



MCGILL UNIVERSITY

ETHICAL AND LEGAL ASPECTS OF

RESEARCH INVOLVING HUMAN SUBJECTS

CONDUCTED IN THE FACULTY OF MEDICINE

AND AFFILIATED HOSPITALS

POLICIES AND PROCEDURES

1993

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Foreword

McGill University established a “*Policy on the Ethical Conduct of Research Involving Human Subjects*” that was approved by the Board of Governors on March 28, 2003. (Appendix A). Earlier (1993), the Faculty of Medicine and its affiliated Hospitals had produced a document entitled “*Ethical and Legal Aspects of Research Involving Human Subjects Conducted in the Faculty of Medicine and Affiliated Hospitals - Policies and Procedures*” that was modified in 1994, in 1999 and again in 2004. This modification in March 2007 puts the Policies and Procedures of the Faculty of Medicine in context with the University Policy, the establishment of the Federal Wide Assurance held by the Research Ethics Boards of the Faculty and Hospitals, as well as with the requirements of the Civil Code of the Province of Québec and the Plan d’action ministériel en éthique de la recherche et en intégrité scientifique.

Research involving human subjects constitutes a significant proportion of all research in the Faculty of Medicine and its affiliated Hospitals. Such research can only be undertaken after proper review and approval. Until the release of the Tri-Council Policy Statement “*Ethical Conduct for Research Involving Humans*” the guidelines that were followed included those of the Medical Research Council of Canada and Regulations from the Department of Health and Human Services (DHHS) in the United States when research was supported by funds from the NIH or other US Federal agencies. **The Canadian Federal Funding Council guidelines were supplanted by the Tri-Council Policy Statement released in August 1998, and all Research Ethics Boards in the Hospitals, and on the University Campus, now must apply these guidelines.** The new policy statement (Appendix B) is more extensive in several areas, such as dealing with ethical issues of genetic research and research involving gametes, embryos and fetuses. Under Federal Wide Assurances held by the Faculty of Medicine and the Hospitals, US Government funded research on humans now can be approved under the Tri-Council Statement and not under the US Code of Federal Regulations.

In 1993, in an effort to achieve uniform and consistent application of guidelines across all Research Ethics Boards of the Faculty, The Dean of Medicine and the Director of the Biomedical Ethics Unit created a Faculty steering committee for ethics in health sciences with subcommittees to address: teaching, clinical ethics and research ethics. The mandate of the Research Ethics Committee of the Faculty (RECF) is to:

- i. Act as a central Policy and Procedures Committee for Research Ethics Boards (REBs) to address common issues. (Its original role in establishing REBs at major geographic locations throughout the campus, hospitals and research institutes where research involving humans is conducted has been achieved).
- ii. Create uniform policies and procedures and adapt them as necessary in accordance with the Tri-Council Policy Statement and applicable Federal and Provincial Laws. To attempt, as far as is possible, to achieve uniformity in function among the Faculty REBs.
- iii. Provide a means for the various REBs to share in activities such as education of REB members and researchers, development of various forms, and in the implementation of policies.
- iv. Provide a wide forum to discuss those guidelines that address newer, more complicated ethical issues and to share information and experiences involving novel ethical issues. To make recommendations and policies emanating from these discussions for the conduct of research at the McGill Faculty of Medicine and its Affiliated Institutions, and to add these to the Policies and Procedures Document.

Members of the first RECF were appointed by the Dean and the approval of the Directors of Professional Services was sought for the members that represented the Hospitals. That committee developed a set of guidelines that is the pre-cursor of this document and functioned to oversee the creation of the ethics boards at the various hospital sites. It was envisioned that, thereafter, the membership of the RECF would include the chairs of these REBs.

Deliberations of McGill REBs must be consistent with applicable laws. In clinical drug trials, pursuant to subsection 30(1)^a of the Food and Drug Act, the Regulations Amending the Food and Drug Regulations (1024-Clinical Trials) must be followed (Appendix C). The REBs must also follow provincial laws including, as relevant, the Québec Civil Code (QCC) (Appendix D), la Loi sur les services de santé et les services sociaux des établissements (LSSSS) (Appendix E) and the Plan d'action ministériel en éthique de la recherche et en intégrité scientifique (Appendix F). The basic framework that must be followed for the review is the Tri-Council Policy Statement that was approved by the Medical Research Council (now CIHR), the Natural Sciences and Engineering Research Council, and the Social Sciences and Humanities Research Council. It is intended that all research on humans carried out in Canada meet, as a minimum, the policies of the Tri-Council Statement. The nature of the research and its sponsorship may require that the REB consider other documents as well. Other guidelines that might be established in specialized research areas such as Genetic Research and DNA Banking should also be consulted. The McGill IRB and the REBs of the Affiliated hospitals have adopted Guidelines for a Consent Form used for Genetic Research and DNA Banking protocols (copy in Appendix L) and Guidelines for Data and Tissue Banking (copy in Appendix M).

It is intended that the policies and procedures described in this document for research involving humans and conducted in the Faculty of Medicine at all times be consistent with the Tri-Council Policy Statement, the general policies of the University and applicable provincial and Federal laws. Sharing of policies and procedures encourages uniformity in operation among REBs in the hospitals and the campus.

I – Introduction

The History of the Human Subjects Protection System

The contemporary, international attention to protection of human subjects in research began concurrently with the Nuremberg Code, (Appendix G) developed for the Nuremberg Military Tribunal as standards by which to judge the human experimentation conducted by the Nazis. The Code captures many of what are now taken to be the basic principles governing the ethical conduct of research involving human subjects. The first provision of the Code states that “the voluntary consent of the human subject is absolutely essential.” Freely given consent to participation in research is thus the cornerstone of ethical experimentation involving human subjects. The Code emphasizes this point further by providing the details implied by such a requirement: capacity to consent, freedom from coercion, freedom to withdraw from participation and comprehension of the risks and benefits involved. Other provisions require careful preliminary studies (e.g. in animals) before enrolling human subjects, set strict limits to the risks that may be imposed on human subjects, demand careful preparation to reduce risks to a minimum, and mandate the establishment of a favourable risk/benefit ratio. Similar recommendations were made by the World Medical Association in its Declaration of Helsinki (Appendix H): Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects, first adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, and subsequently amended in Tokyo, Japan, 1975, in Venice, Italy in 1983, in Hong Kong, 1989, in South Africa in 1996 and in Edinburgh, Scotland in 2000. The Declaration added to the Nuremberg Code a description of the kind of information which prospective subjects are entitled to receive, a requirement for review of a written protocol by an independent committee, and a distinction between therapeutic and non-therapeutic research.

In the United States, **regulations** protecting human subjects first became effective in 1974 eight years following the issuance of NIH’s Policies for the Protection of Human Subjects. The regulations established the Institutional Review Board (IRB) as a main mechanism through which human subjects would be protected. During a four-year period the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research studied a variety of forms of and settings for research and issued recommendations applicable to these settings (i.e. research on children, prisoners, the mentally impaired etc.). As a final result of their deliberations the Commission set forth the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects. This document, entitled “The Belmont Report”, (Appendix I) forms the foundation for the present system of research ethics review for all institutions conducting research with support from the United States Government. The latest revisions to the United States regulations were adopted in 1991 (Appendix J). McGill University, through the Faculty of Medicine, previously held a Multiple Project Assurance (MPA) with the Department of Health & Human Services (DHHS) for review of those projects that were submitted to U.S. Federal Agencies. Since 2003, the Faculty and its affiliated hospitals have established Federal Wide Assurances with the DHHS. Under this agreement, our Research Ethics Boards can use the Tri-Council Policy and not the US Federal Code of Regulations in reviewing protocols supported by agencies such as National Institutes of Health.

In Canada the Medical Research Council built upon the tradition developed by the codes of ethics described above and developed guidelines which focus on research in the health sciences. The first guidelines were issued in 1978. They were updated in 1987 by a Standing Committee on Ethics in Experimentation of the MRC to the “*Guidelines on Research Involving Human Subjects*” to promote the development of ethical awareness in investigators, Research Ethics Boards (REBs) and the wider community. In 1998, the Medical Research Council, Natural Sciences and Engineering Research Council and the Social Sciences and

Engineering Research Council collaborated on a Tri-Council Policy Statement “*Ethical Conduct for research Involving Humans*”. Copies of the Policy Statement should be available in all laboratories, divisions and departments in the Faculty of Medicine where research on human subjects takes place. Through the Policy Statement the Councils ensure that public funds are spent only on research that is ethically acceptable.

In 1989 the MRC, Health & Welfare Canada and the Royal College of Physicians & Surgeons of Canada established the National Council on Bioethics in Human Research (NCBHR) that has been renamed in 1998 to National Council on Ethics in Human Research, an independent Council that aims to ensure that the Policy statement is uniformly implemented by REBs across Canada. NCEHR will assist universities and their affiliated institutions in assessing the functions of their REBs and in implementing the Tri-Council Policy Statement.

In 1999 the Government of Québec required that ethics boards be designated by the Minister of Health and Social Services in order to be able to carry out the responsibilities referred to in Article 21 of the Civil Code of the Province of Québec (Appendix D). The QCC and the Plan d’action ministériel en éthique de la recherche et en intégrité scientifique (Appendix F) outline the additional requirements for research ethics boards that review research protocols involving vulnerable populations. In addition, the Fonds de la recherche en santé du Québec has produced a document “*Guide d’éthique de la recherche et d’intégrité scientifique*” for use by research ethics committees in Québec “<http://www.frsq.gouv.qc.ca/>”.

II – The Research Ethics Board (REB)

A. Jurisdiction

The REB is an administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of the institution with which it is affiliated. The REB reports to the Principal of the University for research conducted on campus or to the Board of Directors of the Hospital for research conducted in a Hospital. In the Faculty of Medicine University authority is delegated to the Dean of Medicine (who may delegate to the Associate Dean, Research).

The REB has the authority to approve, require modification of, or disapprove research proposals within its jurisdiction. Research that has been reviewed and approved by an REB may be subject to further review and possible disapproval by the officials of the institution; however, those officials may not approve research that has been disapproved by the REB.

The REB is obliged to review all research performed within the jurisdiction of the institution it serves. An institution can, however, establish more than one REB depending on the needs.

It is recommended that each hospital affiliated with McGill University establish one REB and that non-hospital based research in the Faculty including, but not limited to, School of Physical and Occupational Therapy, School of Nursing, School of Occupational Health, School of Human Communication Disorders and basic science departments be reviewed by one REB.

If required, a large hospital such as the McGill University Health Centre may establish more than one REB. Under no circumstances, however, should an REB be formed on an ad hoc basis or be constituted within a department of the Faculty.

The REB has responsibility to review research performed within the boundaries of its institution including research performed by non-affiliated or non-employed members from another institution. The REB has the responsibility to review a staff member's research that the institution administers even if such research is carried out in a different geographical location. The extent to which an REB serves a part-time physician who carries out research in a private setting is left to the discretion of the Board of Directors of the Hospital.

Where multiple hospitals participate in the same research protocol, inter-hospital agreements may be developed and one REB designated to review the research. Currently the McGill University IRB reviews protocols for research on campus and in the allied health schools and also for multi-site protocols carried out at more than one hospital. This designated REB should involve the local REBs and at minimum should provide minutes of its meeting to these REBs. It should be noted that only the review of the protocol is delegated in such a scenario for logistical purposes and to avoid duplication of effort; local responsibilities such as liability for acts by staff, availability of research subjects, resources and nursing staff are the responsibility of each hospital.

Although a delegated REB can approve a multi-center protocol or a single-center protocol referred to it, the Institution in which the research will take place may, through its own REB, subsequently disapprove or decline to participate in the study. However, a study which has been disapproved by the delegated REB cannot subsequently be presented for review at one of the delegating Institution's REBs. The opportunity to delegate review should not be utilized as a means to attempt to appeal a negative decision by a delegated

committee.

McGill University has a Federal Wide Assurance (Section VI) with the Department of Health & Human Services for research on humans funded by agencies of the U.S. Government. Each affiliated hospital also holds Federal Wide Assurances and has signed an IRB Authorization Agreement with McGill to recognize that the University IRB can act for them on review of protocols to be carried out at multiple hospital sites. The hospital REBs are delegated to also act on behalf of the University in conducting reviews and continuing oversight of research on humans conducted by University Faculty and trainees located at the hospital. Agreements have been signed with the McGill University Health Centre, Douglas Hospital, Jewish General Hospital, and St. Mary's Hospital. The Shriners' Hospital does not have its own REB and has designated the University IRB as its ethics board of record. The IRB committee is housed in the McIntyre Medical Building. Investigators should consult the IRB web site <http://www.medicine.mcgill.ca/research/irb/> for further information.

B. Membership of REBs

The REB must be sufficiently qualified through the expertise, independence and experiences of its members and the diversity of their background to promote respect for its advice and decisions in safeguarding the rights and welfare of human subjects.

In addition to possessing the professional competence necessary to review specific research activities, the REB must be able to ascertain the acceptability of the proposed research in terms of institutional regulations, applicable law (federal, provincial and municipal) and standards of professional conduct and practice. No REB, however, may consist entirely of members of one profession.

Membership of the committee is described by Article 1.3 of the Tri-Council Policy:

The REB shall consist of at least five members, including both men and women, of whom:

- (a) at least two members have broad expertise in the methods or in the areas of research that are covered by the REB;*
- (b) at least one member is knowledgeable in ethics;*
- (c) for biomedical research, at least one member is knowledgeable in the relevant law; this is advisable but not mandatory for other areas of research; and*
- (d) at least one member has no affiliation with the Institution, but is recruited from the community served by the institution.*

In addition, for Research Ethics Boards that have been designated by le Ministère de la Santé et des Services Sociaux under Article 21 of the Québec Civil Code, there are additional requirements on the membership:

- (e) at least 20 % of the committee must be community members*
- (f) the individual knowledgeable in the relevant law must not be the legal counsel for the Institution*

The Committee highly recommends that the REB membership also include a patient advocate. This individual is particularly important when an REB regularly reviews research that involves a vulnerable category of subjects (children, elderly people, mentally ill persons, among others). The Faculty of Medicine recommends that one member of the REB (**and including his/her immediate family**) not be affiliated with the institution served by the REB. In the McGill setting a non-affiliated member might be a physician or scientist who is not in the employ of the University or Hospital to which the REB reports.

Each REB must consist of at least five members. Considering the breadth of research in McGill's affiliated hospitals and on campus, it is likely that most committees will consist of more than five members and shall include sufficient membership to address the need for scientific assessment in the areas of investigation most frequently submitted to the REB (i.e. cardiology, oncology, surgery, psychiatry, nursing, etc.) as well as to deal effectively with the number of protocols submitted.

The Chair of the REB is appointed by the Institution - McGill or the relevant affiliated Hospital Board of Governors. The members of the REB are recommended by the Chair and approved by the Institution. In addition to the chair, a co-chair should be appointed for large committees. The term of appointment for members and chair(s) should be 3 years (renewable) with staggered appointments. The members of the Faculty of Medicine IRB are appointed, and when appropriate, re-appointed or terminated by the Dean.

No member of an REB may participate in review of any project in which the member has a conflicting interest. He/she may be requested by the IRB to provide information, but should not be present when a decision is made.

A quorum of a REB is discussed in Article 1.7 of the Tri-Council Policy Statement and requires, as a minimum, that the members in attendance must possess the range of background and expertise stipulated in Article 1.3. In addition, for REBs designated under Article 21, the requirements of le Plan d'action ministériel en éthique de la recherche et en intégrité scientifique must also be met.

Meetings should be held monthly or more frequently if dictated by workload.

When required, consultants may be invited to meetings to provide expert advice to the committee on specific protocols.

C. Responsibilities and Functions of the REB

(i) Mandate

Whenever the REB reviews a protocol it should ascertain whether it has jurisdiction over the approval of the protocol, i.e. is it research and does it involve human subjects. The REB reviews all research* involving human subjects (irrespective of source of funding) during the course of which an investigator obtains data through intervention or interaction with the individual or obtains identifiable private information, for the purpose of developing or contributing to generalizable knowledge.

** Research is a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. (45 Code of Federal Regulations 46.102(d) Appendix J)*

Inquiries, interventions and collection of information carried out solely for the purposes of education, clinical care or the management of facilities are not considered research within the spirit of this document.

Each REB shall decide and announce a "minimum lead-time" for the submission of research protocols prior to the date of formal review. The REB shall not be obligated to review protocols not submitted within this time period or lacking the required information (see below).

The review and approval of certain types of research may be carried out by responsible individuals in the Faculty or Hospital (Associate Dean, DPS or head of the Pathology Department), and do not require the approval by the REB. The types of research for which review and approval are not required are:

- Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
- Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behaviour, unless: (i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.
- Review of medical records for "a study, teaching or research purposes" which, under the "Act Respecting Health Services and Social Services" (Article 19.2), can be authorized by the Director of Professional Services (DPS) of a Health Institution. However, the DPS has to ensure that there is a valid justification for the chart review, and that the confidentiality of the information will be protected (Article 125) (The appropriate Articles of "*An act respecting access to documents held by public bodies and the protection of personal information*" are found in appendix K).
- Note that Quebec Civil Code which came into force January 1994 requires informed consent for the use of any biological specimen for research (Appendix C). Moreover, the Tri-Council Policy Statement, article 1.1, stipulates that "research involving human remains, cadavers, tissues, biological fluids, embryos or foetuses shall also be reviewed by the REB".

Expedited review by an REB may take place when the REB delegates to the chair the right to carry out review of protocols or amendments thereto. Expedited review may occur if 1) studies involve no more than minimal risk (see II C.ii., Responsibilities) or involve minor changes to previously approved protocols and 2) if such expedited or interim decisions are "reported to the full REB in appropriate ways, permitting the REB to maintain surveillance over decisions made on its behalf" (Discussed under Article 1.6 of the Tri-Council Policy Statement). Expedited initial review is not permissible at any time for research falling under Article 21 of the QCC.

Investigational New Drugs (IND) or novel interventions when undertaken outside the realm of a research protocol do not require REB review. A physician may, however, seek the advice of the REB which should not normally be refused. The REB can choose to function also in an advisory capacity; indeed this may be desirable in the pursuit of educational objectives.

When reviewing protocols involving new drugs, the REBs must take into consideration the future availability and cost of the drug.

(ii) Responsibilities

A major responsibility of the REB is to assess the risks and benefits of proposed research.

The phrase ‘risk-benefit’ ratio itself is misleading, as has been noted by several authors. Risks are understood to be the product of an undesirable effect (consequence) that may or may not occur (probability). On the other hand, ‘benefit’ ordinarily means a desirable consequence, and makes no reference to the uncertainty of its occurrence. It is misleading to think of the undesirable effects of research as only possible, with its desirable effects as certain. It would be preferable to speak instead of a ‘potential to harm vs. potential to help’. Since the risk-benefit phrase is entrenched within discourse on the ethics of human research, though, that phrase will be used in this document.

As a rule, subjects must not be clinically disadvantaged as a result of participating in research studies, and it is the REB’s responsibility to review the adequacy of protection presented within the protocol in question towards that end. To evaluate the risk-benefit ratio, a number of issues must be considered: What is risk? How can risks be minimized? Are there thresholds of risk that trigger different ethical considerations and review? How can risks be balanced against benefits?

What is Risk?

The idea of risk calls to mind physical injury. This is too narrow a concept; for that reason, many prefer to refer to ‘risks and discomforts.’ While encompassing pain and injury, and the possibility of contributing to the future likelihood of pain and injury, an REB considering the risks associated with a research study need to comprehensively consider events or effects that may occur due to research participation which are undesirable from the point of view of the individual subject, along a continuum that at one point represents pain, but that includes further down the line other unpleasant consequences such as shame, up to and including such everyday annoyances as boredom.

The risks to which research subjects may be exposed can be more formally classified as physical, psychological, social, and economic.

Risks can include foregone benefits as well. Placebos may not be inherently risky but “*their use in clinical trials is generally unacceptable when standard therapies or interventions are available for a particular patient population*” (Tri-Council Policy Statement, article 7.4).

Some risks of research are subtle. Participation in some studies bear social risks, e.g., those associated with violations of privacy or of confidentiality. These social risks can, depending upon the case, have very serious consequences, to a person’s employment, insurability, relationships, etc. Other harms may be inchoate but no less real: for example, a healthy subject who becomes one of the ‘worried well’ as a result of insight inflicted in the course of participating in (or, being invited to participate in) a study designed to detect some sub-clinical condition.

Judgments regarding social risks must be made with realistic regard to social conditions, and in some cases be established relative to the norms of subjects. Concepts of privacy and confidentiality may also differ among cultures and must always be viewed from the perspective of the culture studied, as well as from the perspective of the investigator.

In many clinical studies, the major risks that subjects face are those generated by reason of the disease they have or the standard treatment that is provided to treat that disease. The REB’s primary concern is of course with those risks that the subjects will experience by reason of research participation. A cancer study may involve two different chemotherapy regimens, one of which is standard and the other of which is experimental. Although the subjects will be at serious, even grave, risk in the course of this research, there

may be little risk specifically generated by the research itself, if the two regimens have similar profiles of side-effects. The research risks to be found in this study may be, instead, more frequent blood tests and x-rays than would be done in the clinical management of the patient being treated for cancer. (Of course, this will not be true of research risks associated with a protocol studying, for example, dose intensification beyond the standard.) Similarly, if the research is designed to measure the behavioral results of physical interventions performed for therapeutic reasons (e.g., effects on memory of brain surgery performed for the relief of epilepsy) then only the risks presented by memory tests should be considered when the REB performs its risk/benefit analysis. The REB should recognize, however, that distinguishing therapeutic from research activities can sometimes require very fine line drawing. The distinction between research risks and those therapeutic risks a patient encounters regardless of research is also important to bear in mind when considering consent to research.

Conflicting guidance is found within the codes concerning whether an REB should consider long-range risks associated with research. The 1987 MRC Guidelines stated: “*Consideration must be given primarily to the risk of physical or psychological harm to the subjects. Attention should also be paid to the degree of harm that the subjects, as a group, may suffer, as well as to any potential or foreseeable harm to society as a whole if the research is allowed to proceed.*” A narrower view is taken by the US regulations 45 CFR 46.111(2): “*The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of research on public policy) as among those research risks that fall within the purview of its responsibility.*”

How can risks be minimized?

Even before considering a study’s risk-benefit ratio, the investigator and the REB should consider whether any of its risks can be diminished. Any risk that can be eliminated or minimized without effecting the validity of the trial is itself therefore unjustified, although, were that risk essential to the trial’s conduct, it could well have been acceptable.

In considering minimizing risks, a variety of questions might arise. Are all of the interventions necessary? Are there non-interventional means of obtaining the same information? Can procedures already being done for clinical purposes be used instead of a research intervention: e.g., can a researcher’s blood test ‘piggy-back’ upon a clinical investigation?

The scope of a proposed study also needs to be considered. As stated in the 1987 MRC Guidelines, and consistent with the Tri-Council Policy Statement, the smallest possible number of subjects should be exposed to the risks of research. However, risk minimization must be consistent with norms of valid and valuable research, and so it should not result in the REB’s demanding changes that will make the proposed study underpowered.

Are there thresholds of risk that trigger different ethical considerations and review?

The Tri-Council Policy Statement states that an REB should adopt a proportionate approach to ethics assessment i.e. “it should be based on the general principle that the more invasive the research, the greater should be the care in assessing research” (article 1.6). The Tri-Council Policy Statement also defines “minimal risk” in research as follows:

“if potential subjects can reasonably be expected to regard the probability and magnitude of possible harms implied by participation in the research to be no greater than those

encountered by the subject in those aspects of his or her everyday life that relate to the research then the research can be regarded as within the range of minimal risk”

The United States regulations further establish a number of risk thresholds:

minimal risk;
minor increment over minimal risk;
more than a minor increment over minimal risk.

In the US regulations, minimal risk means that “*the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life, or during the performance of routine physical or psychological examinations or tests*”. The common interpretation of the “risks of everyday life”, and the one intended by the authors, is that the ‘everyday life’ in question is determined by the baseline characteristics of the subject. For example: A healthy child’s everyday life does not include repeated needlesticks, hence, their performance would represent at least a “minor increment over minimal risk”. A diabetic child’s everyday life is different, and if the research in question does not involve additional needlesticks beyond the normal range the child experiences the risks would be, for that child, minimal. No definition is provided of “minor increment” or “more than a minor increment”.

An REB may consider performing “expedited review” (See II C.i , Mandate) of proposals involving no more than minimal risk, i.e., the study may be reviewed and approved by the chair or his/her designate subject to ratification by the REB. Expedited initial reviews are never acceptable for research covered by Article 21 of the QCC.

The thresholds also play a role with respect to review of research involving children and cognitively impaired persons. The Tri-Council Policy Statement requires that “*individuals who are not legally competent shall only be asked to become research subjects (...) when the research does not expose them to more than minimal risks without the potential for direct benefits for them*” (Article 2.5). In such cases, US regulations stipulate that studies involving more than a minor increment above minimal risk but presenting the prospect of direct benefit to the individual subject may be approved. However, research with no prospect of direct benefit, may be approved only by a specially Constituted Federal Committee.

Quebec’s Civil Code also sets a threshold for the same purposes:

“A minor or a person of full age who is incapable of giving consent may not be submitted to an experiment except in the absence of serious risk to his health and of objection on his part if he understands the nature and consequences of the act; the consent of the person having parental authority or of the mandatary, tutor or curator is necessary” (Appendix D, Article 20, Amended).

It remains unclear whether these thresholds mark off exactly the same threshold of allowable risk in research on cognitively impaired subjects. They do seem however to have taken a similar approach to the same problem: REBs, and perhaps other constituted committees recognized by the Minister of Health, have an important role in ensuring that the safety of children and others not be sacrificed for the sake of research (Appendix D).

Thresholds of this nature are not commonly found concerning research involving competent, adult subjects. The assumption is that competent subjects can be relied upon to look after their own interests. But this point only holds with respect to risk thresholds; the risk-benefit ratio itself still needs to be satisfactory, even if the research will only use competent subjects.

How can risks be balanced against benefits?

This question has no single, clear answer which will serve on behalf of all REBs. In principle, perhaps, agreement could be reached with respect to whether the risks to an individual subject are proportional to, or outweigh, his or her own hoped-for benefits. However, most readings of the regulations require that benefits to society, and to science itself, be considered (and potentially be crucial) in judging whether an acceptable ratio is present; and the risks to an individual may be formally incommensurable with benefits to a collectivity. By way of guidance, however, the 1987 MRC guidelines stated that benefits to a particular group ‘count’ more when it is that group which is assuming the risks of research than when the risks are borne by one set of people while the benefits will be reaped by another.

Conflicting interests.

REBs should determine whether the investigators are competent in the area being studied, and whether they serve dual roles (e.g., treating physician, teacher, or employer in addition to researcher) that might complicate their interactions with subjects. For example, an investigator’s eagerness for a subject to continue in a research project (to obtain as much data as possible) may conflict with his/her responsibility as a treating physician to discontinue a therapy that is not helpful or that results in significant adverse effects without countervailing benefit. Like wise, teachers or supervisors who conduct research could (wittingly or unwittingly) coerce student or employee-subjects (in this scenario “vulnerable” subjects) into participating. Thus, any potential conflicts of interest must be identified and resolved before REB approval is granted.

Research must be both valid and of value.

The **validity of research** depends upon the integrity of study results. If a research study is so methodologically flawed that little or no reliable information will result, it is unethical to put subjects at risk or even to inconvenience them through participation in such a study. One question that every REB member asks is “**To what degree is it our responsibility to review the underlying science of the proposed research?**” Clearly, if it is not good science, it is not ethical.

It is suggested that REBs should establish their authority to criticize the scientific merits of protocols and to exercise that authority to require that investigators correct design flaws identified by the REB before receiving REB approval, but that REB should recognize their limits in this regard as well. Although REB members do not need to be experts in scientific methodology or statistics, they should understand the basic features of experimental design, and they should not hesitate to consult experts when aspects of research design seem to pose a significant problem.

It is important that individual members experience the ongoing process of working through problems together and thereby develop the REB’s own “jurisprudence” and standard of operations. In the long run this will ensure consistency and objectivity.

An institution may wish to preface a review by an REB by its own internal scientific review. This should not supplant the work of the REB, but be viewed as a measure to ensure quality control and diminish the submission of premature or poorly designed protocols that waste the resources of the REB.

(iii) Process and Records

It is preferable that the REB reach its conclusion about a protocol by consensus. Consensus is useful in that the prolonged debate and need for compromise can lead to a creative discussion. However, a voting mechanism must be available for arriving at a decision and recording of dissenting opinions when consensus is not attainable after a prolonged discussion.

Minutes of the REB meetings must be kept in sufficient detail to record the following information: Attendance; actions taken by REB (including a record of the voting if applicable); the basis for requiring changes in or disapproving research; and a written summary of the discussion of contentious issues and their resolution.

The chair of the REB should communicate the REB's decision to the applicant in writing with minimal delay. A copy of the decision should be sent to the chair of the department where the research will be conducted. However, the REB may need to prolong the period required for final decision in those instances where appraisal by external referees are required. When research is sponsored by granting agencies or the pharmaceutical industry it is the investigator's responsibility to communicate with those parties as well as the research administration of the University (RGO, Contract Office) or the Hospital Research Institute and forward signed certificates from the REB. The institution's research administration, on the other hand, may not activate a research account until a signed certificate has been received.

The REB is required to perform review of approved research projects at least on an annual basis. More frequent reviews may be required based on the associated risks.

The responsibility for continued monitoring of approved research is as important as the initial review and approval. It is only after research has begun that the appropriateness of the consent procedure can be judged and that the risks can be evaluated and the preliminary results used to compute the actual risk/benefit ratio; the REB can then determine the correctness of the initial judgment.

It is important to note that the risk/benefit ratio may change over time. At the time of initial review, the REB should determine whether an independent **data and safety monitoring board** or committee is required, and should also set a date for reevaluating the research project.

During the course of a study, unexpected side effects may occur or knowledge resulting from another research project may become available. The REB may then need to reassess the balance of risks to benefits. In light of the reassessment, the REB may require that the research be modified or halted altogether. Alternatively, special precautions or criteria for inclusion may be relaxed. Between reviews, it is largely the researchers' responsibility to keep the REB informed of significant findings that affect the risk/benefit ratio. In larger studies or clinical trials, a data and safety monitoring committee may be responsible for keeping the REB up-to-date. Even isolated incidents of unanticipated adverse reactions must be reported to the REB. The REB must then decide whether the research should be modified.

When communicating its initial decision to the investigator, the REB must also clearly indicate that the approval is valid only for a specified, period of time (maximum one year) and instruct the investigator on the need for reporting accrual rates, general progress, and untoward effects and the time of such reporting.

The REB may use the following questions as a guide for ongoing review:

1. Are the actual risks and benefits as anticipated?

2. Have any subjects been seriously harmed?
3. Has the REB been informed of any unforeseen problems or accidents that may have occurred?
4. Should the REB request that the investigator(s) submit scheduled progress reports more often than annually?
5. Since the last REB review, have subjects been informed of any important new information that might affect their willingness to continue participating in the research?
6. Have any new findings, knowledge, or adverse effects come to light that should be, but have not been, communicated to subjects?
7. Does the progress of the project together with the results of other new research indicate that the REB should either impose special precautions or relax special requirements it had previously imposed?
8. Do the consent documents need to be revised?
9. Are the procedures agreed upon at the beginning of the research still being used?
10. Does the protocol adequately provide for continuing assessment of the balance between risks and benefits?
11. Should REB approval be continued, or should approval be suspended or terminated?

A more active process of monitoring research practice may be desirable, but few specific mechanisms can be cited. With the cooperation of each Hospital administration, its patient representative may devote an agreed upon period of time to review a randomly selected sample of research subjects and determine by retrospective interview the extent of familiarity and understanding by the study subject of the facts of the research and the consent process that was utilized. Such an approach is presently ongoing in one of McGill's teaching hospitals.

The REB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the REB's requirements or that has been associated with unexpected serious harm to subjects. If the REB decides to suspend or terminate its approval of a research project, such a decision shall be reported promptly to the investigator(s), department chair, appropriate institution officials, and the sponsoring agencies or companies (if any). The REB's report must include a statement of the reasons for the suspension or termination.

Records of the REB's functions should include copies of all research protocols reviewed, minutes of meetings, membership, correspondence with investigators and records of continuing reviews.

Records relevant to clinical trials and unique to the REB must be retained for 25 years as per Canada Food and Drug Regulations – Division 5 (C.05.012). REB records of research projects that are not subject to Canada Food and Drug Regulations – Division 5 must be kept for at least three years after termination of the research. All consent documents must be retained by the investigator and should also be part of a patient's record. The latter should, if part of the physician's private records, be kept in accordance with "Regulation respecting the keeping of records by physicians" (Medical Act and Professional Code) for at least five years.

D. Confidentiality of Records

The University and the hospitals being "public bodies" must conform with the "*Act respecting access to documents held by public bodies and the protection of personal information*". While the intent of this Act is to give access to documents, two significant restrictions to such access essentially require or enable the institution to maintain in confidence most of the contents of REB records (see Appendix J for relevant

excerpts of the Act) because release of information would compromise the rights respecting intellectual property of the institution itself or of third parties or the confidentiality of nominative information concerning a person. Moreover, a public body may refuse access to the minutes of its meetings of its members until 15 years have expired.

Thus, although the notion of meetings and deliberations of REBs being open might have some attractiveness, such a practice would in the opinion of the Research Ethics Committee of the Faculty of Medicine be improper.

E. Summary of Institutional Responsibilities.

1. An Institution (university or hospital) engaged in research involving human subjects must ensure that research performed within its jurisdiction or by members of its staff has the approval of a multidisciplinary Research Ethics Board (REB) and must establish such a REB within the Institution and provide adequate infrastructure for its proper function.
2. Institutions with a large number of research projects may establish more than one REB, but may not discharge their responsibility for review through ad-hoc committees or committees formed entirely within University or Hospital departments. In the Faculty of Medicine, REBs report to the Principal via the Dean of Medicine (for research on campus) who may delegate authority to the Associate Dean (Research). Hospital-based REBs report to the Hospital Board of Directors.
3. Where multiple McGill affiliated hospitals participate in the same research protocol, inter-hospital agreements may be developed and one REB be designated for review. Such an agreement exists among the hospital REBs, designating the McGill IRB.(Section VI)
4. Each REB must as a minimum include five members with qualifications that meet the requirements of Article 1.3 of the Tri-Council Policy Statement, and should probably include several more considering the breadth of research in the Faculty and affiliated hospitals. Where applicable, the Institution must follow the Plan d'action ministeriel en éthique de la recherche et en intégrité scientifique regarding REB composition. Members should be appointed by the Dean upon recommendation by the Chair, IRB (for campus based research) or the Hospital Board upon recommendation of the Chair, REB, for a minimum of three years (renewable). The Dean of Medicine decides whether to renew a member for an additional term upon consultation with the Chair. For large committees it is advisable to appoint a co-Chair. Frequent turnover of members is not recommended since it is important for an REB to establish its own jurisprudence and experience in working through problems together.

A quorum of a REB is discussed in Article 1.7 of the Tri-Council Policy Statement and requires, as a minimum, that the members in attendance must possess the range of background and expertise stipulated in Article 1.3. Membership shall ensure that the committee has the professional competence and experience to render mature, consistent and considered judgments and promote respect for its decisions.

5. Meetings shall be held monthly or more frequently if required. The REB shall review the probability of risks and benefits as well as the validity and value of the proposed research. When needed, consultants may be invited to meetings to provide expert advice. The REB may also invite the

investigator to provide information about a protocol, but neither the investigator nor anyone with a conflicting interest may participate in the review and deliberations of the REB. While it is preferable that the REB reaches its conclusion by consensus, a voting mechanism must be available.

6. The REB must communicate its decision to the investigator in writing and must indicate the period for which approval is valid (maximum one year) and whether special requirements are associated with the approval.
7. Minutes of REB deliberations must be kept for a minimum of three years after termination of the study and must be kept in sufficient details to record attendance, actions taken (including a record of voting), and a summary of the discussion of the contentious issues and their resolution. Records relevant to clinical trials and unique to the REB must be kept for 25 years.

III – Responsibilities of the Investigator

A. Who can submit protocols and how.

Any Faculty member with the rank of Assistant Professor or above including part-time or GFT-H appointees may submit protocols and act as principal applicants. Hospital employees including attending staff, and other professionals may also submit protocols to the REB of their employing organization. Students, graduate students, postdoctoral fellows, residents and fellows are not eligible to submit protocols as principal, responsible applicant. Visiting academics (i.e. visiting professors) may act as principal applicants if this is consistent with the activities envisioned by the host department and the Dean. Adjunct professors are not normally eligible to submit protocols as principal applicants.

The qualifications and experience of the principal applicant should be considered when reviewing proposals. Proposals that require skills beyond those held by the principal applicant should be modified to meet those skills, have additional qualified personnel added, or be disapproved.

Protocols involving interventions or assessments that require a professional license must include co-applicants possessing such license (physician, nurse, physical or occupational therapist, dentist, psychologist).

At the time of submission to the REB, the protocol must be countersigned by an individual with supervisory responsibility for the activities in the institution. Normally this will mean a department chair, a hospital department chair or a director of a Research Institute, or a Director of Clinical Research at a Research Institute.

Protocols shall contain complete descriptions of the proposed research: its purpose, experimental design, risks and benefits, cited references, justification for using the proposed subject population, plans for recording and maintaining data, plans for independent monitoring if needed, and plans for subject recruitment (including copies of advertisements). A copy of the informed consent document must also be included (see below). A copy of the budget should be included to enable the REB to determine if there is a potential for conflict of interest.

The investigator shall inform the REB of any actual, potential or perceived conflicts of interest. If personal remuneration (from a company) is anticipated or if the investigator or a member of his/her immediate family has a financial interest in the company that sponsors the research, this must be disclosed to the REB. If a financial interest exists, the details shall be reported in confidence to the Dean (or Hospital CEO for a hospital employee) who shall determine if the investigator has a conflict of interest or the appearance thereof according to prevailing University or Hospital Policy on Conflict of Interest and if special oversight during the conduct of the project is required.

When the proposed research is a multi-institutional study the investigator's own summary (couched in non technical terms), justification for participation and patient availability must be appended. Normally such documentation should not exceed two pages.

While the investigator must not be present during REB deliberation or participate in the review or voting, the investigator may be invited by the REB to provide information on the protocol.

It is the investigator's responsibility to provide regular reports to the REB at least on an annual basis or as

instructed in the approval letter. Also, the investigator must report immediately to the chair of the REB any adverse reactions (even isolated or apparently unrelated incidents). Any significant changes to the protocol must be submitted for review and approval by the REB. Minor changes shall be reported during regular reporting.

B. Obtaining Free and Informed Consent

(i) General

Canadian courts have had two occasions to delineate the obligations of disclosure in the context of research with no intended benefit for the subjects. In Halushka v. U. of Sask., (1965), 53 D.L.R. (2d) 436, the court found the investigators liable for not giving a “*full and frank disclosure of all the facts, probabilities and opinions which a reasonable man might be expected to consider before consenting to the experiment.*” It further eliminated any privilege a clinician might have, in certain rare instances, to withhold information for a patient’s benefit, stating: “*There can be no exception to the ordinary requirements of disclosure in the case of research as there may well be in ordinary medical practice. The example of risk being properly hidden from a patient when it is important that he should not worry can have no application in the field of research.*”

In Weiss v. Solomon [1989] R.J.W. 731, a Quebec court found that both an investigator and the REB acting on behalf of the Institution had failed in their duty to make or ensure disclosure of risks involved in the research (the institution was held liable for the committee’s negligence). The Court cited the Halushka case, describing the obligation of disclosure in research as meriting “*the highest possible standard*”.

Thus, informed consent is one of the primary ethical and legal requirements underpinning research with human subjects; it reflects the basic principle of respect for persons. It is too often forgotten **that informed consent is an ongoing process, not a piece of paper or a discrete moment in time**. Informed consent assures that prospective human subjects will understand the nature of the research and can knowledgeably and **voluntarily** decide whether or not to participate. This assurance protects all parties - both the subject, whose **autonomy** is respected, and the investigator, who otherwise faces legal hazards. The “proxy consent” of someone other than the subject is not the same as the subject’s own consent, although it may be an acceptable substitute when a subject is unable to give informed consent.

The elements of informed consent include the following:

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject’s participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
2. A description of any reasonably foreseeable risks or discomforts to the subject;
3. A description of any benefits to the subject or to others which may reasonably be expected from the research;
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
5. A statement describing the extent to which confidentiality of records identifying the subject will be

maintained, and anticipated uses of the data;

6. For research involving more than minimal risk, an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
9. An explanation of possible commercialization of the results, and any apparent, actual or potential conflict on the part of investigator, institution or sponsor.

Investigators may seek consent only under circumstances that provide the prospective subject or his or her representative sufficient opportunity to consider whether or not to participate, and that minimize the possibility of coercion or undue influence. Furthermore, the information must be written in language that is **understandable** to the subject or representative.

Since subjects always retain the right to withdraw from a research project, their continuing consent is important. Investigators and REBs should be aware that subjects often seem to forget they are involved in research or have difficulty distinguishing research interventions from diagnostic and therapeutic interventions. When a research proposal is first approved, the REB should determine whether consent should be renegotiated as a formal matter during the course of the research. If renegotiation is required, the frequency and/or events that will trigger this process should be decided upon and made clear to the investigators.

Investigators must also inform subjects of any important new information that might affect their willingness to continue participating in the research. For instance, a totally independent study might find an unanticipated adverse effect (e.g., birth defects or carcinogenicity) in a drug or substance being used in research. REBs should determine whether any new findings or reports of adverse effects (in the present study or other studies) should be communicated to subjects. The REB should also receive copies of any such information conveyed to the subjects.

While the consent must be in writing, a subject may verbally withdraw from participation in research (See Appendix Québec Civil Code, Article 24).

(ii) Special Considerations

When the proposed subjects are seriously ill, or, for some other reason, might not be able to make decisions about continuing in the research (e.g., children or cognitively impaired individuals), the REB may suggest that family members be closely involved with the research to evaluate its impact on the subject and to request that the subject be withdrawn from the study if conditions warrant.

The legal capacity of cognitively impaired individuals or of children to consent must be considered in light

of relevant Provincial legislation. A concept has developed that a child or adult incapable of giving legally and ethically acceptable consent may give an “assent” which signifies a level of autonomy, although this would not replace the voluntary, informed consent of the child’s parent(s) or the guardian. The condition under which children can volunteer for non-therapeutic research of no benefit to them are contentious.

Article 21 of the Quebec Civil Code provides that minors and adults incapable of giving a legally valid consent may only be included as research subjects in the absence of their objection and providing that they understand “*the nature and consequences of the act.*” Article 21 would require that, at a minimum, where children or adults with cognitive impairments are capable of some understanding, they be given explanations of the proposed research in appropriate language, and that those capable of assenting express no objections to participating.

(iii) Modification of Consent Procedures

The REB may under special circumstances approve a waiver of some or all of the consent requirements provided that **all** of the following apply:

1. the research involves no more than **minimal risk** (see above) to subjects;
2. the waiver or alteration will not adversely affect the rights and welfare of the subjects;
3. the research could not practically be carried out without the waiver or alteration; and
4. whenever appropriate, the subjects will be provided with additional pertinent information after they have participated in the study.
5. The waived or altered consent does not involve a therapeutic intervention

Most commentators suggest that the REB also determine whether the knowledge being sought is important enough to justify whatever invasion of privacy may be required either to obtain information about un-consenting (or unaware) subjects or to involve them in research under false pretenses.

Sometimes, especially in epidemiological studies, scientists need to review thousands of records to identify appropriate subjects for their study. It is often difficult, if not impossible, to obtain the permission of everyone whose records are contained in the files. For this preliminary part of the research, REBs will generally waive the consent requirement if:

1. they are satisfied that the information contained in the files is not particularly sensitive;
2. the investigator has devised procedures to protect the confidentiality of the information to be collected; and
3. the study could not practicably be carried out if consent were required.
4. Under the Quebec Health & Social Services Act, the authorization of an institution’s DPS is required.

Contacting potential subjects to obtain further information must be approached with considerable care. The investigator shall submit plans to the REB on how the initial contact with potential subjects will be made (e.g., through employer, physician, institution having custody of the records, or directly by the investigator) and what information will be conveyed at that time.

When patients give information about themselves to a doctor or hospital for the purpose of facilitating diagnosis or treatment of disease, they do so in a relationship of trust. They generally expect that the information will be shared only as necessary for their health care. **Nor do they necessarily intend that**

stored specimens obtained at the time of examination or treatment (surgery) or at autopsy be used for research.

On January 1, 1994, a Bill came into effect in Quebec of which article 22 states that “*A part of the body, whether an organ, tissue or other substance, removed from a person as part of the care he receives may, with his consent or that of the person qualified to give consent for him, be used for the purposes of research.*”

It is recommended that hospitals develop “general purpose” consent forms to be used at admission and containing paragraphs referring to the potential use of tissue for research which has the “Institutional” approval (see Appendix L for examples).

(iv) Recruitment of Volunteers

When research is not conducted in association with medical care, recruitment and payment of volunteers must be carried out under conditions that minimize the possibility of coercion or undue influence. Generally the subjects should be recruited by open, written invitation rather than by personal solicitation. Determination of what constitutes appropriate incentive is often difficult. It is important that the investigator and the REB are familiar with accepted standards within their community as well as the anticipated discomforts and inconveniences of a study.

Under the Quebec Civil Code (Article 25) “*an experiment may not give rise to any financial reward other than the payment of an indemnity as compensation for the loss and inconvenience suffered.*” Thus, reimbursement for travel, babysitting, and so forth may also be provided in addition to loss of earnings, but may not constitute an inducement. Standard payments may be established for each tissue or fluid sample collected, depending on the type of sample (blood, urine, or saliva) and the time (day or evening) the sample is to be collected. Alternatively, subjects may be paid an hourly rate or a fixed amount, depending on the duration of the study and whether the study requires admission to a research ward.

In compliance with Measure 9 of the Plan d’action ministérielle, an investigator conducting research involving human subjects within institutions that fall under the responsibility of the MSSS or where there is an MSSS designated REB, is required to maintain a list of participants for a period of at least one year after the project ends. The list must include the name and contact information of the participant, the REB project number and the start and end date of the project. This requirement does not extend to projects where subjects will be totally anonymous or to records research.

(v) Record-Keeping

The McGill Policy on Research Ethics recommends that all original data be maintained for a period of at least 5 years from the date of publication. Records must include the approved ethics application and all supporting documents, signed consent forms, amendments, renewals, closing reports and adverse event reports. Researchers are responsible for ensuring that the data is maintained in accordance with the confidentiality and security promised to the study participants. Researchers are responsible for following other requirements applicable to their particular research (ex. Health Canada’s Food and Drug Regulations requires records to be kept for 25 years).

C. Summary of Investigator’s Responsibilities

An investigator wishing to conduct **research on human subjects** (i.e. a systematic investigation, including research development, testing and evaluation designed to develop or contribute to generalizable knowledge) must submit a research protocol approved by a departmental chair, a departmental committee, or a specifically authorized individual within the Hospital, for review by the investigator's institutional REB. Only faculty members with the rank of assistant professor or higher (part- or full-time) or Hospital attending staff or other Hospital professionals may submit protocols and act as principal, responsible applicants.

The applicant shall ensure that the protocol includes complete descriptions of the proposed research: purpose, design, justification for using the proposed subjects, risks, benefits, cited references, plans for recording and analyzing data, plans for subject recruitment, and a copy of the informed consent. The applicant shall complete a "checklist" and an "application for approval of a research protocol" and shall follow the consent form requirements (see appendix L for examples).

If the REB approves the protocol it is the investigator's responsibility to keep the REB informed of significant findings that affect the risk/benefit ratio. Even isolated incidents of unanticipated, adverse reactions must be reported to the REB. Also, the investigator must apply for renewal of REB's approval at least annually or more frequently if required by the REB. Any revisions to the protocol also require the REB's approval (see amendment submission form, appendix L).

An investigator conducting research involving human subjects within institutions that fall under the responsibility of the MSSS or where there is an MSSS designated REB, is required to maintain a list of participants for a period of at least one year after the project ends.

Data and records need to be maintained for a period of at least 5 years from the date of publication and other requirements applicable to their particular research.

Researchers are responsible for ensuring that the data is maintained in accordance with the confidentiality and security promised to the study participants.

When the study is terminated, the investigator shall submit a "protocol termination form" (appendix L).

If a research protocol is supported by a third party under a contractual agreement with the Institution, the investigator shall respect the terms of the contract which are applicable to his/her performance, i.e. maintenance of confidentiality and records. The investigator shall also disclose to the REB any conflict of interest or the appearance thereof which could adversely affect, or appear to affect, the investigator's objectivity or professional association with the research subjects.

IV – Appeals of the Decisions of Research Ethics Boards

The Research Ethics Committee of the Faculty of Medicine has established a procedure whereby the various REBs on campus and in the Hospitals collaborate on the Appeals process. A committee is named by the Dean of Medicine from among the members of the existing REBs with sufficient alternates to ensure that the committee hearing a case would not use members from the original REB. The Boards of all affiliated Hospitals have agreed that they are bound by the results of the appeal process.

Procedures for Appeals from the Decisions of Research Ethics Boards in the Faculty of Medicine, McGill University

March 1, 1999

The Research Ethics Appeal Committee of the Faculty (hereafter “Appeal Committee”) is established in accordance with Article 1.11 of the Tri-Council Policy Statement “*Ethical Conduct for Research Involving Humans*” to hear appeals of decisions of Research Ethics Boards (hereafter “REBs”) of the Faculty and those of Affiliated Hospitals.

1. Notice of appeal

- 1.1. Notice of Appeal must be filed with the Associate Dean (Research) of the Faculty of Medicine within 6 months of the rejection of a protocol by a Research Ethics Board. The notice must clearly state the grounds upon which the appeal is filed.
- 1.2. The Associate Dean shall determine that a definite impasse exists between the researcher and the REB whose decision has been appealed.
- 1.3. The Associate Dean shall then charge the Chair of the Appeal Committee (or the Co-chair as appropriate) to call the Appeal Committee to hear the case. The Associate Dean shall ensure that all parties have copies of the notice of appeal.

2. Composition of the Appeal Committee

- 2.1. The Appeal Committee shall be named annually by the Dean of Medicine with consideration to recommendations received from the Research Ethics Committee of the Faculty. With the exception of the Chair of the Institutional Review Board, no member can serve more than three consecutive terms.
- 2.2. The composition of the Appeal Committee shall be as follows: The Chair shall be the current Chair of the Institutional Review Board of the Faculty of Medicine. The Dean of Medicine shall name the following members: three Chairs and alternate of hospital-based Research Ethics Boards, one of whom is designated as co-chair; a lawyer and alternate; an ethicist and alternate; two community members and alternate from different Research Ethics Boards. The Co-chair shall act as Chair if the appeal is from a decision of the Institutional Review Board. No members of the Appeal Committee hearing a particular appeal can be affiliated with that REB.

- 2.3. A quorum consists of the Chair(or Co-Chair), two hospital-based REB Chairs, a lawyer, an

ethicist, and one community member. The appeal committee shall appoint ad hoc experts as required and described in the Tri-Council Statement “Ethical Conduct for Research Involving Humans”.

3. The Appeal

- 3.1. It is not the intention that the appeal process should simply substitute the opinion of one group of reasonable individuals with that of another. The Appeal Committee shall therefore have jurisdiction to hear appeals based only on failure to follow proper procedures, a conflict of interest or evidence of bias.
- 3.2. The appeal shall involve two distinct stages; i) to determine whether grounds exist that would require that the protocol be considered anew and ii) a de novo consideration of the protocol if grounds for appeal are established.
- 3.3. In the first stage, the mandate of the Appeal Committee is to determine whether the protocol received fair and reasonable consideration, and not to make a de novo decision on the ethical merits of the protocol.
 - 3.3.1. The Appeal Committee shall receive for its consideration the notice of appeal, all the documentation provided to the Research Ethics Board, and the minutes of the REB regarding the protocol. The investigator shall appear expressly to present evidence to establish the grounds for appeal as outlined in 3.1. The Chair of the REB or representative shall also appear simultaneously. The parties are not assisted by advisors.
 - 3.3.1.1. At the hearing, the Investigator presents evidence to support grounds (article 3.1) that would invalidate the Research Ethics Board decision. The Chair of the REB responds. The Appeal Committee can question both parties. Each party is given a single opportunity for brief summation, with the Investigator speaking last.
 - 3.3.1.2. The Appeal Committee may elect to hear witnesses if, in its opinion, it is relevant to reaching a decision on the grounds of the appeal.
 - 3.3.2. The Chair of the Appeal Committee shall provide a written decision of the Appeal Committee concerning the grounds of the appeal with copies to the investigator, the REB and the Associate Dean (Research).
- 3.4. If the Appeal Committee finds that there has been a failure to follow proper procedures, or evidence to support a possible conflict of interest or bias, it proceeds to the second instance.
 - 3.4.1. In a second meeting the committee shall undertake a de novo decision on the ethical merits of the protocol in question. All the documents made available to the local REB and the relevant minutes of the REB are to be available to the Appeal Committee. The Appeal Committee must afford the researcher an opportunity to appear to answer questions.
- 3.5. The Appeal Committee shall meet within 30 days of receipt of the written notification of the

appeal, and shall render a written decision on the grounds of appeal within 30 days of that meeting. If grounds are established, a written decision on the ethical merits of the protocol shall be provided within an additional 60 days.

- 3.6. The decision of the Committee is final and a written decision is provided to the researcher, the REB and the Associate Dean Research of the Faculty of Medicine.

4. Responsibilities

- 4.1. The Institutional Review Board of the Faculty of Medicine and each Hospital Research Ethics Board, with the approval of the Board of Directors of the Hospital, agree that the decisions of the Appeal Committee are binding.
- 4.2. The original Research Ethics Board assumes the sole responsibility for administering and monitoring a protocol approved by the Appeal Committee.

5. Reporting

- 5.1. The Dean of Medicine shall make an annual report on the activities of the Appeal Committee to the Vice Principal Research.
- 5.2. Hospital-based Research Ethics Review Boards are responsible for reporting to the Board of Directors of their Hospital any Appeal Committee decisions relevant to their own function.

V – Liabilities

A. Legal Liability

The law concerning civil liability applies to the review of research protocols and the conduct of research itself. REBs are not legal entities and therefore cannot themselves incur legal liability. However, investigators, members of REBs and the institutions in which they operate may be held responsible for damage caused by their fault.

In order to establish civil liability in Quebec, the person alleging that another committed a fault must prove that: 1) he or she suffered an injury; 2) that the defendant failed to act reasonably diligently in the exercise of his or her profession; and 3) that the injury was caused by the defendant's negligent conduct.

In the case of **Investigators**, liability can arise when the requirements for research set out in the Code (Appendix D) or the actions or omissions in the conduct of the research fall below the standard of reasonable skill and diligence of practitioners at the appropriate level of qualification in the circumstances. In other words, whether a professional acted diligently in the exercise of his or her profession will be measured by what a reasonable professional of the same required degree of experience or standing would do in comparable circumstances. International codes of research ethics, the Tri-Council Policy statement or other applicable research ethics guidelines may be evidence of standards.

If compliance with an ethical requirement is part of what a reasonably careful and competent professional of the same standing would do in the circumstances, it may be considered as a part of the legal standard.

As agents of the institution, **members of an REB** can control the conduct of investigators to prevent reasonably foreseeable injuries to research subjects. Committee members accept their appointments knowing that the central focus of their work is the protection of research subjects. It is possible, therefore, that members can be held responsible for damage caused by their negligence/fault although it would be difficult to define with precision the "skill and diligence expected of a similarly situated committee member in comparable circumstances". Procedures for review vary from committee to committee. Individual committee members with greater expertise may be held to a more extensive or demanding content in fulfilling the standard of care. It is also possible that some members may be able to prove that, while approval of a protocol may have been negligent, they relied upon the expertise of another committee member or an outside reviewer in deciding to approve it. Whether they would be liable for the latter's negligence would depend on whether such reliance was reasonable in the circumstances.

An **institution** itself may be responsible for injury caused by its own negligent actions or omissions if its own duty, in particular its duty to establish a responsible system of operations, to act with skill and diligence can be established. The nature of an establishment's duty would include, at a minimum, such factors as use of appropriate care to assure the qualifications of those allowed to conduct research in the institution and implementation of adequate review mechanisms, including the establishment and proper function of REBs. Institutions may also be vicariously liable for the negligent actions of their employees, for investigators who conduct research within the institution, and for members of REBs who act as agents for the institution when reviewing research.

B. Liability Insurance

For purposes of liability insurance coverage, employees acting within the scope of their University responsibilities are covered under the insurance of their employer. Thus, McGill employees (i.e. salaried by the University or from funds administered by the University) who conduct research on human subjects or participate in the review of research protocols as members of an REB are included in the University's insurance coverage. Also included in this coverage, by resolution of the Executive Committee of the Board of Governors held on October 14, 1997, are members who serve on a McGill REB, but are not McGill employees (such as community members).

Health professionals, investigators conducting research in a Hospital and non-Hospital employees serving on a Hospital REB are covered by the Hospitals' (AHQ) insurance.

VI – Agreements

Federal Wide Assurance and IRB Authorization Agreements

The Faculty of Medicine, acting for McGill University, maintains a Federal Wide Assurance (FWA 00004545) with the Department of Health and Human Services in the USA as do our affiliated Hospitals. We have signed IRB Authorization Agreements with the Hospitals that allow the McGill IRB to review research that occurs at more than one Hospital site, with the intent to simplify the process and avoid duplication. The same agreement states that each Hospital REB is authorized to act simultaneously for McGill University for the review and oversight of research involving human subjects by McGill Faculty and trainees at that Hospital site. This satisfies the requirement that the University also review research carried out by its researchers in the hospitals, again without duplicating the process.

Research conducted under the FWA is subject to review by the Office of Research Integrity (ORI) should there be allegations of scientific misconduct. The Associate Dean Research, Faculty of Medicine, has been authorized by the Vice Principal Research to file the annual report to the ORI on possible allegations of scientific misconduct involving DHHS supported research. This report is filed on behalf of McGill University and its affiliated Hospitals.