Health Canada Santé Canada

# ETHICAL REVIEW OF RESEARCH INVOLVING HUMANS

## Administrative Policy and Procedures Manual[1] for Health Canada Research Ethics Board (REB)

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**ISSUED BY:** REB Secretariat

**APPROVED BY:** Research Ethics Board

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Before you submit.....”

## REB Submission Checklist:

- completed application form including all necessary signatures
- study protocol
- completed independent science review
- itemized response to science issues raised
- consent and assent forms
- contract (if applicable)
- previously approved by another REB (if applicable, a copy of all submitted documentation, including the letter of approval)

## TABLE OF CONTENTS

**Introduction**
About this Manual
The *Tri-Council Policy Statement Ethical Conduct for Research*
Authority of Health Canada's Research Ethics Board (REB)
Mandate of Health Canada's REB

**Step 1 - Is An Ethical Review Required?**
Research
Surveillance
Supplemental Services
Performance Reviews
Quality Assurance
Secondary Use of Data in Research
Data Linkage
Use of Human Biological Material in Research
Use of Biobanks in Research
Use of Foetal Tissue in Research
Public Policy/Modern History
Specific Research Projects
-- Genetic Material in Research
-- Grants and Contribution

**Step 2 - Awareness of Privacy Legislation**
Privacy Legislation 18
Privacy Impact Assessment Policy 18
Personal Information Bank 18
Personal Information Protection and Electronic Documents Act 18
Provincial and Territorial Privacy Legislation 18

**Step 3 - Types of Ethics Review**
Full Review 20
Review of a Protocol Previously Approved by Another REB 20
Expedited Review 20
Time Sensitive Review 21
-- Criteria for time sensitive review 21

**Step 4 - Preparing the Application**
Application Form 23
The Research Protocol 25
Research Consent and Assent Forms 26
Scientific Peer Review 27

Submission Process 28

**Step 5 - REB Review and Approval Process**
REB Review 30
REB Recommendations 30

**Step 6 - Appeal of Decision**
Reconsideration of the Negative Decision for the Ethical Review of the Study 32
Appeal of a Negative Decision Following Reconsideration 32

**Step 7 - Continuing Ethical Review**
Adverse Effects/Unexpected Events 34
Study Amendments or Modifications 34
Annual Re-Approval Process 34
Completion/Termination 34

**Definitions** 36

# Introduction

## About this Manual

Health Canada's Policy and Procedures Manual provides guidance to Health Canada scientists and managers in regard to Departmental research involving humans. Since research ethics is a continually evolving subject, this manual may be modified from time to time. It is the responsibility of readers to ensure that they are using the most recent version.

The REB Operational Guidelines also provide important information on the Board's operations and should be read in conjunction with this manual.

## The *Tri-Council Policy Statement Ethical Conduct for Research Involving Humans*

Health Canada has adopted the *Tri-Council Policy Statement Ethical Conduct for Research Involving Humans* (*TCPS*) as the governing standard for all Departmental research involving humans. The *TCPS* presents a model that has emerged in the international community in recent decades. This model generally involves the application of national norms by multidisciplinary, independent local REBs for reviewing the ethical standards of research projects developed within their institutions. The Health Canada REB has been established and operates in accordance with the *TCPS*.

The *TCPS* also established ethical principles that have been widely adopted by diverse research disciplines and, as such, they express common standards, values and aspirations of the research community. Health Canada adheres to these ethical principles in all Departmental research involving humans. The *TCPS* states:

"**Respect for Human Dignity:** The cardinal principle of modern research ethics is respect for human dignity. This principle aspires to protecting the multiple and interdependent interests of the person — from bodily to psychological to cultural integrity. This principle forms the basis of the ethical obligations in research that are listed below.

In certain situations, conflicts may arise from application of these principles in isolation from one other. Researchers and Research Ethics Boards must carefully weigh all the principles and circumstances involved to reach a reasoned and defensible conclusion.

**Respect for Free and Informed Consent:** Individuals are generally presumed to have the capacity and right to make free and informed decisions. Respect for persons thus means respecting the exercise of individual consent. In practical terms within the ethics review process, the principle of respect for persons translates into the dialogue,

process, rights, duties and requirements for free and informed consent by the research subject.

**Respect for Vulnerable Persons:** Respect for human dignity entails high ethical obligations towards vulnerable persons — to those whose diminished competence and/or decision-making capacity make them vulnerable. Children, institutionalized persons or others who are vulnerable are entitled, on grounds of human dignity, caring, solidarity and fairness, to special protection against abuse, exploitation or discrimination. Ethical obligations to vulnerable individuals in the research enterprise will often translate into special procedures to protect their interests.

**Respect for Privacy and Confidentiality:** Respect for human dignity also implies the principles of respect for privacy and confidentiality. In many cultures, privacy and confidentiality are considered fundamental to human dignity. Thus, standards of privacy and confidentiality protect the access, control and dissemination of personal information. In doing so, such standards help to protect mental or psychological integrity. They are thus consonant with values underlying privacy, confidentiality and anonymity.

**Respect for Justice and Inclusiveness:** Justice connotes fairness and equity. Procedural justice requires that the ethics review process have fair methods, standards and procedures for reviewing research protocols, and that the process be effectively independent. Justice also concerns the distribution of benefits and burdens of research. On the one hand, distributive justice means that no segment of the population should be unfairly burdened with the harms of research. It thus imposes particular obligations toward individuals who are vulnerable and unable to protect their own interests in order to ensure that they are not exploited for the advancement of knowledge. History has many chapters of such exploitation. On the other hand, distributive justice also imposes duties neither to neglect nor discriminate against individuals and groups who may benefit from advances in research.

**Balancing Harms and Benefits:** The analysis, balance and distribution of harms and benefits are critical to the ethics of human research. Modern research ethics, for instance, require a favourable harms-benefit balance — that is, that the foreseeable harms should not outweigh anticipated benefits. Harms-benefits analysis thus affects the welfare and rights of research subjects, the informed assumption of harms and benefits, and the ethical justifications for competing research paths. Because research involves advancing the frontiers of knowledge, its undertaking often involves uncertainty about the precise magnitude and kind of benefits or harms that attend proposed research. These realities and the principle of respect for human dignity impose ethical obligations on the prerequisites, scientific validity, design and conduct of research. These concerns are particularly evident in biomedical and health research; in research they need to be tempered in areas such as political science, economics or modern history (including biographies), areas in which research may ethically result in the harming of the reputations of organizations or individuals in public life.

**Minimizing Harm:** A principle directly related to harms-benefits analysis is non-maleficence, or the duty to avoid, prevent or minimize harms to others. Research subjects must not be subjected to unnecessary risks of harm, and their participation in research must be essential to achieving scientifically and societally important aims that cannot be realized without the participation of human subjects. In addition, it should be kept in mind that the principle of minimizing harm requires that the research involve the smallest number of human subjects and the smallest number of tests on these subjects that will ensure scientifically valid data.

**Maximizing Benefit:** Another principle related to the harms and benefits of research is beneficence. The principle of beneficence imposes a duty to benefit others and, in research ethics, a duty to maximize net benefits. The principle has particular relevance for researchers in professions such as social work, education, health care and applied psychology. As noted earlier, human research is intended to produce benefits for subjects themselves, for other individuals or society as a whole, or for the advancement of knowledge. In most research, the primary benefits produced are for society and for the advancement of knowledge."

## Authority of Health Canada's Research Ethics Board (REB)

The REB is an independent Board that serves to help ensure that all research involving humans carried out or funded by Health Canada meets the highest ethical standards and that safeguards are developed which provide the greatest protection to participants who serve as research subjects. The Board, therefore, has both educational and review roles. REB serves the research community as a consultative body and, thus, contributes to education in research ethics. It also has responsibility for reviewing the ethics of research to determine whether the research should be permitted to start or to continue. The REB is concerned solely with the protection of humans involved in research.

The REB may recommend approval, rejection, proposed modifications to, or termination of any proposed or ongoing research involving humans which is conducted by or on behalf of the Department. The Board reviews applications according to the considerations set forth in the *TCPS* as the minimum standard.

The REB, which was established by the Deputy Minister of Health Canada in 2002, reports to the Chief Scientist of Health Canada.

## Mandate of Health Canada's Research Ethics Board (REB)

The REB shall review all Departmental research involving humans in circumstances where the research is:

- intra-mural (occurring within the limits of Health Canada);
- carried out on Health Canada premises that involves technical or consultation support including equipment, laboratories, or other facilities;
- undertaken in collaboration or partnership between Health Canada and external researchers;
- funded through grants and contributions; and
- carried out under contract with Health Canada.

It is important to note that within the REB scope of review, the REB Secretariat should be consulted in circumstances whether:

- the research is funded or not;
- the funding is internal or external;
- the subjects are from inside or outside Health Canada;
- the subjects are paid or unpaid;
- the research is conducted inside or outside Canada;
- the research is conducted inside or outside Health Canada;
- the research is conducted by staff or by students;
- the research is conducted in person or remotely (ex.: by mail, electronic mail, fax or telephone);
- the information is collected directly from subjects or from existing records not in the public domain;
- the research is to be published or not;
- the focus of the research is the subject;
- the research is observational, experimental, correlational or descriptive;

- a similar project has been approved elsewhere or not;
- the research is a pilot study or a fully developed project;
- the research is to acquire basic or applied knowledge; and
- research is primarily for teaching or training purposes or whether the primary purpose is the acquisition of knowledge.

***All Health Canada research involving humans must be reviewed and approved by the REB. Approval from the Chief Scientist must be obtained in writing before the research begins.***

# Step 1. Is an Ethical Review Required?

All Health Canada research involving humans (which includes pre-testing of survey instruments, for example questionnaires, consent forms) requires an ethical review by the Research Ethics Board (REB) of Health Canada and approval from the Chief Scientist must be received in writing before the research begins.

## Research

Is an activity designed to test a hypothesis, permit conclusions to be drawn and develop or contribute to generalizable knowledge;

- 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 relationship to health;

- The involvement of human subjects is required where 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.

The research involving humans as "research subjects" includes the use of human remains, cadavers, tissues, biological fluids, embryos or foetuses. Research involving humans may also include the collection of information from or about humans, such as through surveys, and from records of nonliving humans that are not in the public domain.

Researchers whose research involves humans must complete an application form and submit the required documentation to the REB Secretariat in order to obtain an ethical review. *Approval must be obtained in writing before the research begins.*

From time to time, researchers may be unsure as to whether or not their proposed work is research. The REB Secretariat should be consulted in all cases where there is such doubt.

## Surveillance

Surveillance is often defined as the ongoing collection, analysis and interpretation of health data, essential to the planning, implementation, and evaluation of public health practice, closely integrated with the timely dissemination of the data to those who need to know. The final link in the surveillance chain is the application of the data to prevention and control. A surveillance system includes a functional capacity for data collection, analysis and dissemination linked to public health programs. Sources of surveillance data can include disease outbreak reports and mortality and morbidity reports based on death records or laboratory diagnosis.

It is important to note that some surveillance activities may not need ethical review, such as surveillance activities for the purpose of improving programs in Health Canada.

Consequently, there is an ill-defined boundary between research and surveillance activities. Since this determination can only be made on a case-by-case basis, the advice of the Research Ethics Board (REB) should always be sought in such circumstances by contacting the REB Secretariat.

If an ethical review is required, this could be considered by the REB Chair or the Deputy Chair to qualify for an expedited review. Researchers whose research involves humans must complete an application form and submit the required documentation to the REB Secretariat in order to obtain an ethical review.

*Approval from the Chief Scientist must be obtained in writing before the research begins.*

## Supplemental Services

Health Canada officers, due to their highly specialized expertise, are often requested by a Principal Investigator (PI) from another institution to provide analytical services to a specific project, for example where a Health Canada officer analyzes anonymous or anonymized human biological material samples without engaging in their collection.

The PI must obtain an ethical review from his/her institution's REB, before the research begins. Once the PI has obtained the approval to proceed by his/her institution's REB, the Health Canada officer is now required to obtain an ethical review by the Health Canada REB. Health Canada REB approval must be obtained in writing before the Health Canada official takes possession of the data or biological material and begins the analysis thereof.

Application
A questionnaire has been developed by the REB Secretariat to assist Health Canada officers in obtaining an ethical review/approval by the Health Canada REB. The purpose of this questionnaire is to screen the general parameters of the project that has received an approval by the outside REB.

The Health Canada officer should submit the following documentation to the REB Secretariat:

- Completed Supplemental Services questionnaire
- Provide a copy of the PI's application to his/her REB, and
- Copy of the PI's REB letter of approval.

Review Process
The REB Chair or the Deputy Chair will undertake an ethical review of the questionnaire, research protocol and Health Canada's component of the research to determine if the project in which Health Canada is taking part can be considered as a supplemental service rather than research (a turnaround time of one (1) week is necessary).

1. Research component:
   The REB may consider this request to qualify for an expedited review by the Board and schedule this project for discussion at the upcoming REB meeting. *Approval from the Chief Scientist must be obtained in writing before the research begins;* or

2. Exclusion criteria for Supplemental Services component
   If, after submission of this questionnaire to the Board, the REB Chair or the Deputy Chair determines that:
   - the officer's activities in the project consist solely of performing an analytical service;
   - Health Canada is not involved in the collection of the data or biological material; and
   - Health Canada does not plan to be acknowledged or be a partner/co-author in the publications resulting from the project;

   the Board may inform the Chief Scientist that this component of the project does not require an ethical review/approval by the REB. The Board will provide such a response in writing to the Department. The Chief Scientist will inform the Health Canada officer in writing to proceed without an ethical review.

The REB Secretariat should be consulted in all cases prior to the Health Canada official agreeing to perform these analytical services.

## Performance Reviews

Performance reviews or testing within normal educational requirements are generally not subject to a Research Ethics Board (REB) review. If it is clear that a study is related

directly to assessing the performance of an organization or its employees or students, within the mandate of the organization or according to the terms and conditions of employment or training, REB review would not be required.

However, if a performance review or project contains an element of research in addition to an assessment, an ethical review by the HC REB may be required. An application form must be completed and the required documentation submitted to the REB Secretariat. REB approval must be obtained in writing before the research begins.

From time to time, researchers may be unsure as to whether or not their proposed work is research. The REB Secretariat should be consulted in all cases where there is such doubt.

## Quality Assurance

Quality assurance studies are generally not subject to a Research Ethics Board (REB) review. However, it is important to distinguish research from quality assurance for the purposes of a 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.

If the project has an element of research, an ethical review is required and this could be considered by the REB Chair or the Deputy Chair to qualify for an expedited review. Researchers whose research involves humans must complete an application form and submit the required documentation to the REB Secretariat in order to obtain an ethical review. *Approval must be obtained in writing before the research begins.*

The REB Secretariat should be consulted if unsure as to whether or not the proposed project should receive an ethical review by the REB.

## Secondary Use of Data in Research

Secondary use of data refers to the use of stored information and/or human biological material, initially collected for a purpose involving a specified research project or for individual health care or education but subsequently proposed for use in a different research project.

Special ethical concerns are posed by such research when the data could be linked to an individual or community, who might then be identified in a published report and/or the subject has objected to their data or sample being used in a second or subsequent studies.

Research Ethics Board (REB) approval shall be sought for the 'secondary use' of data for research involving humans. To provide approval in such circumstances, the REB must ensure that:

- the potential to derive personally identifiable information is essential to the research;
- appropriate measures are in place to protect the privacy of the individual by ensuring the confidentiality of the data;
- potential harm to subjects is minimized;
- subjects have not objected to the secondary use of their data; and
- a proportionate approach is taken in addressing the sensitivity of these issues.

Mechanisms to be considered by the REB in providing approval for secondary use of data collected within a research study include:

- Assurance of reasonable informed consent, as reflected in the information and consent documentation in the primary protocol;
- The documentation should outline, at least in general terms, both the positive and negative implications of the linkage of research data to the subject personally;
- Dependent on the proportional risk associated with the data, the REB may require evidence of an appropriate strategy to obtain current consent from or inform the contributing subjects, or their representatives, or to sample the opinion of a subset of the participating group, before initiating the secondary use of their data.

Researchers who wish to contact individual to whom data refer, shall seek the authorization of the REB prior to contact.

The study must be brought to the HC REB for an ethical review whether or not it is impossible to identify individuals or communities from their records or biological material. When an ethical review is required, this could be considered by the REB Chair or the Deputy Chair to qualify for an expedited review. This can be obtained by completing Appendix B and submitting the required documentation to the REB Secretariat.

The REB will carefully appraise the possibility of identification, in particular with regard to the extent of the harm or stigma which might be attached to identification.

The REB Secretariat should be consulted if unsure as to whether or not the proposed project should receive an ethical review by the REB. REB approval must be obtained in writing before the research begins.

## Data Linkage

Advances in the ability to link databases create both new research opportunities and new threats to privacy. These techniques may provide avenues for addressing previously unanswerable questions and for generating better social and health-related information.

The values underlying the ethical obligation to respect privacy oblige researchers and the REB to exercise caution in the creation and use of data linkage. The REB will also consider relevant statutory frameworks, and the criteria required by government for authorization of use of data in data banks.

Whether the data are to be used statistically or otherwise, confidentiality of the information must be maintained by all members of the research team. When a merged database identifies a person or a group who might be at significant risk of harm, it may be appropriate to contact those at risk or the appropriate authorities. In such circumstances, REB approval must be obtained prior to notifying the record holder.

For applications where data linkage might occur, making research subjects identifiable, the researcher must submit an application form and the required documentation to the REB Secretariat for an ethical review by the REB, to ensure that individuals, groups or communities do not become identifiable. REB approval must be obtained in writing before the research begins.

## Use of Human Biological Material in Research

Human biological material, from which donors may be identifiable, can only be used with the consent of the donors or their legal guardian, at the time of its retrieval.

Researchers who wish to contact these individuals shall seek the authorization of the Research Ethics Board (REB) prior to contact.

The REB must always be notified of the use of previously collected human biological material in research. The researcher must submit an application form and the required documentation to the REB Secretariat for an ethical review, prior to initiating the research. REB approval must be obtained in writing before the research begins.

The REB Secretariat should be consulted if unsure whether the proposed project should receive an ethical review by the REB.

## Use of Biobanks (Biorepositories) in Research

Biobanks are an important resource for identifying the causes and mechanisms of a large number of diseases, including ones that are widespread among the population.

While biobanks hold out the prospect of significant breakthroughs in medical and pharmaceutical research, they also arouse anxiety and distrust. The main concern is donor protection. What is feared is the uncontrolled use of samples and data.

Prior to conducting a research project involving the use of biobank samples and/or data, researchers are required to seek an ethical review by the Health Canada Research Ethics Board (REB). The researcher is to complete an application form and submit the required documentation to the REB Secretariat. Approval must be obtained in writing before the research begins.

## Use of Foetal Tissue in Research

Research involving the use of foetal tissue should be guided by respect for the woman's dignity and integrity. Researchers should obtain the free and informed consent of the individual whose foetal tissue is to be used for research.

Consent for such research can be obtained prospectively from women undergoing abortions. In such circumstances, the following consent clause should be appended to the consent to termination.

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

Research that involves the use of foetal tissue must be submitted to the Research Ethics Board (REB) for review by completing an application form and submitting the required documentation to the REB Secretariat. REB approval must be obtained in writing before the research begins.

## Public Policy/Modern History

Research Ethics Board (REB) review is generally not required for research involving public policy issues or the writing of modern history even though all of these might well involve human subjects.

The REB Secretariat should be consulted if unsure as to whether or not the project requires an ethical review by the REB.

Note: In all circumstances where personal data is being collected, applicants must consider the requirements of the *Privacy Act* and applicable Treasury Board Directives and, if necessary, seek legal advice.

## Specific Research Projects

**Genetic Material in Research -** The use of genetic material in research poses unique ethical issues. In seeking Research Ethics Board (REB) review for such research, the form included in Appendix H and the required documentation must be submitted to the REB Secretariat for an ethical review by the REB.

**Grants and Contributions -** Grants and Contributions funded research must be submitted to the Research Ethics Board (REB) for review. Before any funds are released, the researcher and/or manager of the funding unit must submit the form included in Appendix M and the required documentation to the REB Secretariat and receive an ethical review/approval from the REB.

# Step 2 - Awareness of Privacy Legislation

Researchers should be aware of their obligations as stipulated in the *Privacy Act* and other applicable regulations.

**Privacy Legislation**
The purpose of the *Privacy Act* is to provide citizens with the right to access personal information held by the government and protection of that information against unauthorized use and disclosure. For further information pertaining to the *Privacy Act*, please contact the Privacy Officer in the Access to Information and Privacy Division of Health Canada at (613) 954-8744.

**Privacy Impact Assessment Policy**
The Government of Canada is committed to protecting the personal information of Canadians. The *Privacy Impact Assessment Policy*, in conjunction with other relevant legislative and policy considerations, is integral to the design, implementation and evolution of all programs and services. Institutions are responsible for demonstrating that their collection, use and disclosure of personal information respect the *Privacy Act* and privacy principles throughout the initiation, analysis, design, development, implementation and post-implementation review phases of their program and service delivery activities. For further information on this subject, please contact the Director of the Access to Information and Privacy Division, Health Canada, at (613) 946-3179.

**Personal Information Banks**
The Privacy legislation states that government institutions shall not collect personal information unless it relates directly to an operating program or activity. The policy requires that institutions have administrative controls in place to ensure that they do not collect any more personal information than is necessary for the related programs or activities. This means that institutions must have parliamentary authority for the relevant program or activity, and a demonstrable need for each piece of personal information collected in order to carry out the program or activity. For further details on how to proceed with the registration of the personal information bank, please contact the Privacy Officer in the Access to Information and Privacy Division of Health Canada, at (613) 954-8744.

**Personal Information Protection and Electronic Documents Act (PIPEDA)**
The purpose of *PIPEDA* is to promote electronic commerce and adequate protection of the personal information collected, used or disclosed by any organization subjected to this Act, during commercial activities. *PIPEDA* also gives protection of personal information communicated or recorded by electronic means.

**Provincial and Territorial Privacy Legislation**
Each province and territory possesses its own legislation concerning privacy for the collection, use and disclosure of personal information by government agencies. Some researchers funded or affiliated with Health Canada working in another research

location may be subjected to this particular legislation in addition to the two Federal laws on privacy. In private sectors, some provincial legislation on privacy are deemed similar to the federal legislation thus, in certain circumstances, the researchers concerned can follow the provincial legislation. When it is unclear, a researcher may consult the REB Secretariat.

# Step 3 - Types of Ethics Review

## Full Review

All departmental research projects involving humans will be subject to a full review by the Research Ethics Board (REB) wherein all REB members shall review the research proposal. In particular circumstances, the REB may review applications as expedited reviews or as time sensitive reviews.

## Review of a Protocol Previously Approved by an Outside 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* (*TCPS*) must also be submitted to the Health Canada REB for review. This is in keeping with Health Canada's accountability for research carried out within the Department's jurisdiction or under its auspices.

The researcher is required to complete Appendix I and forward a copy of the entire application approved by the other REB to the REB Secretariat, as well as a copy of the REB's letter of approval.

## Expedited Review

In order for an application to be subjected to an expedited review, the Principal Investigator must demonstrate how the research meets any of the following criteria:

- The study is non-invasive**.** Harms cannot include breaking of the skin, noxious procedures, and invasive questionnaires in vulnerable circumstances/context or significant nuisance/inconvenience.

- The study is 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 foetal 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**.**

- Database or health record research.

The Principal Investigator must complete Appendix B, if the research meets at least one of the above criteria and submit the required documentation to the REB Secretariat.

The REB Chair or the Deputy Chair will determine if this application is meeting the requirements of an expedited review. If the Chair of the Deputy Chair does not agree that the research qualifies for an expedited review, the researcher will be informed that the application will receive a full review at the next monthly meeting.

## Time Sensitive Review

The *Tri-Council Policy Statement* (*TCPS*) provides that, "subject to all applicable legislation and regulatory requirements, research involving emergency health situations shall be conducted only if it addresses the emergency needs of individuals involved and then only in accordance with criteria established in advance of such research by the REB". The REB may allow research that involves health emergencies to be carried out without the free and informed consent of the subject or the subject's legally authorized third party (parent or guardian) if all of the following apply:

- "a serious threat to the prospective subject requires immediate intervention;
- either no standard efficacious care exists or the research offers a real possibility of direct benefit to the subject in comparison with standard care;
- either the risk of harm is not greater than that involved in standard efficacious care, or it is clearly justified by the direct benefits to the subject;
- the prospective subject is unconscious or lacks capability to understand risks, methods and purpose of the research;
- third-party authorization cannot be secured in sufficient enough time, despite diligent and documented efforts to do so; and
- no relevant prior directive by the subject is known to exist."

Criteria for Time Sensitive Review

In circumstances that are deemed emergency health situations, the Research Ethics Board (REB) established certain criteria that have to be met to qualify for a time-sensitive review. Researchers must ensure that their research project meets the following criteria prior to submitting an application for a time sensitive review:

- the research is urgent. Researchers propose to begin their research within the next twenty-four (24) to forty-eight (48) hours; or

- the research is of high priority. Researchers propose to begin their research within the next three (3) to ten (10) days.

Examples of circumstances appropriate for time sensitive review are:

- Epidemiological studies where incidences of the study target are limited, such as outbreak investigations of a new disease such as SARS;

- Studies of time limited events;

- Research whereby waiting for the next REB meeting would place individuals at risk;

- Approval by the REB is urgently required due to circumstances beyond the researchers' control. Submission of the study for ethical review within required timelines is considered to be in his/her control and not subject to this type of review.

Applications for time sensitive review by the REB must be submitted electronically to the REB Secretariat. Researchers should demonstrate clearly how the research meets the criteria for time sensitive review. It should be noted that circumstances might arise where the REB may not be able to review a time sensitive application despite its best efforts to do so.

The REB Chair or the Deputy Chair will determine if the application meets the criteria for time sensitive review. If the REB Chair or the Deputy Chair determines that the application does not meet the time sensitive review criteria, the application will not be reviewed until the next scheduled REB meeting.

However, if the REB Chair or the Deputy Chair determines that the application warrants time-sensitive review, it will be deemed a "high priority" review. The REB Secretariat will then schedule a time for a face-to-face or a teleconference meeting with REB members to review the application. The Chair will advise the Chief Scientist of the Board's recommendation and the decision will be communicated in writing to the Principal Investigator by the Chief Scientist. Approval by the Chief Scientist must be obtained in writing before the research begins.

The REB established the procedures for time sensitive reviews in January 2004. The REB will review these procedures periodically to ensure its effectiveness and its relevance.

# Step 4 - Preparing the Application

A complete Research Ethics Board (REB) application package has six (6) main components:

- the completed application form with all necessary signatures;
- the research protocol;
- the consent and assent forms;
- completed science peer review and itemized response;
- copy of contract (if applicable);
- all documentation submitted and approved by another REB (if applicable).

## Application Form

The Application for Ethical Approval of Studies Involving Humans in Appendix A must be completed and submitted to the REB Secretariat. If the proposed research meets the criteria for an expedited review, the application form in Appendix B must be submitted.

The following provides explanatory information about some of the questions on the application form for a full ethical review:

**#1 - Project Title**
Full title of the research project must be provided. The title must be the same as the title found on the research protocol. The same title and assigned REB file number must be used consistently in all future REB correspondence.

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

**#2 and 3 - Address for Correspondence**
The name of the person (whether it is the PI or another person), address and telephone number, must be provided as a contact for the REB application. Do not leave this blank.

**#5 - Privacy Legislation**
This provides an assurance to the REB that the researcher is aware of his/her obligations as stipulated in the *Privacy Act* and other regulations.

**#6 - Third Party Implications**
The researcher will need to identify if there is any potential for identifying third parties.

**#9 - Sponsoring Company (if applicable)**
The contract, if any, for this study/project must be reviewed and approved by the Director of the Division to whom the researcher reports and be included with the application to be submitted to the REB Secretariat for obtaining an ethical approval. Conflict of interest disclosure information must be provided, e.g. commercial interests, consultative relationships.

**#10 - 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 REB, it must be independently reviewed to ensure scientific validity.

The REB Secretariat has developed a Scientific Peer Review form to assist the researcher in ensuring the research is scientifically sound.

If not applicable, there will be a need to obtain the signature of the Director General to whom the researcher reports, prior to obtaining an ethical review by the REB.

**#11 - Signatures of Approval**
The research must be authorized by the relevant Branch(es) and/or Division Head(s) 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 that sufficient funds are available to complete the study 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.

**#16 - Recruitment**
Special care must be taken when recruiting students, post doctoral fellows, colleagues, employees, family or friends as research 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 findings could affect their present or future employment relationship.

**#18 - 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 must also be stated.

**#19 and 20 - Potential Harms and Potential Benefits**
The potential for harm and benefit of the research must be described in simple lay terms, at a grade six (6) to eight (8) reading level.

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

The *Tri-Council Policy Statement* (*TCPS*) states:

“Potential harms are usually understood in relation to risks, which are defined in terms of the magnitude of the 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."

**#21 - Monitoring**
The proposed methods of monitoring the study for adverse events must be provided.

## 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, question(s) and/or hypothesis;
- the relevant literature;
- study objectives;
- the research design and methodology (inclusion/exclusion criteria, sample size, justification and analytical 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 or costs to participants and others;
- alternative treatments or procedures available in place of study procedure;
- how potential for harm/costs will be minimized - including the risk of breach of privacy and confidentiality;
- process for obtaining informed, voluntary, consent and assent.

## Research Consent and Assent Forms

### Informed Consent

Informed consent is an ongoing process that starts with the researcher's first contact with the individual and continues until the study is complete or the participant withdraws. The informed consent and any other written information given to participants should provide adequate information for the participant to make an informed decision about his/her participation. Researchers should be aware of the consent requirements established by the Research Ethics Board (REB).

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. The researcher should document that the subject consented to participate in the research.

There are also cases in which the subject is not legally competent to consent, such as children or persons with Alzheimer's. In such cases, a qualified person such as a parent, or legally authorized third party, must provide his/her consent 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.

### Assent

It is also necessary to seek a child's (seven (7) to fifteen (15) years of age) assent to participate in a particular study.

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 does not involve interventions

likely to be of benefit to the subjects and the children can comprehend and appreciate what it means to 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 will 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 will 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 discomfort and inconvenience the child may experience if he/she agrees to participate.

Researchers should review the consent requirements established by the REB to ensure adequate written informed consent or assent is provided to the participants.

If there is any doubt about whether all or part of the consent form will be clear to potential subjects, it should be pre-tested. The pre-testing will require that the researcher obtains an ethical review by the REB prior to initiating this process.

Note: When study interventions consist solely of administering a questionnaire, a separate consent form is not required. Rather, the process must include a cover introductory letter (or telephone script) outlining the salient issues, such as introduction of investigator(s) (and/or caller), how the person was selected, where the contact name was taken from, purpose of study, length of time to complete the questionnaire, confidentiality issues and any alternatives to participation. With the completion of the questionnaire, implied consent is inferred.

## Scientific Peer Review

Independent scientific peer review must occur prior to submission for ethical review and approval by the Research Ethics Board (REB) of Health Canada. In addition to including a copy of the completed Report on Scientific Peer Review, an itemized response to issues raised and research director signoff is also required prior to submission to the REB Secretariat.

In some instances, where external scientific review has been undertaken and funding granted (ex.: CIHR, CRTI, NIH), Health Canada scientific review may be waived. In

these situations, a copy of the completed scientific review must be included with the application. A waiver of the Health Canada science review will be decided on a case-by case basis by the REB Chair or the Deputy Chair.

For the Health Canada funded research, the Principal Investigator (PI) must obtain the required delegated authority for the research to proceed. The research must be authorized by the relevant Branch and/or Division Head whose signature confirms:

- The scientific integrity of the research,
- The feasibility of conducting the research at Health Canada,
- That funding is available to complete the study, and
- That appropriate monitoring will occur.

## Submission Process

This process is for all types of submissions for example

- Full or expedited review
- Review of protocol previously reviewed by an outside REB
- Time sensitive

For an ethical review by the REB:

Please submit one (1) original hard copy, ten (10) photocopies and one (1) electronic version of:

- the completed ethics application,
- the research protocol,
- Scientific peer reviews,
- signoff by a research director for those projects reviewed by research forums,
- the information sheet and the consent/assent forms on the required letterhead,
- Documentation for the recruitment of potential participants
- contract (if applicable).

Application Deadline:

As members of the Research Ethics Board (REB) are volunteers, the REB Secretariat established a two (2) week deadline for the submissions of applications to the REB. This deadline is to provide the members with sufficient time to review the protocols submitted to the REB Secretariat, prior to the scheduled REB meeting.

The REB Secretariat will:

- review applications for completeness; and

- assign a REB file number to the application. All subsequent correspondence with the REB Secretariat should quote the file number and the title of the research protocol.

Once the application is complete, it will be included on the agenda for the upcoming REB meeting, if received by the REB Secretariat prior or on the deadline for submission otherwise it will be scheduled for the following REB meeting.

The Principal Investigator will be informed by the REB Secretariat via email of the need to make a 5-10 minute presentation to the Board summarizing the project, informing the Board of any ethical issues considered and be present to answer any questions raised by the members. The REB Secretariat will provide the time and location for which his/her research project will be heard by the Board.

# Step 5 – Research Ethics Board (REB) Review and Approval Process

## REB Review

The REB will consider Health Canada research to be ethically sound when;

- the research is scientifically sound,
- the potential benefits significantly outweigh the potential for harm or other risks,
- there is adequate process for informed consent and where applicable, an assent to participate in the research, and
- there is justice and fairness in selection of participants.

The REB meets monthly (except during the summer) and face-to-face to consider applications except in exceptional circumstances for time sensitive reviews. Principal Investigators (PI) may be invited to give short presentations on their research. The REB Secretariat should be contacted for assistance in preparing the presentation.

REB recommendations will be communicated to the PI by the Chief Scientist within fifteen (15) days of the meeting at which a decision was made.

## Research Ethics Board (REB) Recommendations

Research must not commence until ethical approval is received in writing. The research under review will receive one (1) of the following recommendations from the REB:

**Approval**:

The REB may recommend to the Chief Scientist of Health Canada that the research is ethically sound and should proceed as submitted to the REB. A letter from the Chief Scientist to the Principal Investigator (PI) provides the needed approval for the study to proceed. Approval is for a period of one (1) year. Research must be renewed annually until it is complete.

**Approval with Revisions**:

The REB may recommend to the Chief Scientist of Health Canada that the research is ethically sound subject to the condition that certain revisions be made. The conditions will be summarized in the letter of approval to the PI from the Chief Scientist. A revised copy of the protocol must be submitted to the REB

Secretariat. It is the responsibility of the investigator to promptly respond to the REB concerns.

**Deferral of Approval:**

The REB may recommend to the Chief Scientist deferral of approval:

- pending receipt of additional information from the PI, or
- where major revisions are required to the application being reviewed.

The REB Secretariat will provide the PI with a copy of the transcript of the members' discussions within five (5) days of the meeting and request that these modifications be implemented by the PI.

It is the responsibility of the investigator to promptly respond to the REB's concerns.

The additional information or the required revisions must be re-submitted to the REB Secretariat for final REB review.

The REB will review the additional information or the proposed revisions and make recommendations as appropriate to the Chief Scientist. With the advice of the REB, the Chief Scientist will then review the revisions made. Upon finding them acceptable, a letter from the Chief Scientist will be issued to the PI, giving approval for the study to proceed. Research may only start when the PI has received this letter of approval from the Chief Scientist.

**Not Approved**:

If, in the opinion of the REB, the proposed research is unethical, the Chief Scientist will write a letter to the PI stating that the research must not proceed. The Chief Scientist or any other departmental or agency official shall not override the advice of the REB on the ethics of a research project. Should a PI decide to appeal a negative decision, the proposed research will not proceed unless the appeal has been successful and the PI has been granted permission to proceed in a letter from the Chief Scientist.

Where the REB has advised that the proposed research is ethical and the Chief Scientist has informed the PI in writing that the research may proceed, Health Canada or the Public Health Agency of Canada could still refuse to allow the research to proceed for other reasons.

# Step 6 - Appeal of Decision

The following sets out an appeal procedure that can be exercised by the Principal Investigators (PIs) in the event of a negative review by Health Canada's Research Ethics Board (REB) or the imposition of conditions that the PI disagrees with. It is intended to ensure the utmost fairness in the REB's procedures.

## Reconsideration of the Negative Decision for the Ethical Review of the Study

In accordance with Article 1.10 of the *Tri-Council Policy Statement* (*TCPS*), if a negative decision has been received from the Research Ethics Board (REB), researchers have the right to request, and the REB has an obligation to provide, reconsideration of decisions affecting a research project.

Any PI, who disagrees with the results of an ethical review by the REB, must provide a clear, detailed basis for the disagreement and relevant documentation that will support his/her request for reconsideration by the REB. This information must be sent by letter or by email to the REB Secretariat within ten (10) days of receiving the transcript from the REB Secretariat providing the results of the ethical review. The REB Secretariat will forward the e-mail or letter to the REB.

A meeting between the REB and the PI will be scheduled at the earliest possible REB monthly meeting. The PI will be invited to further discuss the project with the Board in order to reach a final consensus on the issues that are still subject to disagreement. The PI may not be present for the final deliberations of the REB. The PI will receive a letter or an email from the REB Secretariat within two (2) weeks of the meeting providing him/her with the results of the reconsideration.

If agreement is reached between the PI and the REB, the REB will recommend to the Chief Scientist that the research proceed as submitted to the Board. A letter of approval from the Chief Scientist to the PI would provide the needed approval for the study to proceed.

## Appeal of a Negative Decision Following Reconsideration

Article 1.11 of the *Tri-Council Policy Statement* (*TCPS*) provides that, in cases where researchers and the Research Ethics Board (REB) cannot reach agreement through discussion and reconsideration, an institution should permit review of a REB decision by an appeal board, provided that the board's membership and procedures meet the requirements of the *TCPS*.

If a consensus was not reached between the REB and the Principal Investigator (PI) during the reconsideration of the Board's earlier decision, the PI can initiate an appeal process within Health Canada.

Appeals are not allowed on the grounds that the PI disagrees with the REB on the ethics of the research project. An appeal will only be considered if the PI can show evidence of a:

- Perception of bias;
- Lack of due process;
- Apparent conflict of interest; or
- Other failure of the systematic part of the review process.

To initiate an appeal process, the PI must send an appeal letter to the Chief Scientist and the REB Secretariat, setting out the basis for the appeal and providing supporting evidence. Upon receipt of the appeal letter, the Chief Scientist will assemble an Appeal Board to review the evidence submitted by the PI. The Appeal Board will advise the Deputy Minister of Health Canada as to whether a failure occurred in Health Canada REB's ethical review process for the project under appeal.

The Appeal Board composition will reflect the expertise profile of Health Canada's REB. Members of the REB will not sit on the Appeal Board. The Appeal Board can seek assistance from other experts in fields relevant to the appeal.

The Appeal Board will meet within two (2) months of receiving the letter from the PI. The PI and the REB Chair will be invited to present their evidence to the Appeal Board. The REB Secretariat may also be asked to appear before the Appeal Board. The Appeal Board will consider all relevant evidence before reporting its decision to the Deputy Minister.

The Deputy Minister will consider the advice of the Appeal Board in deciding the appropriate action to take in regard to the project. If the Deputy Minister finds that a failure in the review process conducted by the REB has occurred, the project will be referred back to the REB for review.

If the Deputy Minister does not find that a failure occurred in the REB ethical review process, the decision made by the REB will stand.

The Deputy Minister's decision is final and binding.

# Step 7 - Continuing Ethical Review

## Adverse Effects/Unexpected Events

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

## Study Amendments or Modifications

Prior to making any study amendments or modifications, the form in Appendix D must be submitted to the REB Secretariat. Revised consent forms, as appropriate, should also be enclosed. A recommendation of approval of the amendments or study modifications is at the discretion of the Research Ethics Board (REB) Chair. The Chair may require a full Board review.

## Annual Re-Approval Process

Research Ethics Board (REB) approvals are valid for one (1) year. The research must be reviewed annually until it is completed.

The annual approval process involves the following steps.

- Six (6) to eight (8) weeks prior to the REB meeting of the anniversary month of the initial approval, the REB Secretariat will send the annual renewal form in Appendix K to the Principal Investigator (PI).

- This form must be completed, and returned to the REB Secretariat with supporting documents, as appropriate.

- The REB will review the submission and the results of the review will be provided to the PI.

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

## Completion/Termination

Upon completion of the research, the Principal Investigator (PI) must submit to the REB Secretariat, the Completion/Termination form in Appendix L, and provide:

- A brief description of the outcome/results; and
- If there were any deviation to the Research Ethics Board (REB) approved protocol.

This instructs the Secretariat to close the file.

If subjects undergo continued, periodic assessment after completion of a study intervention, or if continued correspondence about the research is anticipated (e.g. adverse event reports) the research must be designated as ongoing. Subject follow-up should be complete before the form in Appendix L is submitted.

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

# Definitions

"**Coded samples**: Sometime termed “linked” or “identifiable,” these samples are supplied by repositories to investigators from identified specimens with a code rather than with personal identifiable information, such as a name or Social Insurance Number.

**Identified samples**: These samples are supplied by repositories from identified specimens with a personal identifier (such as a name or patient number) that would allow the researcher to link the biological information derived from the research directly to the individual from whom the material was obtained.

**Unidentified samples**: Sometime termed “anonymous”, these samples are supplied by repositories to investigators from a collection of unidentified human biological specimens.

**Unlinked samples**: Sometime termed “anonymized”, these samples lack identifiers or codes that can link a particular sample to an identified specimen or a particular human being.

**Human Biological Material**: consists of the human body and its parts – tissue and fluids of the human body – obtained from living and nonliving subjects, with the exception of human gametes, human embryos, foetuses and foetal tissue.

**Third party**:  a person, group or company besides the two primarily involved in the research project.  If a third party is mentioned in the protocol, there is a need for the Principal Investigator to inform the REB that a third party is being identified in the research project.