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Research Ethics Board

Policy and Procedures

ETHICAL REVIEW OF RESEARCH INVOLVING HUMANS

"Before you submit....." Research Ethics Board (REB) submission checklist:

- completed application form including necessary signatures
- study protocol
- completed science review
- itemized response to science issues raised
- consent and assent forms
- contract sign off (if applicable)

Contact:

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Introduction

Authority of the Research Ethics Board (REB) at Health Canada

"The design and performance of each experimental procedure involving humans should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed."

Second Principle, Declaration of Helsinki, 2000

The institution in which research involving human subjects is carried out shall mandate the REB to approve, reject, propose modifications to, or terminate any proposed or ongoing research involving humans which is conducted within, or by members of, the institution, using the considerations set forth in this Policy as the minimum standard.

Tri Council Policy Statement, Ethical Conduct for Research Involving Humans, Article 1.2

The mandate of the REB at Health Canada is to ensure that "all research involving humans carried out by Health Canada, or by investigators associated with Health Canada, meets the highest scientific and ethical standards" and that "safeguards are developed which provide the greatest protection to participants who serve as research subjects.

The REB at Health Canada is an independent, decision-making board that reports to the Chief Scientist of Health Canada. The REB is guided by the ethical principles found in the Tri-Council Policy Statement, Ethical Conduct for Research Involving Humans. The REB is concerned solely with the protection of human involved in research. It will provide the Department with an independent review mechanism and fulfil an educational function for Health Canada managers and researchers.

Scope of the REB Mandate:

The REB will review all research involving humans. It will review research applications in circumstances of:

- intra-mural research,
- all research carried out on Health Canada premises that involves technical or consultation support including equipment, laboratories, or other facilities,
- research undertaken in collaboration or partnership between Health Canada and external researchers,
- grants and contributions funded research projects,
- contract research.

REB Membership

The REB consists of eight members and includes two ethicists, one from the St. Boniface General Hospital in Winnipeg, and the other from the University of Alberta, one researcher from outside Health Canada, two researchers from within Health Canada and two community representatives. The REB also consists of one member with legal expertise from the University of Toronto. The tenure of the membership to the Research Ethics Board will be for a period of three years to a maximum of six years.

Reviewed by another REB

A protocol that has been previously reviewed and approved by an outside REB that is guided by the ethical principles found in the Tri-Council Policy Statement, Ethical Conduct for Research Involving Humans, ***must*** still be submitted for Health Canada REB review. A REB application - Appendix I has been developed for this purpose.

Please Note: If doubt or uncertainty remains about what requires REB approval, the protocol should be submitted to the REB Secretariat for a decision.

STEP 1
IS AN ETHICAL REVIEW REQUIRED?

All research involving humans at Health Canada must be reviewed and approved by the Research Ethics Board (REB). Approval must be obtained in writing before the research begins.

1. Definitions

Research

- is an activity designed to test an hypothesis, permit conclusions to be drawn and thereby to develop or contribute to generalizable knowledge.[1] Generalizable knowledge consists of theories, principles or relationships, or the accumulation of information on which they are based, that can be corroborated by accepted scientific methods of observation and inference. In the present context "research" includes both medical and behavioural studies pertaining to human health. Usually "research" is modified by the adjective "biomedical" to indicate its relation to health.
- involving human subjects is required at some time for progress in medical care and disease prevention depends upon an understanding of physiological and pathological processes or epidemiological findings. The collection, analysis and interpretation of information obtained from research involving human beings contribute significantly to the improvement of human health.
- uses scientific methods and standardized protocols.

Surveillance

- is a routine public health activity, one of the really fundamental features of functioning public health system.
- applies research methods in a routine matter. It is a systematic ongoing collection, collation and analysis of data and the timely dissemination of information to those who need to know so that action can be taken.

[1] Council for International Organizations of Medical Sciences (CIOMS), International Ethical Guidelines for Biomedical Research Involving Human Subjects, 2002.

Quality Assurance

It is also important to distinguish research from quality assurance for the purposes of REB review.

Quality assurance aims to:
- evaluate and review the quality of a service, or a product within a particular institution;
- identify problems or deficiencies in delivery;
- design activities and procedures to overcome these deficiencies; and
- monitor the effectiveness of corrective measures.

Quality assurance does not require REB approval when it:
- is intended solely for internal use within an individual institution;
- only measures the integrity of the functions delivered by the organization or performance of staff internal to the institution while carrying out their duties and responsibilities; and
- is not intended, through publishing, to contribute to generalizable scientific knowledge about treatments and procedures.

2. Secondary Use of Data in Research

Secondary use of data refers to the use, in research, of data contained in records collected for a purpose other than the research itself. Examples include health records and clinical databases.

This issue becomes of concern only when data can be linked to individuals and becomes critical when the possibility exists that individuals can be identified in published reports. [2]

In instances when data has been anonymized, REB approval may not required.

In instances when identifying information is involved, REB approval is required. If sensitive information is involved, ex.: HIV status, mental health status, or there is a significant risk that confidentiality may be breached, subject consent is also required.

An abbreviated REB Application - Appendix B for an expedited REB approval process has been developed for research involving secondary use of data.

[2] Tri-Council Policy Statement 'Ethical Conduct for Research Involving Humans', 1998 s. 3C

3. The Use of Human Tissue in Research

REB review and approval of research involving human tissue are also required.

Consistent with the Tri Council Policy Statement, individual, prospective consent must be obtained from the tissue donor at the time of tissue retrieval. For previously collected tissue, when the tissue is "anonymized" , there is no need to seek permission. Tissue that is not anonymized, may only be used with consent of the donors.

4. The Use of Fetal Tissue in Research

Guided by the Tri Council Policy Statement, the REB requires that consent for research be obtained prospectively from women undergoing therapeutic abortions.

The following consent clause should be appended to the consent to termination.

> *"You are requested to consent to the use of fetal and placental tissues in scientific research. You may choose not to give consent. The decision whether to consent will not affect your right to an abortion, including your rights to any health care. All tissue information will remain anonymous and will not be identifiable in any way."*

5. The Use of Genetic Material in Research

In response to the unique ethical issues presented by genetic research, a template for Consent for Genetic Testing - Appendix H has been developed.

6. Grants and Contributions

Grants and contributions programs are important mechanisms through which Health Canada works in partnerships to establish a wide variety of health programs that maintain and enhance the health of all Canadians and support First Nations and Inuit people. As these are funded by Health Canada, an ethical review must be undertaken by the Health Canada REB. It is the responsibility of the researcher to ensure that approval has been received from the Research Ethics Board. No funding will be released until such approval has been obtain. The researcher must submit a REB Application - Appendix M to the REB Secretariat.

STEP 2
PREPARING THE APPLICATION

A complete Research Ethics Board (REB) application package has five main components:

- the completed application form with all necessary signatures;
- research protocol;
- consent and assent forms;
- completed science review and itemized response;
- research director sign off and contract sign off (if applicable).

1. The Application Form

The REB Application - Appendix A is to be completed for ethical approval of studies involving humans. For an expedited review by the REB, the REB Application - Appendix B should be completed. Criteria for an expedited review can be found under Step 3, Section 3.

The following provides explanatory information about some of the questions on the application form:

#1 - Project Title
Please provide the full title of the research project. The title must be the same as the title found on the research protocol. Please use the same title and assigned REB file number consistently in all future REB correspondence.

#2 - Investigators
The principal investigator (PI) will assume full responsibility for the study as detailed in the research protocol and must sign the application.

Address for Correspondence
Please include the name of the person (whether it is the PI or another person), address and telephone number, to contact regarding REB issues. Do not leave this blank.

#6 - Sponsoring Company (if applicable)
The contract, if any, for this study/project must be reviewed and approved by the Director of the Division and be included with the application to be submitting to the REB Secretariat for obtaining ethical approval. Conflict of interest disclosure information must be provided, ex.: commercial interests, consultative relationships.

#7 - Scientific Peer Review
In order for research to be ethically acceptable, it must be scientifically sound. If research does not have sufficient scientific merit, generalizable knowledge cannot be anticipated and the reason for undertaking the research vanishes. Even a negligible risk of harm resulting from research that may not yield meaningful results is inherently unethical. Therefore, before the research can be reviewed by the REB, it must be reviewed to ensure scientific validity. Please refer to Section 4 for detailed information on the review process.

#8 - Signatures of Approval
The research must be authorized by the relevant Branch(es) and/or Division(s) Heads at Health Canada. The Branch/Division Head's signature confirms the scientific integrity of the research, the feasibility of conducting the research at Health Canada, and that appropriate monitoring will occur.

All signatures must be obtained before the application can be processed. If signatures are missing, the application will not be processed.

#13 - Recruitment
Special care must be taken when recruiting colleagues, employees, family or friends as control subjects. A staff member may feel obligated to participate to please his/her employer, or be concerned that refusal to participate may threaten his/her position. Alternatively, the investigator, by reason of the relationship, may feel unable to fully inform the person of an unexpected or negative finding of the study. This is particularly problematic when the finding could affect their present or future employment relationship.

#15 - Interventions
All interventions (procedures and medications) that are not part of the standard care of the patient must be clearly stated in this section. If there are none, this also needs to be stated.

#16 and 17 - Potential Harms and Potential Benefits
Please describe the potential for harm and benefit in simple lay terms.

There is always a potential for harm (if only as an inconvenience to the subject) to participation in research. This must be stated in this section. If there are no potential benefits, this must also be stated.

Article 1.6 of the Tri-Council Policy Statement states:

> "Potential harms are usually understood in relation to risks, which are defined in terms of the magnitude of a harm and the probability of its

occurrence. Both potential harms and benefits may span the spectrum from minimal through significant to substantial. A proportionate approach to ethics review thus starts with an assessment, primarily from the viewpoint of the potential subjects, of character, magnitude and probability of potential harms in the research."

#18 - Monitoring
Please describe the proposed methods of monitoring this study for adverse events.

2. The Research Protocol

A research protocol is a separate document clearly describing the science and the ethics of the research.

The scientific component should include a discussion of:
- the research problem, background analysis and hypothesis;
- the relevant literature;
- study objectives;
- the research design and methodology (inclusion/exclusion criteria, sample size, justification and statistical methods for assessing results);
- the budget and available resources;
- contract with sponsor (where applicable).

The ethics of the research may also include a discussion of the following:
- potential benefit to participants and others;
- potential harm to participants and others;
- alternative treatments or procedures;
- how potential for harm will be minimized – including the risk of breach of privacy and confidentiality;
- process for obtaining consent and assent.

3. Research Consent and Assent Forms

Consent is informed when it is given by a person who understands the purpose and nature of the study, what participation in the study requires the person to do and to risk, and what benefits are intended to result from the study. The research must provide the information that a reasonable volunteer would want to know in this situation, and must ensure that the person understands the information. This includes informed discussion of alternatives to participation in the research. The process must be free of both coercion and excessive inducement to participate (as a guideline to what is excessive, the risk involved should be acceptable to the subject even in the absence of

inducement). Direct costs (if any) to participants (ex.: cost of travel, meats, etc.) can be reimbursed.

Typically, the process of informed consent involves:

- information sheets containing an explanation of the purpose of the research, expected duration of participation and procedure. If concealment is necessary, the subject should be told that not all the details of the research can be revealed, but s/he will get a full explanation later. Concealment is usually only acceptable in psychology research;
- description of any foreseeable risk or discomfort;
- description of any probable benefit;
- description of any viable alternatives to participation. Patients who have sought clinical treatment must be offered the standard treatment as an alternative. Only in the absence of an established standard treatment can the use of placebo controls be justified;
- a description of how confidentiality and anonymity will be assured, and any limits to this assurance;
- a statement of whether compensation for harm is available, if the research involves more than minimal risk. This might mean counselling if the research is upsetting;
- any conflict of interest for researchers must be disclosed;
- an explanation of whom to contact for information or in case of harm;
- a specific indication that participation is voluntary, that the person can refuse without penalty, and that participants can withdraw at any time;
- when the subject is satisfied that he/she understands the information, and has had opportunity for discussion, the subject may sign the consent form, and should retain a copy;
- the form should name both the researcher and the sponsor of the study.

The information and consent form should be in clear, simple language equivalent to a grade eight level.

In certain cases, it is not necessary that the person actually sign the form. This includes cases where to sign would endanger the subject, as in research on stigmatized or illegal behaviour; and situations in which the subject can refuse behaviourally, such as by throwing out a survey or hanging up on an interviewer. Researcher should indicate in writing that the subject consented to participate in the research.

There are also cases in which the subject is not competent to consent, such as children or persons with Alzheimer's. In such cases, a qualified other person such as a parent must provide authorization for participating in the research, and be given the opportunity to observe the study as it progresses, so that they can judge if they want to withdraw the subject. It would be appropriate for the individual's physician and/or principal caregiver to be involved in the consent process and its periodic review. It is

also necessary for the child (7-15 years of age) to agree to participate in research.

While children may be legally incapable of giving informed consent, they nevertheless may possess the ability to assent to or dissent from participation. Out of respect for children as developing persons, children should be asked whether or not they wish to participate in the research, particularly if the research (1) does not involve interventions likely to be of benefit to the subjects; and (2) the children can comprehend and appreciate what it means to be a volunteer for the benefit of others.

Mature or emancipated minors may also provide consent. A mature minor is a person who can demonstrate adequate understanding and decision making capacity. Emancipated minors result from a variety of situations such as marriage, parenthood, self support and military membership.

The REB must determine for each protocol - depending on such factors as the nature of the research and the age, status, and condition of the proposed subjects - whether all or some of the children are capable of assenting to participation.

When the REB determines that the assent of the child is required, it must also determine that the provisions for obtaining and documenting assent are adequate. The child should be given an explanation of the proposed research procedures in a language that is appropriate to the child's age, experience, maturity and condition. This explanation should include a discussion of any discomforts and inconveniences the child may experience if he or she agrees to participate.

Templates of the research consent forms and assent form are provided in Appendix E, Appendix F, and Appendix G. If there is any doubt about whether it will be clear to potential subjects, it should be pre-tested.

Note: When study interventions consist solely of administering a questionnaire, a separate consent form is not required. Rather, a cover introductory letter (or telephone script) outlining the salient issues, ex.: purpose of study, length of time to complete the questionnaire, confidentiality issues and alternatives to participation must be enclosed with the questionnaire. With the completion of the questionnaire, implied consent is inferred.

4. Science Review

Scientific peer review must occur prior to submission for ethical review and approval.

Research Forum Scientific Review
Sponsored research or 'unfunded' projects must be scientifically reviewed in the investigator's research forum. For some protocols, a reviewer external to the division with additional methodological or content expertise should be invited to the research forum to critique the protocol. In addition to including a copy of the completed Report on Scientific Peer Review - Appendix C, an itemized response to issues raised and research director signoff is also required prior to submission to the REB.

In some instances, where external scientific review has already occurred and funding occurred, internal Health Canada scientific review may be waived. In these situations, please include a copy of the completed scientific review. Waiver of internal Health Canada science review will be decided on a case by case basis by the REB Chair.

5. Submission Process

For Full and Expedited Review, please submit 1 original and 8 copies of:
- the complete ethics application;
- the research protocol;
- Health Canada scientific reviews;
- sign-off by research director for those projects reviewed by research forums;
- the consent and assent forms on Health Canada letterhead;
- contract review and sign-off.

i) REB Secretariat staff will review applications for completeness
ii) The application with be assigned a REB file number. All subsequent correspondence with the REB Secretariat should quote the file number and the title of the research protocol.
iii) The application, once complete, will be included on the agenda of the next REB meeting.

STEP 3
RESEARCH ETHICS BOARD (REB)
REVIEW AND APPROVAL PROCESS

1. Review Criteria

Research in humans can be ethically justified only when:
- the research is scientifically sound;
- the potential benefit significantly outweighs the potential for harm;
- there is an adequate process for informed consent along with the child's assent to participation (where applicable); and
- there is justice or fairness in selection of participants.

2. Review Process

Research Ethics Board (REB)decisions are reached by consensus. The REB membership is designed to reflect professional and scientific values, the values of Health Canada and those of the broader community. All REB deliberations are conducted with a sensitivity to such a diversity of community values and to promote ethical research.

The review process consists of the following:
- each application is assigned to all REB members prior to a REB meeting;
- following the REB meeting, the REB Administrator sends a letter to the primary investigator with a summary of the Board's deliberations;
- the primary investigator initiates the follow-up process on outstanding issues by contacting the REB Secretariat;
- once the Board approves the investigator's written response to any outstanding issues, the REB Chair send a letter of approval to the primary investigator in accordance with established REB procedures.

3. Expedited Review

All applications will go to the full Board for review unless they qualify for an expedited review. Decisions regarding expedited review are at the discretion of the REB Chair.

Expedited Review Criteria
The study is non-invasive. Harms cannot include breaking of the skin, noxious procedures, invasive questionnaires in vulnerable circumstances/context or significant

nuisance/inconvenience.

The study may be retrospective, including chart reviews, and subjects are to be contacted for additional information not found in the chart. However, 'cold calling' by the investigator is not permitted and when a child is involved, at a minimum, a caregiver familiar to the patient /parent must be included in the 'request loop'.

The study involves no direct subject contact, may involve anonymous waste or leftover tissue, and only aggregate data is being reported. However, studies involving fetal waste tissue or genetic material ***must*** still be submitted for full Board review.

The study involves non-invasive product testing or quality assurance activities and publication is planned.

A protocol that has been previously reviewed and approved by an outside REB that is guided by the ethical principles found in the Tri-Council Policy Statement, Ethical Conduct for Research Involving Humans, ***must*** still be submitted for Health Canada REB review. A REB Application - Appendix I has been developed for this purpose.

Database or health record research. See Section 4.

Expedited Review Process
The review process will include two reviewers, ex.: Chair plus one other REB member (who may have specific expertise). As part of this process, the scientific reviewers/expedited reviewers will be asked whether there are any special or ethical issues that the Board should know about.

4. Database or Health Record Research

In response to the new requirements of the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans, all new projects involving database or health records research, when data can be linked to individuals (data has not been "anonymized") or when individuals can be identified in published reports, must be submitted for REB review and approval. A short REB application - Appendix B has been developed for this purpose.

These projects will be reviewed by the REB and immediately following REB review, the Primary Investigator will be informed by the Reporting Authority of the decision to either approve the project or to forward it to the full REB for further review.

Projects will be forwarded to the full REB if the chair deems the information to be

collected is sensitive and requires subject consent (ex.: HIV status, mental health status, pedigree to be published). The full REB meets when required.

In instances where subject consent must be obtained and this is impossible or economically unfeasible, the researcher may propose an appropriate strategy for informing the relevant parties, ex.: through an HIV/AIDS advocacy group.

5. REB Decision

The research under review will receive one of the following decisions from the REB:

Approval: Ethical approval is given in writing only. ***Research cannot commence until ethical approval is received in writing***. Approval is given for one year. Approval must be renewed annually until the research is complete. A copy should be submitted to the REB Secretariat.

Approval with Revisions: The study is given approval on the condition that revisions are made, as summarized in the letter from the Reporting Authority. Approval will not be considered by the REB until the revisions are received, therefore, a revised copy of the protocol should be submitted to the REB Secretariat. ***It is the responsibility of the investigator to promptly respond to REB concerns***.

Not Approved: If there are a significant number of outstanding issues, the protocol may not be approved. The REB will assist the researcher to resolve these issues. If a satisfactory solution is not reached, the investigator may be invited to a subsequent REB meeting to discuss the issues further.

Please Note:

If there is no communication from the investigator for 4 months during the approval process, the REB will assume the project is not being pursued and the file will be closed and archived. Once files are closed and archived, investigators must submit a new application to reinitiate the approval process.

STEP 4
CONTINUING ETHICAL REVIEW

1. Research Monitoring

Adverse effects or unexpected events resulting from the research must be reported to the Research Ethics Board (REB) Secretariat immediately by completing the Adverse Event Report - Appendix J. For some protocols, the REB may require that a monitoring committee be established.

2. Study Amendments or Modifications

Study amendments or modifications must be submitted by completing the Amendment Request - Appendix D to the REB for approval prior to commencement. Revised consent forms (as appropriate), should also be enclosed. Approval is at the discretion of the chair and may require full Board review.

3. Annual Progress Report

All applications receive approval for one year from the REB. The research must be re-approved annually by the REB until the study is completed.

The annual approval process involves the following:

- six to eight weeks prior to the REB meeting of the anniversary month of the initial approval, an Annual Progress Report - Appendix K will be sent to the primary investigator;
- this form must be completed, and sent to the REB Secretariat with supporting documents, as appropriate;
- once the study has been re-approved, written approval will be provided to the primary investigator. A copy should be submitted to the REB Secretariat.

Projects that are at least 5 years old must include an updated science review at the time of annual renewal. This is to ensure that the study can still be justified in view of new information found in the literature. The primary investigator is responsible for soliciting the review and ensuring the completed form is submitted to the REB Secretariat.

4. Completion/Terminations

Upon completion of the research, the investigator must submit a Completion / Termination Form - Appendix L to the REB Secretariat for review. This instructs the REB Secretariat to close the file. If patients or subjects undergo continued, periodic assessment after completion of a study intervention, or if continued correspondence about the study is anticipated (ex.: adverse event reports) the study must be kept open. Patient follow-up should be complete before the termination is submitted.

Note:
All continuing correspondence must contain the REB File Number and the title of the research used in the original application.