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Ethical Challenges in ICU Research

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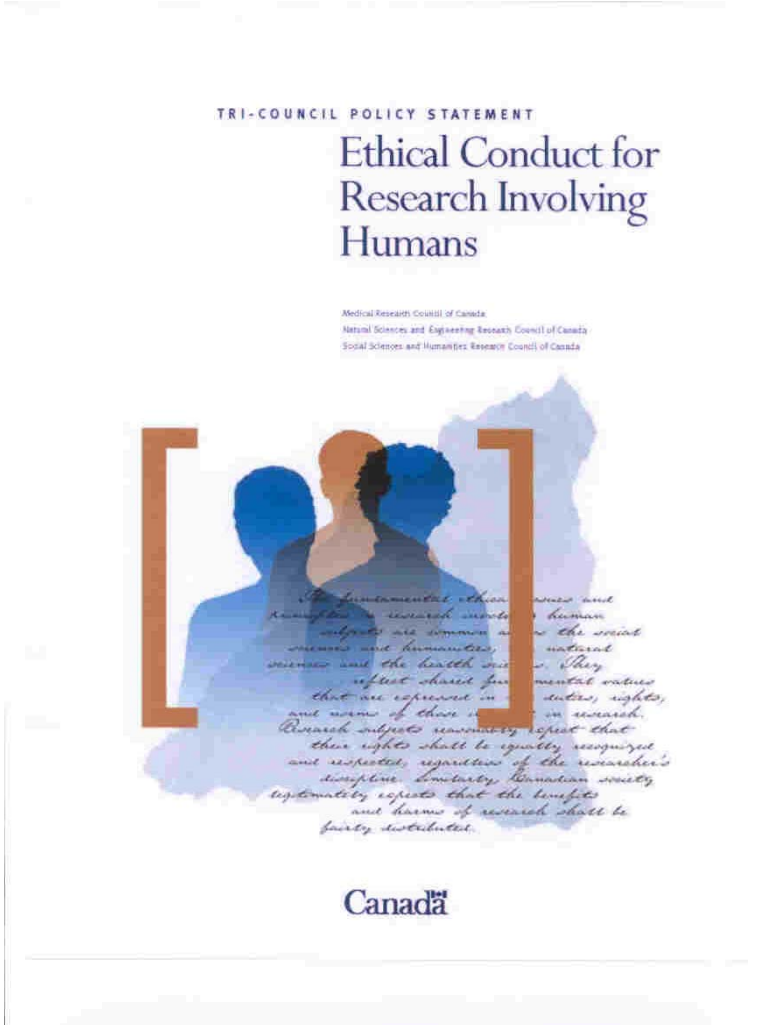
Tri-Council Policy Statement

- Joint statement of CIHR, NSERC, SSHRC
- Applies to all research funded by Councils or conducted at an institution that receives Council funding
- Available at www.pre.ethics.gc.ca



Tri-Council Policy Statement

- First edition adopted in 1998
- Second edition is in preparation (first draft December 2008; new draft December 2009)
- Document has been entirely rewritten
- More detailed attention to REB issues
- Guidance on qualitative research, aboriginal research

Chapter 11: Clinical trials

- “As part of their ongoing medical care, patients with serious medical conditions are often treated with therapies or undergo interventions or procedures having significant risks. These patients may be invited to participate in clinical trials.”

Chapter 11: Clinical trials

- Article 11.5 “In clinical trials, with appropriate scientific and clinical justification, it may be acceptable to allow research involving higher risk interventions with patient-participants in which such heightened risk is primarily attributable to the therapy and not to the research, or which is consistent with the risk normally undertaken by participants in their usual clinical care.”

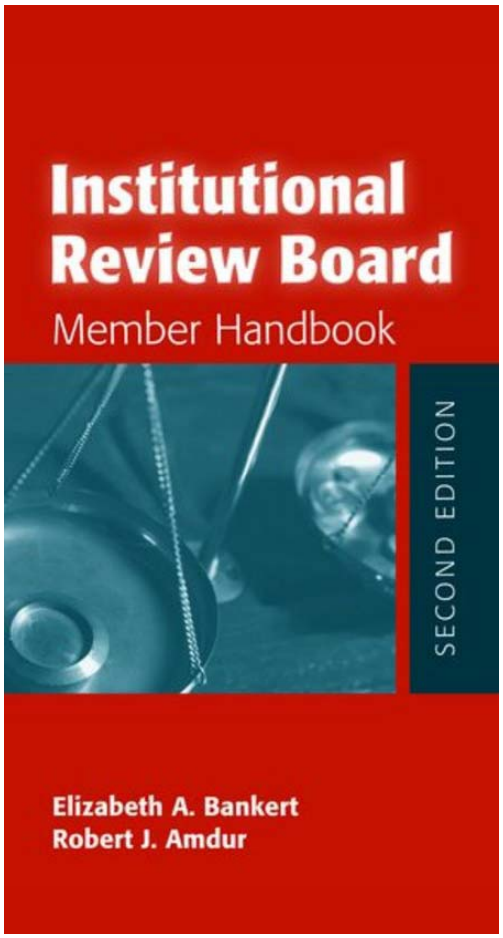
Clinical trials: Balancing risks

- “Some kinds of standard or recognized treatments (for example, surgery, chemotherapy or radiation therapy) themselves pose substantial risks. An REB may approve a study that involves such high-risk therapies if there are no other reasonable alternative therapies available to patient-participants and if the research-attributable risk is no greater, or only minimally greater, than that to which participants would routinely be exposed.”

Problems

- Seems to base REB review on risks associated with the patient's clinical condition rather than the research study
- Aggregating research risk has problems, including allowing some degree of substandard care in research
- Language of "no other reasonable alternative therapies available to patient-participants" will preclude much ICU research when there exists (imperfect) therapeutic alternatives

Component analysis



- Systematic and comprehensive approach to the ethical analysis of benefits and harms in research
- Endorsed by U.S. National Bioethics Advisory Commission (2001)
- *Nature Medicine* 2004; 10: 570

Component analysis

- Clinical research often contains a mixture of procedures
- Therapeutic procedures (drugs or surgical interventions) are administered with therapeutic warrant, that is, evidence sufficient to justify the belief that they may benefit research subjects
- Non-therapeutic procedures (added blood tests or imaging procedures) are administered without therapeutic warrant and solely to answer the scientific question at hand

Therapeutic procedures

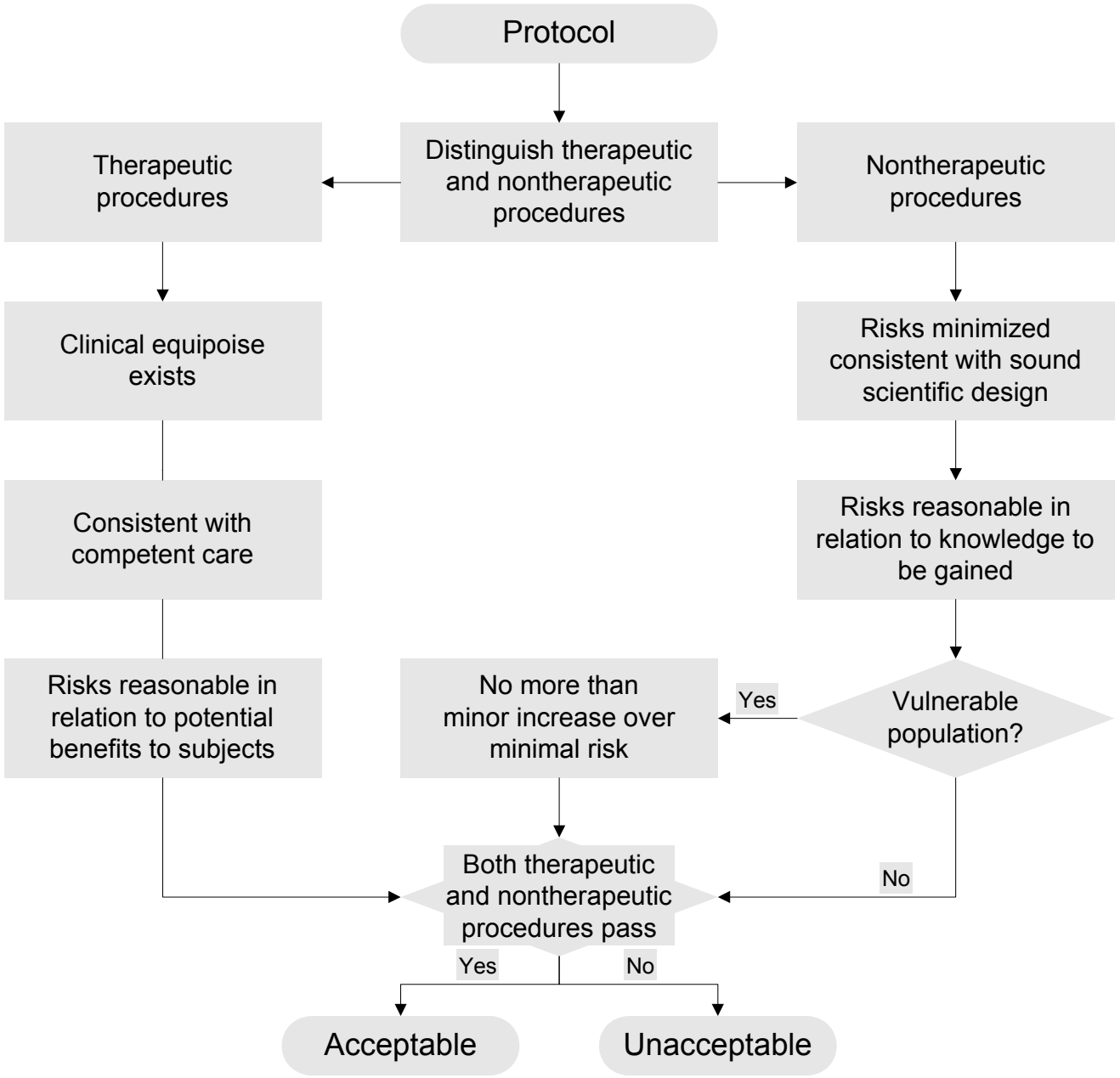
- Therapeutic procedures must fulfill clinical equipoise
- Physicians-researchers owe a duty of care to the patient-subject
- Therapeutic procedures in the various treatment arms must be consistent with competent medical care
- Formally: a state of honest, professional disagreement in the community of expert practitioners as to the preferred treatment

Non-therapeutic procedures

- Non-therapeutic procedures offer no benefit to the subject and hence a harm-benefit test is inappropriate
- These procedures must fulfill two moral rules:
  - 1. Risks associated with non-therapeutic procedures must be minimized consistent with sound scientific design; and,
  - 2. Risks must be reasonable in relation to knowledge to be gained.
- Therefore, a harm-knowledge test.

Vulnerable populations

- Pregnant women, prisoners, children, and incapable adults*
- May not be included in research as a population of mere convenience
- Those who cannot speak for themselves are spoken for by a proxy decision maker
- Threshold for allowable non-therapeutic risks of a minor increase above minimal risk


Protocol
Distinguish therapeutic and nontherapeutic procedures
Therapeutic procedures
Nontherapeutic procedures
Clinical equipoise exists
Consistent with competent care
Risks reasonable in relation to potential benefits to subjects
Risks minimized consistent with sound scientific design
Risks reasonable in relation to knowledge to be gained
Vulnerable population?
Yes
No more than minor increase over minimal risk
No
Both therapeutic and nontherapeutic procedures pass
Yes
No
Acceptable
Unacceptable

Advantages

- ICU research is often thought to involve “serious risk”. Component analysis allows us to disambiguate this claim and focus on the incremental risks posed by study participation
- ICU patients are by definition seriously ill
- Clinical equipoise ensures a rough parity between the procedures that patients would receive in clinical practice and TP in research
- Incremental risks of study participation flow from nontherapeutic procedures

Incremental risk of ICU research

- Review of NT procedures in 70 acute care studies (1996-2000)
- Reviewed and classified by a panel of physicians and ethicists
- Minimal risk – 68 (97.1%)
- *Academic Emergency Medicine* 2005; 12: 1104

TABLE 1. Procedures Administered for Nontherapeutic Purposes in 70 Acute Care Research Studies Using a Waiver of/Exception from Consent

Procedure	Frequency
Review of data in medical records	54
Recording of clinical observations	28
Retrieval of data recordings from monitors	26
Additional patient history and physical examinations	12
Additional blood samples	8
Nontherapeutic ultrasound examinations	4
Additional blood samples from indwelling catheter placed as part of standard care	3
Additional arterial blood sample	1
Additional tests of already collected peritoneal fluid	1
Nontherapeutic ACTH stimulation test	1
CSF fluid samples from an indwelling ventriculostomy catheter	1
Nontherapeutic diagnostic peritoneal lavage	1
Follow-up phone interview with survivors or families	1
CT scan of cervical spine in patients undergoing head CT	1
HIV serology on anonymized blood samples	1
Additional testing of blood drawn for clinical purposes	1

ACTH = adrenocorticotropic hormone; CSF = cerebrospinal fluid.

Conclusion

- Proposed changes to Canada's *Tri-Council Policy Statement* are significant and may have a negative impact on ICU research
- Component analysis is a systematic and comprehensive approach to the ethical analysis of benefits and harms in research
- Component analysis may be a better way of thinking about benefits and harms in ICU research.