NIS Considerations - Canada
An overview of the considerations when conducting Non-interventional Studies in Canada

Stuart McCully • Compliance Healthcheck Consulting UK Ltd • NIS-C-CA-2012
# Table of Contents

## Disclaimer

## Study Classification

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOES MY STUDY REQUIRE RESEARCH ETHICS BOARD REVIEW?</td>
<td>7</td>
</tr>
<tr>
<td>REGULATORY BODIES</td>
<td>8</td>
</tr>
<tr>
<td>DEFINITIONS</td>
<td>8</td>
</tr>
<tr>
<td>Research</td>
<td>8</td>
</tr>
<tr>
<td>Human Participants</td>
<td>8</td>
</tr>
<tr>
<td>KEY CONCEPTS - DATA PRIVACY</td>
<td>10</td>
</tr>
<tr>
<td>Privacy</td>
<td>10</td>
</tr>
<tr>
<td>Confidentiality</td>
<td>10</td>
</tr>
<tr>
<td>Security</td>
<td>10</td>
</tr>
<tr>
<td>Identifiable Information</td>
<td>11</td>
</tr>
<tr>
<td>Types of Information</td>
<td>11</td>
</tr>
<tr>
<td>STUDY CLASSIFICATION</td>
<td>13</td>
</tr>
<tr>
<td>Does my study require Research Ethics Board (REB) Review?</td>
<td>13</td>
</tr>
<tr>
<td>Research that Requires REB Review</td>
<td>13</td>
</tr>
<tr>
<td>Research Exempt from REB Review</td>
<td>13</td>
</tr>
<tr>
<td>Publicly Available Information</td>
<td>13</td>
</tr>
<tr>
<td>Observation of People in Public Places</td>
<td>14</td>
</tr>
<tr>
<td>Secondary Use of Anonymous Information</td>
<td>14</td>
</tr>
<tr>
<td>DECISION TREE</td>
<td>16</td>
</tr>
<tr>
<td>Study Exempt from REB Review?</td>
<td>17</td>
</tr>
</tbody>
</table>
## Study Requires REB Review?

17

## STUDY CLASSIFICATION - USEFUL LINKS

18

---

### Regulatory Requirements

19

- **COUNTRY-SPECIFIC REGULATORY REQUIREMENTS**
  - 19
- **REGULATORY BODIES**
  - 19
- **DEFINITIONS**
  - 20
- **Clinical Trial**
  - 20
- **Definition - Phase IV Study**
  - 20
- **Definition - Observational Studies**
  - 20
- **REGULATORY FRAMEWORK**
  - 22
- **Applicable Legislation & Guidance**
  - 22
- **SUMMARY OF THE NIS REQUIREMENTS IN CANADA**
  - 23
- **APPROVAL & NOTIFICATION REQUIREMENTS**
  - 24
- **Health Canada Approval**
  - 24
- **Research Ethics Board (REB) Approval**
  - 24
- **WHO IS RESPONSIBLE FOR WHAT?**
  - 26
- **REGULATORY SUBMISSIONS ROADMAP**
  - 27
- **REGULATORY SUBMISSIONS DOCUMENTS**
  - 28
- **REGULATORY REQUIREMENTS - USEFUL LINKS**
  - 29

---

### Study Conduct Considerations

31

- **PROCEDURES FOR REB REVIEW**
  - 31
- **Scope of Research Ethics Review**
  - 31
- **Initial Research Ethics Review**
  - 31
- **Determining the Level of Research Ethics Review**
  - 32
- **Two levels of research ethics review may apply:**
  - 32
- **Continuing Research Ethics Review - Reporting Requirements**
  - 33
- **Reports of Unanticipated Issues**
  - 34

---

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2
Consent and Secondary Use of Identifiable Human Biological Materials for Research Purposes

STORAGE AND BANKING OF HUMAN BIOLOGICAL MATERIALS

HUMAN TISSUE RESEARCH CONSIDERATIONS - USEFUL LINKS

Best Practice Considerations

DEFINITIONS

Post-Registration Clinical Study

‘Seeding’ or ‘Experience’ Trials

GENERAL PRINCIPLES

STANDARDS

Clearly Defined Objective

Internal Approval & Governance by Qualified People

Provision & Retrieval of Devices or Diagnostic Equipment to Support the Study

Limited Involvement of Sales Representatives

Compliance with Applicable Legislation & Guidelines

Study Protocol

Data Collection & Evaluation

Compensation & Remuneration

Prohibition of Promotion

Investigator Meetings

Industry-Sponsored Surveillance Studies

FURTHER CONSIDERATIONS AND CLARIFICATION

What rules govern the offering of hospitality to health professionals? Does it make a difference if the hospitality offered to those health professionals will take place in another country?

Is it possible to pay for a doctor in connection with attending a scientific meeting? If so, what may be paid for? Is it possible to pay for his expenses (travel, accommodation, enrolment fees)? Is it possible to pay him for his time?

To what extent will a pharmaceutical company be held responsible by the regulatory authorities for the contents of and the hospitality arrangements for scientific meetings, either meetings directly sponsored or organised by the company
or independent meetings in respect of which a pharmaceutical company may provide sponsorship to individual doctors to attend?

Is it possible to pay doctors to provide expert services (e.g. participating in focus groups)? If so, what restrictions apply?

Is it possible to pay doctors to take part in post marketing surveillance studies? What rules govern such studies?

Is it possible to pay doctors to take part in market research involving promotional materials?

Is there a requirement in law and/or self-regulatory code for companies to make publicly available information about donations, grants, benefits in kind or any other support provided by them to health professionals, patient groups or other institutions? If so, what information should be disclosed, from what date and how?

BEST PRACTICE CONSIDERATIONS - USEFUL LINKS

NIS Definitions

EUROPEAN NIS DEFINITIONS

NIS DEFINITIONS

Non-interventional Study (NIS)

Post-authorisation Safety Study (PASS)

Post-authorisation Efficacy Studies (PAES)

Common NIS Terminology

COMMONLY USED NIS TERMS

COMMON NIS TERMINOLOGY
Disclaimer

Although this Compilation contains information of a legal nature, it has been developed for informational purposes only and does not constitute legal advice or opinions as to the current operative laws, regulations, or guidelines of any jurisdiction. In addition, because new standards are issued on a continuing basis, this Compilation is not an exhaustive source of all current applicable laws, regulations, and guidelines relating to non-interventional studies. While reasonable efforts have been made to assure the accuracy and completeness of the information provided, researchers and other individuals should check with local authorities and/or research ethics committees before starting research activities.
Study Classification

DOES MY STUDY REQUIRE RESEARCH ETHICS BOARD REVIEW?

What are the regulatory requirements for my NIS?

It Depends!
REGULATORY BODIES

<table>
<thead>
<tr>
<th>Competent Authority</th>
<th>Health Canada</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Research Ethics Board (REB)</td>
</tr>
<tr>
<td>Data Protection Agency</td>
<td>N/A</td>
</tr>
</tbody>
</table>

DEFINITIONS

Research

“research” is defined as an undertaking intended to extend knowledge through a disciplined inquiry or systematic investigation (as per Article 2.1 of TCPS-2).

A determination that research is the intended purpose of the undertaking is key for differentiating activities that require ethics review by an REB and those that do not (as per Article 2.1 of TCPS-2).

Human Participants

For the purposes of this Policy, “human participants” (referred to as “participants”) are those individuals whose data, or responses to interventions, stimuli or questions by the researcher, are relevant to answering the research question (as per Article 2.1 of TCPS-2).

Human participants are unique among the many parties involved in research, because they bear the primary risks of the research. These individuals are often referred to as “research subjects.” This Policy prefers the term “participant” because it better reflects the spirit behind the core principles: that individuals who choose to participate in research play a more active role than the term “subject” conveys. As well, it reflects the range of research covered by this Policy, and the varied degree of involvement by participants – including the use of their data or human biological materials – that different types of research offer. The core principles of this Policy – Respect for Persons, Concern for Welfare, and Justice – help to shape the relationship between researchers and participants (as per Article 2.1 of TCPS-2).

Where researchers seek to collect, use, share and access different types of information or data about participants, they are expected to determine whether the information or data proposed
# Regulatory Requirements

## Country-Specific Regulatory Requirements

### Regulatory Bodies

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<tr>
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<td>N/A</td>
</tr>
<tr>
<td>Pharmaceutical Self-Regulation Body</td>
<td>Canada’s Research-Based Pharmaceutical Companies (Rx &amp; D)</td>
</tr>
</tbody>
</table>

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DEFINITIONS

Clinical Trial
An investigation in respect of a drug for use in humans that involves human subjects and that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug (as per Section 2 of the Health Canada Guidance for Clinical Trial Sponsors).

Definition - Phase IV Study
All studies performed after the drug has been approved by the regulator for the market, and related to the approved indication. These studies are often important for optimizing the drug’s use. They may be of any type but must have valid scientific objectives. Commonly conducted studies include safety studies and studies designed to support use under the approved indication such as mortality and morbidity studies, or epidemiological studies (as per Section 2 of the Health Canada Guidance for Clinical Trial Sponsors).

Definition - Observational Studies
According to Chapter 10 of TCPS 2:
In qualitative research, observation is used to study behaviour in a natural environment. It often takes place in living, natural and complex communities or settings, in physical environments, or in virtual settings. Observational studies may be undertaken in publicly accessible spaces (e.g., classrooms, hospital emergency wards, locations where religious services or practices are held), in virtual settings (e.g., Internet chat rooms), or in private or controlled spaces (e.g., private clubs or organizations.)

Observational research is of two kinds: “non-participant” where the researcher observes, but is not a participant in, the action (also known as “naturalistic observation”); and “participant” where the researcher engages in, and observes, the action.

Participant observation is often identified with ethnographic research, in which the researcher’s role is to gain a holistic overview of the studied context through engagement in,
PROCEDURES FOR REB REVIEW

Scope of Research Ethics Review

The following requires ethics review and approval by an REB before the research commences:

- research involving living human participants;
- research involving human biological materials, as well as human embryos, fetuses, fetal tissue, reproductive materials and stem cells. This applies to materials derived from living and deceased individuals.

(as per Article 2.1 of TCPS-2).

Initial Research Ethics Review

Researchers shall submit their research proposals, including proposals for pilot studies, for REB review and approval of its ethical acceptability prior to the start of recruitment of participants, access to data, or collection of human biological materials. REB review is not required for the initial exploratory phase, which may involve contact with individuals or communities intended to establish research partnerships or to inform the design of a research proposal (as per Article 6.11 of TCPS-2).

Application REB review and approval of the ethical acceptability of research is required before recruitment, formal data collection involving participants, access to data, or collection of human biological materials. Similarly, as an integral component of their research design, researchers may undertake pilot studies involving participants. For the conduct of pilot studies, researchers shall seek consent from prospective participants and obtain REB
approval before recruitment or the formal data collection involving participants, or access to data, or collection of human biological materials in accordance with the provisions in this Policy. (as per Article 6.11 of TCPS-2).

Researchers shall submit sufficient details to enable the REB to make an informed review of the ethical acceptability of the research (as per Article 6.11 of TCPS-2).

Some types of research using quantitative, qualitative research, or a combination of these methods, as well as collaborative or community-based research (see Chapters 9 and 10) may entail prior contact and dialogue with individuals or communities as a normal and integral component to establish research collaborations or partnerships prior to the actual design of the research. Other research may, at their initial stages, not involve humans, but require engaging the research team, setting up equipment and other preparatory stages. These activities may precede REB review (as per Article 6.11 of TCPS-2).

**Determining the Level of Research Ethics Review**

In keeping with a proportionate approach to research ethics review, the selection of the level of REB review shall be determined by the level of foreseeable risks to participants: the lower the level of risk, the lower the level of scrutiny (delegated review); the higher the level of risk, the higher the level of scrutiny (full board review) (as per Article 6.12 of TCPS-2).

REBs shall assess the level of risk that the research under review poses to participants to determine the appropriate level of research ethics review (delegated or full REB review). (For a full discussion of the proportionate approach to research ethics review, see Chapter 1, Section C, and Article 2.9 of TCPS-2). This applies to both initial research ethics review (see Article 6.11 of TCPS-2) and continuing research ethics review (see Article 6.14 of TCPS-2).

With the support of their institutions, REBs may develop their own mechanisms under which delegation of the conduct of research ethics review, decision making and the associated reporting processes will occur. Those mechanisms and procedures should be made public. It is the REB, based on its established procedures and through its Chair, that decides on the level of review for each research proposal (as per Article 6.12 of TCPS-2).

**Two levels of research ethics review may apply:**

1. Full REB review
a) Research ethics review by the full REB should be the default requirement for research involving humans.

2. Delegated REB review of minimal risk research

a) The REB delegates research ethics review to an individual or individuals. Delegates shall be selected from among the REB membership with the exception of the ethics review of student course-based research. This can be delegated to the department, faculty or equivalent level as indicated below.

Continuing Research Ethics Review - Reporting Requirements

The REB shall make the final determination as to the nature and frequency of continuing research ethics review in accordance with a proportionate approach to research ethics review. At minimum, continuing research ethics review shall consist of an annual status report (for multi-year research projects), and an end-of-study report (projects lasting less than one year) (as per Article 6.14 of TCPS-2).

Research is subject to continuing research ethics review from the date of initial REB approval throughout the life of the project (see Article 2.8 of TCPS-2). At the time of the initial review, the REB has the authority to determine the term of approval, and the level at which continuing ethics review occurs in accordance with a proportionate approach to research ethics review. As with initial review, continuing ethics review could be full board review or delegated review based on the level of risk of the research (see Article 6.12 of TCPS-2). The level of research ethics review may be adjusted over the life of the project based on the level of risk.

For research projects lasting longer than one year, researchers shall submit, at minimum, an annual report with sufficient details to enable the REB to make an informed judgment about the continued ethical acceptability of the research. For research lasting less than one year, an end-of-study report may suffice (as per Article 6.14 of TCPS-2).

For some types of research (e.g., qualitative research or longitudinal research), there may be some difficulty in establishing start or end dates. In these cases, the REB should work with researchers to determine a reasonable timeline for continuing ethics review, and for determining the completion date dependent on the discipline and method of research. The reporting schedule for continuing ethics review may be adjusted throughout the life of the project. This would be necessary, for example, if the risk level of the research increases as a
USE OF HUMAN BIOLOGICAL MATERIALS FOR RESEARCH PURPOSES

Use of Materials Originating from Human Bodies for Research Purposes

The use of materials originating from human bodies for research contributes greatly to the advancement of knowledge. The sources of these materials can be from patients following diagnostic or therapeutic procedures, autopsy specimens, donations of organs or tissue from living or dead humans, body wastes (including urine, saliva, sweat) or abandoned tissue. Biological materials may also be sought from individuals for use in a specific research project. Once collected, biological materials may be held in biobanks to serve as a research resource for many years (as per Chapter 12 of TCPS-2).

Ethical considerations raised by research involving human biological materials centre on acceptable access to, and use of, the materials, potential privacy concerns arising from the handling of information derived from such materials, and the special status some individuals and groups accord to the human body and its parts. Because the significance of biological materials varies among individuals and groups, it is important to assess the ethics of research involving such materials with an awareness of and sensitivity to the known values, beliefs and attitudes of those from whom the materials originated (as per Chapter 12 of TCPS-2).

TYPES OF HUMAN BIOLOGICAL MATERIALS

Human biological materials that may reasonably be expected to identify an individual, alone or in combination with other available information, are considered identifiable biological materials (or biological materials that are identifiable) for the purposes of this Policy. The
following categories, similar to those found in Chapter 5 in regard to categories of information, provide guidance for assessing the extent to which human biological materials could be used to identify an individual:

**Identified human biological materials**

The materials are labelled with a direct identifier (e.g., name, personal health number). Materials and any associated information are directly traceable back to a specific individual.

**Coded human biological materials**

Direct identifiers are removed from the materials and replaced with a code. Depending on access to the code, it may be possible to re-identify specific individuals (e.g., a principal investigator retains a key that links the coded material with a specific individual if re-linkage is necessary).

**Anonymized human biological materials**

The materials are irrevocably stripped of direct identifiers, a code is not kept to allow future re-linkage, and risk of re-identification of individuals from remaining indirect identifiers is low or very low.

**Anonymous human biological materials**

The materials never had identifiers attached to them and risk of identification of individuals is low or very low.

Due to continuing technological development in genetics, individuals with access to stored human biological materials are increasingly able to use genetic markers to link a non-identifiable sample with an identified sample. For this reason, genetic analysis has made it more difficult to categorize human biological materials as anonymous or anonymized. The definitions above relate to identification of individuals; however, some research involving human biological materials, especially genetic research, may involve identification of groups,
DEFINITIONS

Post-Registration Clinical Study

A post registration clinical study (for the purposes of this Section 18, “study” or “studies”) is any study within the approved indications that is conducted after Health Canada’s Notice of Compliance has been issued for a Prescription Medicine (as per Section 18.1.1 of the Rx&D Code of Ethical Practices - 2012).

‘Seeding ’ or ‘Experience’ Trials

A study with the underlying purpose to familiarize Health Care Professionals and/or patients with the use of a Prescription Medicine or encourage its prescription, often referred to as “seeding” or “experience” trials, is not an acceptable post registration clinical study (as per Section 18.1.2 of the Rx&D Code of Ethical Practices - 2012).

GENERAL PRINCIPLES

The main purpose of a study will be to answer scientific question(s) which requires obtaining and evaluating data on safety and/or efficacy, effectiveness, cost effectiveness, quality of life, functional or other socio-economic factors that have to do with clinical use of the Prescription Medicine (as per Section 18.2.1 of the Rx&D Code of Ethical Practices - 2012).
STANDARDS

Studies must provide a scientific framework for investigation of the medicine in broader or special populations (as per Section 18.3.1 of the Rx&D Code of Ethical Practices - 2012).

Clearly Defined Objective

All studies must have a clearly defined objective which is amenable to scientific review and testing. Duplication or redundancies in studies must be medically and ethically justifiable (as per Section 18.3.2 of the Rx&D Code of Ethical Practices - 2012).

Internal Approval & Governance by Qualified People

The Member must ensure that studies are designed/approved and administered by qualified people in the medical/scientific department, using the same kinds of methodology (i.e. the planning, protocol development, monitoring and data interpretation) that apply to pre-marketing trials (as per Section 18.3.3 of the Rx&D Code of Ethical Practices - 2012).

Provision & Retrieval of Devices or Diagnostic Equipment to Support the Study

As the post-registration clinical study may include the dissemination of devices or diagnostic equipment (including, without limitation, blood pressure monitors and glucose meters) for use by the Health Care Professional or the subject as part of the clinical study, it is the Member’s responsibility to ensure that this material is appropriately distributed prior to the study and collected subsequent to the study, by the medical/scientific department. Members must maintain a record of dissemination to Health Care Professionals and use reasonable methods to retrieve this equipment from the Health Care Professionals upon the completion of the study (as per Section 18.3.3 of the Rx&D Code of Ethical Practices - 2012).