freedman coined the term clinical equipoise as a state where “there is no consensus within the expert clinical community about the comparative merits of the alternatives to be tested” with “honest professional disagreement among ... clinicians.”¹² If such a state exists, a clinical trial is considered ethical, provided it is designed to “disturb” equipoise; that is, it is designed to provide an answer as to which arm of the study is better. The key to Freedman’s concept of clinical equipoise, as opposed to an individual clinician’s uncertainty regarding the superiority of one intervention over another (also known as the “uncertainty principle”),¹³ is that it allows an individual clinician–researcher to have a preference or opinion as to which intervention they believe to be superior and still enroll patients in a clinical trial, provided they “recognize that their less-favoured treatment is preferred by colleagues whom they consider to be responsible and competent.”¹²

WHAT IS SURGICAL RESEARCH?

Beecher’s concerns about the premature introduction of

novel surgical procedures¹ quoted at the start of this paper highlight an ongoing and as yet unresolved controversy regarding the proper way to evaluate novel surgical procedures and ensure adequate oversight of surgical research. The question of when variations in surgical practice or evaluation of outcomes become research and, as such, become subject to the rigors of evaluation by a research ethics board (REB) is not always answered easily. Unlike novel medications, which are subject to Health Canada and US Food and Drug Administration regulations, new surgical procedures have no such agency review before their widespread adaptation into practice. This has raised concerns that “nonvalidated surgical procedures are being smuggled past RCTs and [REBs], our societal checkpoints for innovations.”¹⁰ There is a perception that surgeons seek to “have it both ways: to experiment with innovative surgical procedures within the framework of clinical care and without [REB] oversight at the same time as publishing research ... in professional journals.”¹⁴ Unfortunately, the Canadian standard for human research, the Tri-Council Policy Statement (TCPS) on Ethical Conduct for Research Involving Humans¹⁵ provides no specific guidelines for surgical research. The TCPS states that all research involving humans, as well as research involving human remains, cadavers, tissues, biological fluids, embryos or fetuses requires REB review and approval. The TCPS does not specifically define what constitutes research.

Bernstein and Bampoe¹⁶ have recommended that REB approval should be sought for all procedures performed in the context of an RCT, for novel procedures scheduled to be performed electively and for major modifications of accepted surgical procedures. Whereas it is often difficult to determine when innovative surgical treatment becomes research, “that boundary is certainly crossed once a report is presented at a scientific meeting, or submitted for scientific review.”¹⁷ At this point, all further study should be done in the context of a well-defined research protocol, with particular attention to the informed consent process and submission to local REBs.

Much of what is published in surgical journals involves retrospective case reviews or data culled from prospective databases. Most contend,^{14,18-20} and we agree, that wherever possible, protocols for such research should be submitted to local REBs. For prospective databases whose sole goal is research publication, efforts should be made to obtain informed consent from patients before enrolment in the database. If there is confusion as to whether a particular activity requires REB approval, we recommend consulting the local REB, because requirements may vary in different jurisdictions. Indeed, a recent study of the requirement for ethical review in human research found that 83% of medical journals required independent ethics committee approval, with most of those requiring disclosure of that approval within the paper.²¹ Ten years earlier, only 47% of those journals required ethical review.²²

Evidence suggests that ethical process for research published in some surgical journals is high for prospective

studies (up to 92% are reviewed by an REB) but relatively low for retrospective studies (only 30% are reviewed by an REB).²³ Reitsma and Moreno²⁴ found that only 28% of authors publishing results of innovative surgical procedures in 2000–2001 had submitted their protocol to an REB.

A more difficult question to answer is the following: When is further research no longer required; that is, what constitutes sufficient evidence of the efficacy of a surgical intervention? It is one of the ironies of the evidence-based medicine paradigm that, in the end, a majority of expert opinion is still required before a question regarding the efficacy of a surgical procedure is considered “solved,” regardless of whether it has been studied in an RCT.²⁵ In essence, this is when clinical equipoise no longer exists. Pin-pointing when this occurs (clinically and even statistically) is difficult and is often only recognized in retrospect.²⁶

CONFLICTS OF INTEREST

A recent article in the *New York Times*²⁷ identified that doctors in half of the centres enrolling patients in a trial of artificial intervertebral discs stood to financially benefit if the results of the study favoured the new device, highlighting the importance of both perceived and real conflicts of interest (COI) for surgical researchers. A COI is defined as “a set of conditions in which professional judgment concerning a primary interest (such as a patient’s welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain).”²⁸ As the role of industry in the funding of surgical research increases, so too does the potential for COI. Many surgeon–researchers receive support from industry, ranging from unrestricted research grants, to consultant fees or direct financial interest in a company such as royalties, stock options and significant stock or private ownership interests.²⁹ A study of self-reported COIs by presenters at the annual meeting of the American Academy of Orthopaedic Surgeons showed an increase in the incidence of COIs from 10% in 1985 to 32% in 2002.²⁹

Conflicts were highest among those presenting at symposia (74%). Associations have also been found between the presentation of positive findings and those receiving royalties, stock options or consulting fees.³⁰

To maintain public and professional belief in the integrity of surgical research, it is important that all possible attempts are made to ensure that these COIs do not play any role in the results of such research. Policies governing financial conflicts vary,³¹ ranging from complete prohibition of certain financial arrangements, monetary limits and, at a minimum, disclosure. Most large scientific meetings have guidelines for self-disclosure, and almost all major surgical journals require that financial conflicts be disclosed.

Although not universal, both REBs and biomedical journals are increasingly requiring disclosure of potential COIs among researchers; 48% of all REBs in academic medical centres in the United States required disclosure of financial COIs by researchers to potential research participants.³² Similarly, in a survey of editors of biomedical journals, 77% collect information on COIs on all author submissions.³³ We suspect that this trend will increase in the coming years. The TCPS¹⁵ compels an REB to require a researcher to disclose a COI to prospective participants as part of the informed consent process.

It remains to be seen whether these voluntary measures will be enough to maintain public trust in surgical research.

SHAM SURGERY

Recent RCTs for surgical procedures to treat Parkinson disease³⁴ and knee osteoarthritis⁷ have used a placebo or sham arm in an attempt to account for a possible placebo effect of surgery. The authors of these studies, as well as the REBs that approved them, felt that the potential bias of the placebo effect would invalidate the study results if a sham arm was not used. Advocates for placebo surgery argue that its use is ethically justified provided that the risks are minimized, informed consent of participants is obtained, the potential for bias from the placebo effects of surgery is significant and there is no suitable methodological alternatives to the use of a sham arm in the trial.^{35,36}

Opponents of sham surgery arms in RCTs³⁷ raise concerns because of the risks involved in sham procedures, with no hope for benefit. Other concerns include the potential for “therapeutic misconception” among participants (in this case, the belief among study participants that they will receive active treatment, even when told they may not), overstatement of the placebo effect and, perhaps most importantly, the active deception of the patient by the surgeon that is required when using a sham surgery arm.

The ethics of the use of placebo arms in clinical trials, whether they involve novel drugs or surgical procedures, remains controversial. Although not making specific reference to sham surgery, the TCPS considers the use of placebo controls unacceptable when a standard treatment

Box 1. Tips for ethical considerations in surgical research

- Surgical research should meet the 7 requirements for ethical research as set out by Emanuel and colleagues:¹¹
 1. social or scientific value
 2. scientific validity
 3. fair participant selection
 4. favourable risk-benefit ration
 5. independent review
 6. informed consent
 7. respect for potential and enrolled participants
- The line between regular clinical practice, innovation and surgical research is often difficult to draw. When in doubt, consult your local research ethics board.
- A state of “clinical equipoise” must exist for surgical RCTs to proceed.
- Conflicts of interest by researchers should be disclosed.
- The need for and ethics of sham surgery arms in clinical trials remains controversial. Further debate of this issue and its importance in surgical research is necessary.

RCT = randomized controlled trial.

is available. The use of a placebo as the control arm of a study is allowed under the following circumstances:

- There is no standard treatment, or standard treatment has been shown to be no better than placebo.
- New evidence has given rise to doubt regarding the benefits of standard therapy.
- Effective treatment is not available because of cost or short supply.
- The patient population is refractory to standard treatment.
- An add-on treatment is being compared to standard therapy.
- Patients provide informed refusal of standard therapy for a minor condition (such as the common cold).¹⁵

A final consensus about the ethics of placebo or sham surgery has not yet been achieved, and further debate of this issue, which is of critical importance to surgical researchers, is necessary.

CONCLUSION

Calls for more methodological rigor in surgical research are paralleled by the need for an increasing awareness of ethical issues in surgical research. Useful tips for surgical researchers are provided in Box 1. We have introduced some of the common ethical debates encountered in surgical research in the hopes of creating a springboard for further debate and discussion.

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References

1. Beecher HK. Surgery as placebo. A quantitative study of bias. *JAMA* 1961;176:1102-7.
2. Annas G, Grodin M, editors. *The Nazi doctors and the Nuremberg Codes: human rights in human experimentation*. New York (NY): Oxford University Press; 1995.
3. *World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects*. Available: www.wma.net/en/30publications/10policies/b3/index.html (accessed 2010 Jan. 26).
4. Beauchamp T, Childress J. *Principles of biomedical ethics*. New York (NY): Oxford University Press; 2001.
5. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. The EC/IC Bypass Study Group. *N Engl J Med* 1985;313:1191-200.
6. Cobb LA, Thomas GI, Dillard DH, et al. An evaluation of internal-mammary-artery ligation by a double-blind technic. *N Engl J Med* 1959;260:1115-8.
7. Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 2002;347:81-8.
8. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* 1991;325:445-53.
9. Solomon MJ, McLeod RS. Should we be performing more randomized controlled trials evaluating surgical operations? *Surgery* 1995;118:459-67.
10. McKneally MF. Ethical problems in surgery: innovation leading to unforeseen complications. *World J Surg* 1999;23:786-8.
11. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA* 2000;283:2701-11.
12. Freedman B. Equipoise and the ethics of clinical research. *N Engl J*

- Med* 1987;317:141-5.
13. Weijer C, Shapiro SH, Cranley Glass K. For and against: clinical equipoise and not the uncertainty principle is the moral underpinning of the randomised controlled trial. *BMJ* 2000;321:756-8.
14. Miller FG. Ethical issues in surgical research. *Thorac Surg Clin* 2005; 15:543-54.
15. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada. *Tri-Council Policy Statement: ethical conduct for research involving humans*. Ottawa (ON); 1998 (with 2000, 2002 and 2005 amendments). Available: <http://pre.ethics.gc.ca/eng/policy-politique/tcps-epct/> (accessed 2010 Jan. 23).
16. Bernstein M, Bampoe J. Surgical innovation or surgical evolution: an ethical and practical guide to handling novel neurosurgical procedures. *J Neurosurg* 2004;100:2-7.
17. Margo CE. When is surgery research? Towards an operational definition of human research. *J Med Ethics* 2001;27:40-3.
18. Burger I, Sugarman J, Goodman SN. Ethical issues in evidence-based surgery. *Surg Clin North Am* 2006;86:151-68.
19. Rohrich RJ. Ethical approval of clinical studies, informed consent, and the Declaration of Helsinki: what you need to know. *Plast Reconstr Surg* 2007;119:2307-9.
20. Stirrat GM. Ethics and evidence based surgery. *J Med Ethics* 2004; 30:160-5.
21. Freeman SR, Lundahl K, Schilling LM, et al. Human research review committee requirements in medical journals. *Clin Invest Med* 2008; 31:E49-54.
22. Amdur RJ, Biddle C. Institutional review board approval and publication of human research results. *JAMA* 1997;277:909-14.
23. Block MI, Khitin LM, Sade RM. Ethical process in human research published in thoracic surgery journals. *Ann Thorac Surg* 2006;82:6-11, discussion 11-2.
24. Reitsma AM, Moreno JD. Ethical regulations for innovative surgery: The last frontier? *J Am Coll Surg* 2002;194:792-801.
25. Kulkarni AV. The challenges of evidence-based medicine: a philosophical perspective. *Med Health Care Philos* 2005;8:255-60.
26. Wetterslev J, Thorlund K, Brok J, et al. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol* 2008;61:64-75.
27. Abelson R. Financial ties are cited as issue in spine study. *The New York Times* 2008 Jan. 30; Sect A:1. Available: www.nytimes.com/2008/01/30/business/30spine.html (accessed 2010 Jan. 23).
28. Thompson DF. Understanding financial conflicts of interest. *N Engl J Med* 1993;329:573-6.
29. Zuckerman JD, Prasarn N, Kubiak EN, et al. Conflict of interest in orthopaedic research. *J Bone Joint Surg Am* 2004;86-A:423-8.
30. Okike K, Kocher MS, Mehlman CT, et al. Conflict of interest in orthopaedic research. An association between findings and funding in scientific presentations. *J Bone Joint Surg Am* 2007;89:608-13.
31. Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA* 2003; 289:454-65.
32. Weinfurt KP, Dinan MA, Allsbrook JS, et al. Policies of academic medical centers for disclosing financial conflicts of interest to potential research participants. *Acad Med* 2006;81:113-8.
33. Cooper RJ, Gupta M, Wilkes MS, et al. Conflict of interest disclosure policies and practices in peer-reviewed biomedical journals. *J Gen Intern Med* 2006;21:1248-52.
34. Freed CR, Greene PE, Breeze RE, et al. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. *N Engl J Med* 2001; 344:710-9.
35. Miller FG. Sham surgery: an ethical analysis. *Am J Bioeth* 2003;3:41-8.
36. Horng S, Miller FG. Ethical framework for the use of sham procedures in clinical trials. *Crit Care Med* 2003;31(Suppl):S126-30.
37. Macklin R. The ethical problems with sham surgery in clinical research. *N Engl J Med* 1999;341:992-6.