Guidelines on the Ethics of Clinical Research in Anesthesia

Research Ethics Guidelines

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These revised guidelines were prepared by the Canadian Anesthesiologists' Society's Ethics Committee to assist investigators in consideration of the ethical issues involved in anesthesia research with human subjects. These guidelines cannot be an exhaustive treatment of the subject, nor advise on every study design. Investigators are urged to use these guidelines, to discuss the relevant issues with local ethics consultants and use the resources of local Research Ethics Boards in keeping with the Tri-Council Policy Statement, *Ethical Conduct for Research Involving Humans.*[1]

Preamble

As part of its mandate to promote high-quality research, the Canadian Anesthesiologists' Society recognizes the need to ensure appropriate moral and ethical behaviour on the part of investigators who conduct clinical research with human subjects in Canada.

Moral Framework

For human research, in anesthesia as in any other specialty, investigators are expected to comply with the Tri-Council Policy Statement, *Ethical Conduct for Research Involving Humans Version 2* which uses a principle-based frame- work. Its "cardinal principle", is respect for human dignity. Ethical principles such as respect for free and informed consent, respect for privacy and confidentiality, beneficence (maximizing benefits), non-maleficence (minimizing harm), and respect for justice and inclusiveness must be carefully weighed in circumstances where they may be in conflict.

Requirement for Research Ethics Board Approval

Researchers may carry out research protocols only after approval is obtained from an appropriate institutional Research Ethics Board (REB). The REB should also be responsible for monitoring the progress of each study.

Specialty Specific Areas for Consideration

It is apparent that a number of specialty-related ethical dilemmas arise with certain research protocols. In the unique environment of anesthesia, these include factors such as:

1. Determining how, when, and by whom patients should be approached for consent.

2. Adequate time for patients to reflect on the protocol, and their ability to withdraw at any time. In the latter context, it is recognized that clinical trials involving general anesthetics or other potent central nervous system depressant medications necessarily limit the patient's ability to withdraw from the study at some times.

Because of such ethical dilemmas, the Canadian Anesthesiologists' Society supports the thoughtful interpretation and application of existing guidelines and ethical principles to each human research protocol.

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1 Joint publication of the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, and the Social Sciences and Humanities Research Council of Canada, August 2010 www.pre.ethics.gc.ca

Research with Human Subjects

A. INFORMED CONSENT

Ethical conduct of research requires that informed consent be obtained from participating subjects, or from an appropriate legally responsible delegate.[2] Information regarding the purpose of the study must be explained to prospective subjects or participants in lay terms. The consent form must also state that the individual may refuse to participate, or is free to withdraw from participation, at any time without prejudice to his or her medical care. (See Appendix: Sample Consent Form).

B. TIMING OF OBTAINING INFORMED CONSENT FOR RESEARCH

The amount of time required for patients to make an informed decision about participating in research is an important issue. A problem may arise in anesthesia because anesthesia investigators may not have their first contact with patients until they are in hospital, often on the same day as their scheduled surgical procedure. If prior contact with potential study participants is required by the Research Ethics Board, such contact by a "stranger" either at work or at home, could be perceived by the patient as an invasion of privacy. Conversely, if the investigator will also be the patient's clinical anesthesiologist there is a duty-of-care relationship, and such an approach might be considered coercive. The balance between competing ethical considerations must be carefully evaluated for each research protocol.

The Canadian Anesthesiologists' Society believes that pre-operative consent for clinical research in anesthesia may be obtained after admission to hospital, either before or on the day of the scheduled surgery provided that:

1. Patients are not under the influence of premedication.
2. Risk to the patient is not significantly different from routine clinical care.
3. After verbal explanation from the investigator or research assistant, patients are given time to read the information sheet and consider the risks and benefits.
4. Patients are given an opportunity to raise any further questions or seek clarification on any points concerning the nature of the study, alternatives, risks, benefits, etc.
5. Patients who feel they are under duress, or require more time to make a decision should be excluded from further participation in the study.
6. Investigators document in the health care chart the nature of their consent process for participants who agree to participate in a research protocol.

2 While obtaining consent from a legally responsible or legally authorized representative is accepted in the context of therapy, it is still not without controversy in the research context. The issue of recruiting potentially incapable persons in anesthesia research must be carefully considered by the local Research Ethics Board.

C. PERSONNEL APPROACHING PARTICIPANTS FOR CONSENT

For protocols that require participants to receive advance information because of additional risk to or time commitment from the patient or for administrative reasons connected with the protocol, the principal investigator and the REB should agree upon an ethical and practical mechanism to provide this information.[3]

D. PRIVACY AND PATIENT CONFIDENTIALITY

Privacy involves the right of the study participant to decide the extent to which there is access to personal data that is not already in the public domain. Confidentiality involves the preservation of the subject's anonymity when handling data during research and during its subsequent use in teaching, scholarly presentations, and in publication.

As with any clinical research, privacy and confidentiality must be respected at all times. Investigators should be aware of relevant law restricting the use of personal health information for research purposes in their respective jurisdictions. In this regard, the nature and type of information that is accessed for study purposes should be documented, and if that information is to be used for other reasons, participants should be made aware of this as part of the consent process.

E. THE POTENTIAL FOR RISKS AND BENEFITS

The nature of many clinical trials in anesthesia (e.g., comparison of the recovery characteristics and cost/benefit ratios of different types of general anesthetics) is such that the primary risk is that of the anesthetic itself, not participation in the study protocol. On the other hand, use of invasive monitoring techniques to evaluate cardiovascular effects of a new anesthetic agent may involve the risk of rare but potentially serious complications. It is always the responsibility of the investigator and the REB to ensure that potential benefits outweigh the possible risks.

When consenting to participation in research, participants accept the possibility of risks and benefits. The probability of risk and the magnitude and character of potential harm must be disclosed. The likelihood of a given risk, its duration and likely reversibility must be assessed. Investigators must also be prepared to demonstrate that there is no reasonable alternative methodology that would avoid or reduce possible risks.

Benefits may include potential advantages to the subject, future patients, third parties, society or a segment thereof, and any general increase in human knowledge.

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3 As examples, in centres where the research nurse is viewed as part of the departmental team and may contact potential research patients in advance, the research nurse may notify patients of his/her role as a member of the team and ask if they are interested in participating in a research study. If the patient is interested, the research study nurse explains the study and obtains consent. Consent is then obtained in writing at the earliest opportunity. This is accepted practice by some Research Ethics Boards. In situations where this approach is not acceptable to the respective REB, and for studies involving more than minimal risk, patients may be seen and consented in the Preoperative Assessment clinic. The anesthesiologist should enquire as to whether or not the patient is interested in participating in a research study, and if the answer is affirmative, a member of the research staff may then approach the patient to present the study details and seek informed consent.

F. PLACEBOS

Use of a placebo medication as the control arm in an anesthesia protocol is unethical when there is an established effective treatment for the condition under investigation.[4] Legitimate use of placebos is based on the concept of clinical equipoise, which exists only when there is genuine uncertainty among experts about the relative therapeutic merits of the two arms of a clinical trial. It is expected that a clinical trial will be designed so that, if successful, it will provide evidence in favour of one of the treatments.[5]

For ethical use of a placebo control there must be genuine disagreement among expert practitioners as to preferred treatment. "A nonvalidated treatment may be compared with a placebo control if (1) no standard therapy exists, (2) standard therapy exists but has been shown to be no better than placebo, (3) standard therapy is placebo, (4) standard therapy is toxic and of marginal benefit, or, (5) validated treatment exists but is not available because of cost or limited supplies. Placebo controls are appropriately used when the new, nonvalidated treatment is an 'add-on' to standard therapy (so that the comparison is standard therapy plus new drug versus standard therapy plus placebo)."[6]

G. CONFLICTS OF INTEREST

All potential conflicts of interest must be declared to participants in a clinical trial and included in the consent form and any subsequent publications. Financial or material rewards to investigators must also be declared to the Research Ethics Board. Clinical care must always take precedence over research investigation. When the same anesthesiologist will be both investigating research participants and providing their anesthetic care, the research protocol as approved by the Research Ethics Board must have clear indications as to when the study protocol will be abandoned for the wellbeing or safety of the individual patient.

H. REMUNERATION TO STUDY PARTICIPANTS

Research participants must not be offered rewards so great as to coerce them to take risks in research that they would not otherwise consider reasonable. Equally, research participants must not be expected to subsidize research by suffering monetary or other losses. Bearing these concepts in mind, the amount and type of remuneration must be disclosed to the Research Ethics Board.

I. VULNERABLE POPULATIONS

These populations include patients who lack decision-making capacity, patients of questionable capacity, and those who may be "capable" but vulnerable because of a disease process, culture, or inability to speak a language. Patients undergoing surgery may feel stressed and are potentially vulnerable to coercion – particularly if the treating and investigating physician are the same person. It is unethical to take advantage of vulnerable populations and anesthesiologists should consider this aspect in recruiting participants to a clinical study. In general, capable people should be enrolled where possible over those who are incapable or of questionable capacity.

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4 Tri-Council Policy Statement, www.pre.ethics.gc.ca

5 Freedman B., Equipoise and the ethics of clinical research. N Eng J Med, 1987; 317(3): 141-5.

6 Huston P and Peterson R. Withholding proven treatment in clinical research. N Eng J Med 2001;345(12):912-4

J. GENDER SPECIFIC AND PEDIATRIC STUDIES

Research protocols must use appropriate models and populations, taking into consideration issues of gender and age. In particular, it is important that there be on-going research in anesthesia in women of child-bearing capacity and for the pediatric population as it would be unethical to deny these groups the benefits of advances in the specialty. Investigators and Research Ethics Boards have a particular duty to protect child participants and those from other vulnerable populations from undue risk of harm, especially when consent or permission is obtained through another person. Assent for research should be obtained from children of appropriate age as determined in consultation with the Research Ethics Board.

K. COMPETENCE

Competence to consent to research does not require that patients be competent in all respects for all purposes. Decision making capacity is not a global assessment but a functional assessment and is decision specific. For example, a patient who is incapable of managing financial affairs may be competent to consent to research.

In conducting research that might involve cognitively impaired persons, the protocol must include an assessment of competence. Furthermore, a person who is incompetent, or of doubtful competence, must not be included in research that poses more than minor risks without substantial potential benefits for that person. In addition, if incompetent persons are to be enrolled, the researcher must explain to the REB how third party authorization will be obtained, and that the subject's interests are protected.

Other Resources

1. *World Medical Association.* Declaration of Helsinki: Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects. From URL: http://www.wma.net/en/20activities/10ethics/10helsinki/index.html (accessed October 2011).

2. *Luce JM, Cook DJ, Martin TR, et al.* The ethical conduct of clinical research involving critically ill patients in the United States and Canada: principles and recommendations. Am J Respir Crit Care Med 2004;170:1375-84.

3. *Weijer C, Dickens B, Meslin EM*. Bioethics for clinicians: 10. Research ethics. CMAJ 1997;156: 1153-7.

4. *ICH.* Harmonisation for Better Health. Guideline for Good Clinical Practice E6. From URL: http://www.ich.org (accessed October 2011).

5. *U.S. Department of Health and Human Services; Food and Drug Administration; Office of the Commissioner (OC); Center for Drug Evaluation and Research (CDER); Center for Biologics Evaluation and Research (CBER); Center for Devices and Radiological Health (CDRH); Good Clinical Practice Program (GCPP*). Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs - Improving Human Subject Protection January 2009 procedural. From URL: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf (accessed October 2011).

6. *Health Canada*. Drugs & Health Products > Compliance & Enforcement > Good Clinical Practices > Regulations. From URL: http://www.hc-sc.gc.ca (accessed October 2011).

7. *Office of the Privacy Commissioner of Canada.* The Personal Information Protection and Electronic Documents Act. Readers should also consult relevant provincial privacy legislation. From URL: http://www.priv.gc.ca (accessed October 2011).

8. *Weijer C.* The ethical analysis of risk. J Law Med Ethics 2000; 28: 344-61.