

Assessing the bioethical integrity of a clinical trial in surgery

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A recent article by Thoma and colleagues in the June 2004 *Canadian Journal of Surgery* (volume 47, pages 200–208) nicely takes readers through the process of assessing the value of a randomized clinical trial (RCT) in surgery.¹ These steps are based on the invaluable work of the Evidence-Based Medicine Working Group (EBMWG).² Considerable effort has also gone into standardizing reportage of RCTs.³

Thoma's article has 35 references, of which 2 touch on ethical aspects of clinical research. This same discordance in attention between the scientific and ethical dimensions of clinical research is reflected in the emphases of EBMWG and CONSORT, the Consolidated Standards of Reporting Trials Group.^{2,3} Ethical issues are nonetheless assuming greater prominence in the conduct and interpretation of clinical research.

Although most researchers are virtuous and well-meaning, it is easy to transgress proper ethical boundaries, just as it is easy for a surgeon untrained in trial design to transgress proper methodology. Some ethical dimensions are extremely obvious by common sense, common practice, or common law, such as the need to submit an RCT to one's institutional research ethics board (REB). Others

are subtle and nuanced, such as the nonfinancial conflicts of interest experienced by clinical investigators.

Most of the literature on ethical conduct of research is commentary or theoretical analysis. Although a few papers have attempted to formulate usable frameworks,^{4,5} only 1 was written by a surgeon.⁴ Herein is offered a

simple, practical, and surgically oriented framework for assessing the bioethical integrity of clinical research (Box 1).

1. Was REB approval obtained?

When a hypothesis is to be tested in a surgical trial, most investigators

Box 1. Framework for assessing the bioethical integrity of a surgical clinical trial

1. Was Research Ethics Board approval obtained?
2. Did all patients give well-informed consent?
3. Were eligibility criteria for entry into the study fair and appropriate?
4. Was the harm-to-benefit ratio favourable to the patients who entered the study?
5. How were patients who demanded the experimental therapy off-study handled?
6. Was the study placebo-controlled? If so, was the placebo ethical?
7. Was the effect sought clinically meaningful, or just statistically significant?
8. Were there any conflicts of interest for the study investigators?
9. Were patients who entered the study paid? If so, was it ethical?
10. Did all coauthors' contributions justify authorship?

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know very well that submitting a protocol to the institutional REB is absolutely required. The REB's job is to make sure the research is ethically sound and to suggest ways to improve it, such as simplifying its consent forms.⁶ Most protocols are improved by REB scrutiny, but these boards, it should be pointed out, are often understaffed and overworked, and vulnerable to criticism over how well or poorly they fulfill their mandates.^{6,7} It is not unfair to say that anxiety is growing among investigators about how fairly and promptly their clinical protocol will be assessed.

Nugget: Submit all surgical trials to your REB. Be ready to wait as long as a few months and prepared to receive suggestions, some of which will anger you. Do your best to comply with all suggestions or to explain clearly why you can not. Make the language in the consent form simple but the explanations thorough.

2. Did all patients give well-informed consent?

Informed consent is arguably the most important ethical dimension of research on human subjects, yet arguably the most difficult to truly achieve.⁸ It has 3 fundamental components: adequate disclosure of information; patient capacity to comprehend the information; and voluntariness, or freedom of the patient to make a decision.⁹

A state of clinical uncertainty about the relative merits of the trial's arms (that is, the groups/methods compared) must exist for an RCT to be justified. (This alone is a difficult concept for most patients to grasp.) A patient therefore is unable to know in advance whether participation in the study might be of benefit or not. Furthermore, it is impossible to predict every foreseeable complication of an experimental (or even standard) therapy: in surgery, unforeseeable complications can arise. The

most important component in clinical decision-making for many patients may simply be trust in the clinician/investigator.¹⁰

Nugget: Do your honest best to explain everything a reasonable person would want or need to know before entering a surgical trial. Use simple language and be prepared to have more than 1 meeting if necessary. Respect the patient's autonomy and dignity at all times.

3. Were the eligibility criteria fair and appropriate?

Inclusion and exclusion criteria for surgical trials are made stringent to increase the internal validity of the study; the trade-off may be decreased applicability of the results. Investigators must make sure, as best as possible, that access to clinical trials is equitable and fair to all potential study subjects. Some examples of unfair access are egregious, such as exclusion of vulnerable populations based on race or type of health insurance.¹¹ More common are "near-misses" to attain eligibility. For example, how might a 66-year-old woman with breast cancer feel if a promising new trial of surgically implanted chemotherapy excluded her because the criterion for age was 65 and under?

Nugget: Design surgical trials to make sure the best possible opportunity for a definitive result can be achieved without making the inclusion criteria narrower than absolutely necessary. Be sensitive to those who feel disadvantaged by ineligibility for entry.

4. Was the harm-to-benefit ratio favourable to the patients?

Before any surgical trial, detailed analysis of the potential harms of the experiment arm in particular must be weighed, and all research in animal studies and in phase I and II human studies considered. Complications, quality of life and survival in *each* arm

must be monitored on an ongoing basis, with the provision that the study can be stopped if complications are excessive or the outcome in either arm appears incontrovertibly worse than in the other.¹² An independent safety and monitoring committee, well-versed in possible pitfalls of inaccurate assessment of results (particularly early in a trial)¹³ should oversee surgical RCTs.

Nugget: No matter how exciting a new experimental therapy may appear in animal or early clinical observations, strongly consider all foreseeable harms and be watchful for those that are unanticipated. Ask for an independent monitoring committee to oversee the RCT, with the power to stop it under certain circumstances.

5. How were patients who demanded the experimental therapy handled?

As patients become more informed and self-advocating, many hear about an experimental therapy and feel strongly enough about it to demand the treatment without risking randomization away from the experimental group. How should such situations be handled?

There is little written on this difficult issue,¹⁴ but providing the new treatment on demand is intrinsically unfair to those who agreed to randomization. It could even bias the study results, if there are unknown factors associated with more vocal patients that could correlate with better/worse outcomes—and anything that could bias the result of an RCT must be considered inherently unacceptable.

If another centre is known to provide the experimental therapy off-study, an investigator in this situation should provide the patient with that information.

Nugget: When patients demand experimental therapies off study, you should not comply. Provide the patient with any information available on securing the treatment elsewhere.

6. If placebo-controlled, was the study placebo ethical?

Much has been written about the ethics of placebos in clinical investigation. This is a particularly difficult issue in surgical trials, as any surgical intervention can cause complications and thus substantially affects the benefit-to-harm ratio. The use of surgical placebos may expose participants to levels of risk that *are* unacceptable even if informed consent has been given. There are some who argue that placebos are acceptable under certain circumstances,^{15,16} and others who feel placebos are generally unethical.^{17,18} Surgical trials with an invasive placebo-controlled arm have been conducted; a recent example studied knee arthroscopy.¹⁹

Nugget: Consider any placebo in a surgical RCT that tips the harm: benefit ratio unfavourably to be unethical. Benefit that accrues to the scientific validity of a study cannot come at any foreseeable and therefore avoidable risk to participating patients.

7. Was the effect sought clinically meaningful?

Clinically relevant outcomes are a desirable subset of study outcomes that are *statistically* significant. Traditionally, power calculations have been derived on statistical grounds; they must be done rigorously to avoid the waste of human and fiscal resources associated with underpowered studies.²⁰ There is also an emerging literature on minimally important clinical differences, which patients find relevant when asked,²¹ and indications that there may be a mismatch between patients' expectations of treatment and their actual outcomes from surgical interventions.²² A null study provides an ethically acceptable result, as it may obviate unnecessary human cost (i.e., complications) and fiscal costs by advancing the discontinuation of a fruitless experimental therapy.

Nugget: Make sure power calculations for your RCT are done rigorously, and design your trial to discover differences that are clinically relevant to patients. If such information is unavailable, try to estimate what reasonable people would consider a worthwhile study outcome.

8. Were there any conflicts of interest for the investigators?

Financial conflicts of interest (COIs) at an individual or institutional level have obvious potential as sources of bias or coercion that can influence RCTs. Because these are well recognized, nowadays all such potential COIs have to be transparently communicated to peers.^{23,24} But should patients be made aware of COIs?

This is an issue most investigators avoid confronting. Financial COI could affect an investigator's aggressiveness at recruiting patients to an RCT, for example, and in the extreme scenario could alter his or her judgement about who is an appropriate candidate for a study.

Nonfinancial COIs may be quite subtle. They may exist for many reasons; for example, secretly believe that the experimental therapy works can make an investigator more aggressive at recruiting patients, in a desire to help them. Alternatively or in tandem, aggressive recruitment translates into quicker completion and earlier publication of the study, with resultant career advancement.

Investigators must be aware of such influences. Some purists believe the investigator in an RCT should not be the surgeon actually caring for the patient.²⁵ Others believe that with vigilance to avoid using subtle coercion or taking advantage of patients' profound trust, it is ethically acceptable.²⁶

Nugget: You must be aware of financial and nonfinancial forces that are powerful influences producing tension between your role as investigator and that of healer. Actively resist any temptation to allow them to

unduly influence your behaviour in the role of clinical investigator. Every financial COI must be disclosed.

9. Were study participants paid?

Although a relatively uncommon practice in surgical RCTs, participants in some studies are reimbursed at minimum for expenses like travel and parking associated with extra clinic visits due to the trial. In some trials, however, they are reimbursed above and beyond real costs accrued to them.²⁷ Any payment can be seen as a form of enticement or undue influence for a prospective subject to join an RCT, and therefore must be considered an unethical practice.²⁸ It negatively influences the "voluntariness" component of informed consent already discussed.

Nugget: Do not allow payment of research subjects for participation in your RCT.

10. Did the contributions of all coauthors justify authorship?

Fabricated data, spurious authorship, and duplicate publication continue as unethical practices in the publication of biomedical research.^{29,30} The only exception for multiple identical publications are position papers such as our reference 30, which appears in about 12 different journals. At present, written justification of contributorship is required by many peer-reviewed journals. Every author listed must have earned his or her way onto the manuscript by developing the study concept and design, generating data, writing the paper, substantive editorial work or some combination of these. Persons who have made meaningful contributions must not be omitted. Attention must also be given to the order of authorship, which should be assigned fairly by equitable consensus among the coauthors, according to the relative contributions of each.

Nugget: Make sure authorship of the results of your trial honestly and

fairly reflect the work of all who contributed, and only those who did.

Conclusion

A simple framework relevant to surgeons has been presented that addresses essential elements of the bioethical integrity of a surgical trial. It would be presumptuous to suggest that it is exhaustive or authoritative, but perhaps it can act as a springboard for investigators to consider the ethical dimensions of their work. Good clinical research is ultimately ethically desirable because it represents the attempt by investigators ever to improve surgical outcomes for our patients. However, good intentions are not enough. Good bioethical conduct of clinical research is not widely taught in our surgical curricula—and even if it were, the face of research changes rapidly. New ethical dilemmas will arise continually to challenge surgical investigators.

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References

- Thoma A, Farrokhhyar F, Bhandari M, Tandan V, for the Evidence-Based Surgery Working Group. Users' guide to the surgical literature. How to assess a randomized controlled trial in surgery. *Can J Surg* 2004;47:200-8.
- Guyatt G, Rennie D. *Users' guide to the medical literature: a manual for evidence-based clinical practice*. Chicago: AMA Press; 2002.
- Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001;285:1987-91.
- Bernstein M, Upshur REG. Framework for bioethical assessment of an article on therapy. *J Neurosurg* 2003;98:485-90.
- Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA* 2000;283:2701-11.
- Sengupta S, Lo B. The roles and experience of nonaffiliated and non-scientist members of institutional review boards. *Acad Med* 2003;78:212-8.
- Slater EE. IRB reform. *N Engl J Med* 2002;346:1402-4.
- Joffe S, Cook EF, Cleary PD, Clark JW, Weeks JC. Quality of informed consent in cancer clinical trials: a cross-sectional survey. *Lancet* 2001;358:1772-7.
- Etchells E. Informed consent in surgical trials. *World J Surg* 1999;23:1215-9.
- McKneally MF, Martin DK. An entrustment model of consent for surgical treatment of life-threatening illness: perspectives of patients requiring esophagectomy. *J Thorac Cardiovasc Surg* 2000;120:264-9.
- Gifford AL, Cunningham WE, Heslin KC, Andersen RM, Nakazano T, Lieu DK, et al. Participation in research and access to experimental treatments by HIV-infected patients. *N Engl J Med* 2002;346:1373-82.
- Dent S, Zee B, Dancy J, Hanauske A, Wanders J, Eisenhauer E. Application of a new multinomial phase II stopping rule using response and early progression. *J Clin Oncol* 2001;19:785-91.
- Wheatley K, Clayton D. Be skeptical about unexpected large apparent treatment effects: the case of an MRC AML12 randomization. *Control Clin Trials* 2003;24:66-70.
- Micetich KC, Thomasma DC. The ethics of patient requests in experimental medicine. *CA Cancer J Clin* 1984;34:118-20.
- Miller FG. Sham surgery: an ethical analysis. *Sci Eng Ethics* 2004;10:157-66.
- Hornig S, Miller FG. Ethical framework for the use of sham procedures in clinical trials [review]. *Crit Care Med* 2003;31(3 Suppl):S126-30.
- Bernstein M. Placebos. Is their use ethical in clinical trials? Con: Harm is not always obvious. *Parkhurst Exchange* 2003;11:27.
- Weijer C. Placebo trials and tribulations. *CMAJ* 2002;166:603-4.
- Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykenda DH, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 2002;347:81-8.
- Halpern SD, Karlawish JHT, Berlin JA. The continuing unethical conduct of underpowered clinical trials. *JAMA* 2002;288:258-62.
- Peto V, Jenkinson C, Fitzpatrick R. Determining minimally important differences for the PDQ-39 Parkinson's disease questionnaire. *Age Ageing* 2001;30:299-302.
- Holzner B, Kemmler G, Kopp M, Dachs E, Kaserbacher R, Spechtenhauser B, et al. Preoperative expectations and postoperative quality of life in liver transplant survivors. *Arch Phys Med Rehabil* 2001;82:73-9.
- DeAngelis CD, Fontanarosa PB, Flanagan A. Reporting financial conflicts of interest and relationships between investigators and research sponsors. *JAMA* 2001;286:89-91.
- Naylor CD. Early Toronto experience with new standards for industry-sponsored clinical research: a progress report. *CMAJ* 2002;166:453-6.
- Miller FG, Rosenstein DL, DeRenzo EG. Professional integrity in clinical research. *JAMA* 1998;280:1449-54.
- Bernstein M. Conflict of interest: it is ethical for an investigator to also be the primary care-giver in a clinical trial. *J Neurooncol* 2003;63:107-8.
- Dickert N, Emanuel E, Grady C. Paying research subjects: an analysis of current policies. *Ann Intern Med* 2002;136:368-73.
- Bernstein M. Payment of research subjects involved in clinical trials in unethical. *J Neurooncol* 2003;63:223-4.
- Bevan JC. Ethical behaviour of authors in biomedical journalism. *Ann R Coll Phys Surg Can* 2002;35:81-5.
- Davidoff F, DeAngelis CD, Drazen JM, Nicholls MG, Hoey J, Hojgaard L, et al. Sponsorship, authorship, and accountability. *CMAJ* 2001;165:786-8.