Fraser Health Research Ethics
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GUIDANCE NOTES FOR NEW APPLICATIONS FOR ETHICAL REVIEW BY THE FRASER HEALTH RESEARCH ETHICS BOARD

Adapted with the permission of the University of British Columbia

These Guidance Notes are governed by the current version of the FH Policy "The Ethical Conduct of Research And Related Studies Involving Human Subjects/participants"[1]. Refer to
www.research.fraserhealth.ca
Please note that revisions are highlighted in yellow.

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[1] Other related FH policies are the "FH Research Policy" and the FH Policy "The Collection, Use and Disclosure of Personal Information for Research-related Purposes" http://www.fraserhealth.ca/Initiatives/Research/Default.htm

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INTRODUCTION

The following Guidance Notes (GNs) comprise the FH Research Ethics Board's [FHREB] applicable policies, standard operating procedures, and advice. They are intended to ensure that researchers have the necessary information to complete the current version of the "Application For Initial Ethical Review" correctly, to ensure that correct documents are appended to the application and to construct consent forms that meet FHREB standards.

All FH investigators including Principal Investigators, Co-Investigators, and Affiliated Researchers have an obligation to adhere to:

- The current version of the FH Policy "The Ethical Conduct of Research And Other Related Studies Involving Human Subjects/participants",
- The current version of the Tri-Council Policy Statement (TCPS) on 'Ethical Conduct for Research Involving Humans' (2014) [TCPS 2] which is the Canadian national standard for all research involving human subjects/participants whether conducted inside or outside of Canada, and,
- Other relevant legislation, policies, and guidelines as applicable to the particular research study.

While the GNs are intended to be a general guidance that will apply to most research studies, they are not intended to be a substitute for the original source documents referenced in the GNs. Researchers should refer to the original documents for complete information.

Under certain circumstances, however, the FHREB may also approve exceptions to the standards described here. Similarly, researchers may also request an exception to the standards described here.

The FHREB policies and procedures included in this document correspond to, and therefore comply with the TCPS and the ethical principles for research described in the current Declaration of Helsinki (1964).

In addition, the FHREB is regulated by the following Health Canada legislation for clinical trials involving drugs, radiopharmaceuticals, medical devices and natural health products and also must meet obligations under the "ICH Good Clinical Practice Guidelines"[ICH GCP] as required by Health Canada. The GNs meet the requirements of the following regulations and guidelines as applicable to clinical trial research.

- Food and Drug Act: Food and Drug Regulations

Refer to: http://laws.justice.gc.ca/en/F-27/C.R.C.-c.870/125416.html#rid-125489
Scroll down to Division 5. DRUGS FOR CLINICAL TRIALS INVOLVING HUMAN SUBJECTS/PARTICIPANTS

- Food and Drug Act: Medical Devices Regulations

  Refer to: http://laws.justice.gc.ca/en/f-27/sor-98-282/129684.html

- Food and Drug Act: Natural Health Products Regulations

  Refer to: http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/acts-lois/prodnatur/propose2_regula-regle_doc6_e.html

- ICH Good Clinical Practice Guidelines (ICH GCPs) (1997)
  Refer to:
  http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

The purpose of the FHREB is to determine whether the research question or hypothesis for a study is scientifically and therefore ethically valid; and, if so, whether the research is in compliance with the relevant ethical requirements for carrying out research involving human subjects/participants. **In accordance therefore with TCPS 2 Article 2.1 and ICH GCP Article 3.3.6, the research study cannot begin until the FHREB issues its written approval of the research study.**

EXCLUSIONS:

Updated 2017 November 17: Ethical review is not required for quality improvement, evaluation, monitoring studies that are being conducted for the purpose of carrying out the duties/business of the organization. These are exempt from FHREB review and approval. Refer to TCPS2 Article 2.3, 2.4 and 2.5 and the FH Research Policy.

In addition, research that is conducted with FH employees/privileged physicians as research participants but outside of their work responsibilities (i.e. recruitment is not through FH business emails) and not at a FH site does not require ethical review and approval by the FHREB (e.g. interviews). It is assumed that any such study would be approved by the non-FH researcher's own research ethics board. This also applies to individuals who while they may be patients of the Fraser Health Authority are involved in research studies that are not conducted by FH researchers.

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GUIDANCE NOTE #1: PRINCIPAL INVESTIGATOR

References:

1. TCPS 2 Article 3.2 re "Informing Potential Subjects/participants" refers to the "principal researcher" (i.e. principal researcher) as the individual who "is ultimately responsible for the actions of those acting with delegated authority".

2. Re: Clinical Trials: The Health Canada legislation referred to below includes specific obligations of the 'qualifying investigator' responsible for submitting a 'Clinical Trial Application' to Health Canada and for carrying out the study.

   2.1 Health Canada Food and Drug Act

   Food and Drug Act: Food and Drug Regulations

   Refer to: http://laws.justice.gc.ca/en/F-27/C.R.C.-c.870/125416.html#rid-125489
   Scroll down to Division 5. DRUGS FOR CLINICAL TRIALS INVOLVING HUMAN SUBJECTS/PARTICIPANTS

   Food and Drug Act: Medical Devices Regulations

   Refer to: http://laws.justice.gc.ca/en/f-27/sor-98-282/129684.html

   Food and Drug Act: Natural Health Products Regulations

   Refer to: http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/acts-lois/prodnatur/propose2_regula-regle_doc6_e.html

3. ICH GCP 1.34 defines the investigator as “a person responsible for the conduct of the clinical trial at a trial site” or “the responsible leader of the team.

1.1 RESPONSIBILITIES

1.1.1 All Principal Investigators

Updated 2016 November 16: For the purposes of ethical review, there can be only one principal investigator that assumes responsibility for the conduct of the research study. It is acceptable for another FH site investigator to be deemed as a co-principal investigator for grant submission or publication purposes only.

All Principal Investigators [PI] must have an affiliation with FH [i.e. employee*, privileged physician, academic faculty member who has been granted ‘affiliated status’].

Principal Investigators who are conducting above minimal risk research (research requiring Full Board review) must complete the Tri-Council Policy Statement 2 Tutorial and submit his/her certificate of completion before the first annual renewal.

* Residents who are employed by Fraser Health, i.e. Pharmacy Residents can be listed as PIs on a study.

1.1.1.a Physicians Conducting Studies at FH Sites

Updated 2016 November 16: Physicians conducting studies must have consulting privileges at each site within Fraser Health where the study is being conducted. This also applies to locum physicians as long as they are conducting the study as a FH privileged physician. Refer to Research Policy under Scope 3.1 iii at http://research.fraserhealth.ca/media/Research.pdf. The physician principal investigator must have the initial application for ethical review signed off by their immediate

administrative supervisor in order for it to be reviewed by the FHREB.

As noted in section 3 of the Application Form, the principal investigator bears the overall responsibility for the conduct of the study, including the activities of co-investigators, who are assumed to be acting under the delegated authority of the principal investigator, and is required to act within the requirements of TCPS and the FH Policy "The Ethical Conduct of Research and Other Studies Involving Human Subjects/participants".

Physicians without privileges are not allowed to be the principal investigator for any research study conducted in the Fraser Health Authority.

1.1.1 b. Affiliated Researchers

Affiliated researchers are non-FH researchers who have been granted 'affiliated' status with FH. Affiliated status is obtained when the non-FH researcher's academic institution and FH sign the master Research Collaboration Agreement which lays out the institutional terms under which a non-FH researcher can be affiliated with FH.

Individual academic institutions may have specific requirements that are in addition to signing the Research Collaboration Agreement. The affiliated researcher applicant will be notified if this is the case Affiliated researchers must have an FH co-investigator listed on the study team.

All of FH's ethics policies and procedures apply to any affiliated researcher.

For information on the process to obtain affiliated status, refer to http://research.fraserhealth.ca/approvals-%26-ethics/external-researchers/

Exception: University of British Columbia Affiliated Principal Investigators may submit the UBC ethics application from the RiSE system. This must be accompanied by the information found at the following link.

1.1.1 c. Principal Investigators who hold Clinical Appointments with the University of British Columbia

Principal investigators who hold a clinical appointment with the University of British Columbia, and who are conducting their research only within the Fraser Health Authority as Fraser Health privileged physicians and NOT as UBC affiliated investigators (i.e. the study and any related documents would not mention UBC), do not require ethics approval from the UBC Clinical Research Ethics Board.

The Fraser Health Research Ethics Board assumes responsibility for the review of research conducted by these investigators.

(Updated November 16, 2016) 1.1.1. University of British Columbia Medical Residents who are conducting research in Fraser Health

UBC medical residents must have a FH principal investigator for studies conducted in FH. However, they may submit the UBC ethics application from the RiSE system.

1.2 POTENTIAL CONFLICT OF INTEREST

References:

1. TCPS 2 Article 11E re publication rights of researchers

2. The Canadian Medical Association policy guidelines for Physicians in Interactions with Industry **Article 11**
3. American Association of Medical Colleges Task Force Report on Individual Financial Interest in Human Subjects/participants Research. **http://www.aamc.org/**
4. Current Fraser Health Authority Policy on Conflict of Interest (Refer to FH Pulse for Policies/Corporate)

Even though Investigators may supply the information requested in Section 11 in the Application Form to their departments or hospitals, the FHREB must consider whether this information has any bearing on the ethics of the research study. Note that "immediate family members" includes partners and children (whether living in the household or not). The FHREB does not require that the researcher declare holdings in managed mutual funds in the conflict of interest statements.

Subjects/participants must be informed of significant individual financial conflicts of interest in the consent form.

The FHREB operates according to the 'American Association of Medical Colleges' Task Force Report on Individual Financial Interest in Human Subjects/participants Research. Refer to http://www.aamc.org/ for the complete report. Investigators are also reminded of their obligations under the FH "Research Policy" which are separate and apart from the ethics requirements.

Policy #16: Conflict of Interest
At minimum, potential conflicts must be disclosed to the FHREB and to potential subjects/participants. The Board may require further action of the researcher to minimize or abandon a conflict, require formal oversight procedures for the research (including audits, independent data safety monitoring processes, regular reports to the FHREB), or may disallow the research altogether. The Board may also inform the researcher's immediate supervisor about the conflict of interest.

Researchers are also advised of the following relevant national policies and guidelines:

1.2.1 Publication of Research Findings

The FHREB will not permit any statements that appear to limit the researchers' rights to disclose their findings related to the research in publications or otherwise. (TCPS 2: (11E) Analysis and Dissemination of the Results of Clinical Trials).

1.2.2 Recruitment Fees

The Canadian Medical Association policy on Physicians and the Pharmaceutical Industry Article 12 states: "Because of the potential to influence judgment, remuneration to physicians for participating in research studies should not constitute enticement. It may cover reasonable time and expenses and should be approved by the relevant research ethics board. Research subjects must be informed if their physician will receive a fee for their participation and by whom the fee will be paid." Refer to http://www.cma.ca/cma/common/start.do for the CMA Policy on "Physicians and the Pharmaceutical Industry (Update 2001)" Article 11.

1.2.3 Preceptor Agreements

Disclosure to potential subjects/participants is required where Preceptor agreements exist between a Principal Investigator and a sponsor whereby the Principal Investigator is consulted by the Principal Investigators at community sites for the same study; and where preceptor agreements exist between a Principal Investigator and a sponsor whereby the Principal Investigator is consulted by the Principal Investigators at community sites for the same study.

1.3 CLINIAL TRIAL REGISTRATION

The FH "Research Policy" requires that:

a. Clinical trials which prospectively assign human subjects/participants to intervention and comparison groups to study the cause-and-effect relationship between the medical intervention and the health outcome shall be registered by the industry or FH investigator sponsor with a registry that meets the requirements of the International Committee of Medical Journal Editors.

b. Medical intervention includes drugs, devices, surgical procedures, behavioural or management studies which have the intent to modify a health outcome, with the exclusion of Phase 1 clinical trials.

Clinical trial registration has been accepted as a mandatory requirement for all ethically conducted research by the:

a. World Health Organization; World Health Organization International Clinical Trials Registry Platform (ICTRP) – http://www.who.int/ictrp/en/ ,
b. American Medical Association; American Medical Association Council on Scientific Affairs. Featured Report: Influence of Funding Source on Outcome, Validity, and Reliability of Pharmaceutical Research (A-04), Chicago, IL: American Medical Association, 2004,
c. Ottawa Group; The Ottawa Statement, Part One: Principle for International Registration of Protocol Information and Results from Human Trials of Health-related Interventions. http://Ottawagroup.ohri.ca/statement.html, and,
d. International Committee of Medical Journal Editors; ICMJE. Uniform Requirements for Manuscripts Submitted to Biomedical Journals. http://www.icmje.org/icmje-recommendations.pdf.

In addition, this requirement has been accepted by the pharmaceutical and biotechnology industries. The ethical principle underlying public registration of clinical trials is that the "potential societal benefit promised in most research consent forms cannot be realized if the research study is hidden from society. Because clinical trial registration requires researchers to describe in a public [i.e. not-for-profit] database several specific items that provide the basic outline of a human research trial, it facilitates the realization of the social benefit of a clinical trial by promoting information flow about the trial, inhibiting concealment of trials that fail to show efficacy or that lead to serious adverse effects, allowing systematic reviews of interventions and results, reducing unnecessary duplication, and enhancing the transparency that supports public trust in human research ethics." (Source: Levin, Leonard, A.; Palmer, JG. Institutional Review Boards Should Require Clinical Trial Registration. Arch Intern Med. 167: No. 15. August 13/27, 2007, p. 1576-1579.)

Studies that meet the registration criteria may be registered either at www.ClinicalTrials.gov or at the WHO Search Portal at http://www.who.int/trialsearch/. The WHO Search Portal provides users with access to the Trial Registration Data Sets

provided by ClinicalTrials.gov and Controlled-trials.com in addition to the Australian and New Zealand Clinical Trials Registry.

1.4 INVESTIGATORS CONDUCTING CLINICAL TRIALS REGULATED BY HEALTH CANADA

Investigators conducting clinical trials for either drugs/radiopharmaceuticals, devices, or natural health products used for therapeutic purposes have special obligations that are defined in the regulations that govern each type of experimental therapy. The ICH: GCP Guidelines specify additional obligations for investigators conducting clinical drug trials. Refer to **GN 11** for further details.

1.5 PRINCIPAL INVESTIGATOR-INITIATED CLINICAL TRIALS

Investigators who initiate clinical trials are also deemed to be the sponsor of their study according to the regulations for clinical drug and natural health product trials. These obligations are in addition to those of the investigator responsibilities. Refer to **GN 11** for further details.

1.6 PRINCIPAL INVESTIGATORS CONDUCTING CLINICAL TRIALS FUNDED AND/OR REGULATED BY THE UNITED STATES FEDERAL GOVERNMENT

Investigators who receive funding for studies conducted by a U.S. government department and/or its agencies (e.g. Department of Health and Human Services (DHHS)/National Institute of Health/National Cancer Institute, Department of Defense, U.S. Army) OR are
conducting studies regulated by the Food and Drug Administration are subject to the pertinent U.S. federal regulations. These are part of the Code of Federal Regulations (CFR) mandated by the United States government. The U.S. regulations that pertain to clinical research are:

i) 45 CFR Part 46 for all U.S. federal government department/agency funded research
Refer to: http://www.hhs.gov/ohrp/
For specific regulations refer to: http://www.hhs.gov/ohrp/humansubjects/index.html

ii) For research supported and/or conducted by any agency of the U.S. Department of Health and Human Services
Refer to: http://www.hhs.gov/ohrp/assurances/index.html;

iii) 21CFR Parts 50 and 54 for trials regulated by the Food and Drug Administration
Refer to: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm.

All consent forms for U.S. regulated studies must include reference to the clinical trial registration information.

1.7 CHANGE IN PRINCIPAL INVESTIGATOR

The Principal Investigator for the study must complete and submit an 'Application for Amendment of a Previously Approved Study' form when this responsibility will be assumed by a different investigator. The amendment form should identify the new principal investigator and also include any documents that require revision to change the principal investigator, i.e. consent form, posters, etc.

The new principal investigator must complete and submit the 'Change of Principal Investigator' form. Refer to
http://research.fraserhealth.ca/media/2008%2012%2009%20Change%20of%20PI.doc for a copy of these forms.

Principal Investigators must also ensure that a process is put into place to ensure the ongoing safety of research subjects/participants in the event that the Principal Investigator leaves or retires from FH and the study remains open.

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GUIDANCE NOTE #2: SUBMISSION REQUIREMENTS

All new applications for clinical research must be submitted using the current version of the "Integrated Privacy and Initial Ethical Review Application" form, including those that qualify for delegated review. The process used to review the new applications varies according to the level of risk (i.e. is proportionate to the level of risk) that the subject could experience as a result of the particular type of research procedure used, and is described below.

The Data Access Application [DAA], administered by the Fraser Health Office of Information Privacy, is now integrated into the FHREB application for initial review. Once the initial application is approved by the REB, the FHREB Coordinator will transfer the study files to the Privacy Office to process the DAA.

For Multi-Jurisdictional Studies
The FHREB is a partner organization in the BC Ethics Harmonization Initiative [BCEHI], which aims to streamline the review process for multi-jurisdictional human health research in BC. Researchers applying for ethics review by the FHREB for multi-jurisdictional studies may fill out the BCEHI Coversheet to request a harmonized review with other participating partner organizations.

The FHREB will accept BCEHI partner REBs' application forms for harmonized review. However, a supplemental FHREB application form for affiliated researchers is required in order to provide site-specific information to the FHREB. This application also contains the Data Access Application.

2.1 MINIMAL RISK RESEARCH STUDIES

References:

1. TCPS 2 2B, Article 2.9 re "Minimal Risk" and a "Proportionate Approach to Ethical Review"

2.1.1 Submission Criterion

Minimal Risk is defined in the TCPS 2 as: "…research in which the probability and magnitude of possible harms implied by participation in the research is no greater than those encountered by participants in those aspects of their everyday life that relate to the research. " [TCPS2 B].

2.1.2 Types Of Minimal Risk Research Studies Qualifying for Delegated Review

Studies that may meet the criterion for minimal risk include research that is *limited* to the following sources of data and may undergo delegated review by the FHREB co- Chairs.

2.1.2.1 Primary Sources of Data Obtained For Prospective Research

Collections of hair, nail clippings, deciduous teeth, excreta, salivary secretions, additional swabs, or other external secretions that have been collected in a non-invasive manner and that may also be collected as part of routine clinical care;

1. Placenta or amniotic fluid collected as a consequence of normal labour and delivery, or fetal tissue collected as a consequence of therapeutic abortion or miscarriage;
2. Data recorded using non-invasive procedures routinely employed in clinical practice (e.g. EEG, EKG, ultrasound), but not including questionnaires requesting sensitive information from vulnerable populations or involving significant nuisance or inconvenience;
3. Blood samples collected by venipuncture or a central line installed and that may also be collected as part of routine clinical care;
4. Blood samples collected are less than 2 tablespoons of blood and the protocol clearly stated that the samples would be destroyed immediately after testing for this specific research study was completed and that no samples would be sent outside of BC for testing.
5. Output data obtained as a result of moderate exercise undertaken by healthy volunteers;
6. Exercise interventions involving walking or equivalent intensity.
7. Other clinical non-invasive data that may be collected as part of routine clinical care and used for observational research;
8. Data collection from patients/clients for the purpose of developing a database/registry for research purposes and that is not linked to other non-FH databases.
9. Observational research on standard treatment(s) where the treatment(s) is (are) determined clinically and not assigned by research methodology (e.g. randomization).

a. Consent Requirements

For further information, refer to **GN 19.2**

2.1.2.2 Secondary Sources of Data Used for Retrospective Research

These are studies of a clinical nature that use existing databases/registries or that link information between databases. Refer to **GN 19.2** and **GN23** for specific requirements regarding the protection of subject identity. In contrast to TCPS 2 Article 2.4, the FHREB has approved continuation of the policy of review of all secondary sources of data owned or maintained by Fraser Health and/or data from research registries for research purposes, even if the data is anonymous, such that data linkage cannot reveal identifiable information.

1. Previously collected data from existing documents or records, such as health records or charts. [Studies that include both a review of the medical record/chart and the prospective collection of information using questionnaires/interviews, etc. for behavioural research would be considered prospective, and require consent]
2. Previously collected pathological or diagnostic specimens whereby the tissue is frozen and the cells are dead and there is no further clinical need for the specimen.

a. Consent Requirements

For further information, refer to **GN 19.2**.

2.1.2.3 Case Reports of Individual Patients

The FHREB does not consider a case report to meet the definition of research; this is considered to be a medical/educational activity.* Therefore, FH researchers are not required to obtain FHREB approval prior to beginning the activity. However, the FHREB expects that a process is in place for ensuring that subjects/participants are aware that the author/researcher plans to report about the case.

Researchers who apply to the FHREB prior to preparing a case report for publication, or who have been asked by a journal to provide documentation of REB approval prior to publication of a submitted case report, will generally be given a letter of acknowledgement only, not a certificate of approval. Researchers should inform the FHREB if a journal does not accept the FHREB's decision.

To receive an acknowledgement letter from the FHREB, a draft of the case report should be submitted to the FHREB prior to submission to a journal.

Note that the FHREB would not under any circumstance acknowledge a request for a publication that had already been submitted. Requests for such review to satisfy, for example, publication requirements, will not be accepted.

*A case report for FHREB purposes is a retrospective analysis of one or two clinical cases. If more than two cases are involved in the analytical activity, the activity will normally constitute "research" and be subject to standard policy and guidelines on research ethics review.

2.1.2.4 Stem Cell Research

Reference:

1. TCPS 2 Article 12.10
2. Current Canadian Institute for Health Research "Guidelines for Human Pluripotent Stem Cell Research"

a. Permanent Stable Cell Lines

Ethical review of research that uses permanent stable cell lines in laboratory research (i.e. in vitro) is not required.

b. CIHR Requirements for Ethical Review of Pluripotent Stem Cell Research

As of December 2014, the CIHR Guidelines for Human Pluripotent Stem Cell Research have been integrated into the TCPS 2, chapter 12, section F. These guidelines apply to all new or ongoing human stem cell research that is:

1. funded by the CIHR agencies;
2. conducted under the auspices of an institution that receives any agency funding, whether on site or off site or;
3. conducted elsewhere with any source of funding by faculty, staff or students from an institution that receives Agency funding.

The CIHR Stem Cell Oversight Committee must approve the following types of stem cell

research:

1. all research to derive and study human embryonic stem cell (ES) lines or other stem cell lines from human embryos;
2. all research to derive and study human embryonic germ cell (EG) lines or other stem cell lines from human fetal tissue or amniotic fluid;
3. all research on anonymized human ES lines, or EG lines created in Canada or created elsewhere and imported for research purposes;
4. all research involving the grafting of human ES cell lines, EG cell lines or other human pluripotent stem cell lines into non-human adults; and
5. all research involving the grafting of human pluripotent stem cell lines into legally competent adults.

CIHR requires that stem cell investigators seek REB approval for their **non-clinical research.**

For further details regarding CIHR requirements, refer to:
TCPS 2 (2014)

c. Criteria for Delegated Review

Pluripotent stem cell research qualifies for Delegated Review **with the exception of any research that concerns the derivation of stem cell lines** from human somatic tissue, umbilical cord or placenta OR research involving the grafting of stem cell lines into humans. See **GN 2.1.4** regarding 'Minimal Risk Studies That Require Full Board Review".

Complete the "Application for Initial Ethical Review" as follows:

Page 1 — Under Delegated Review, check all as applicable

Your study protocol must include the following:

a. Description of the research plan
b. Detailed description of the stem cells being used in the research. This should include the following:
   - ❖ Description of whether the Stem Cell Oversight Committee and any other relevant committee has reviewed the proposal;
   - ❖ Description of whether the cell line is "registered" either in Canada or the USA, and;
   - ❖ A declaration of how CIHR regulations 7.1.2 through 7.1.6 have been satisfied.

2.1.3. Use of Information Obtained from Non-FH Affiliated Sites

Studies that involve the analysis of data/tissue obtained from researchers working at any non-FH institutions must also include the consent form used to obtain permission for collection of the data/tissue OR a statement that explains the confidentiality provisions under which consent was initially obtained.

2.1.4 Minimal Risk Studies That Require Full Board Review

The following types of studies must be submitted for full board review:

1. Studies whose purpose is to collect tissue/DNA for the purpose of creating or adding to

a tissue/DNA bank or for genetic research; See **GN 24.4** for further details on consent form requirements;
2. Studies whose purpose is the derivation of stem cell lines from human somatic tissue, umbilical cord or placenta OR research involving the grafting of stem cell lines into humans;
3. Studies whose research population is legally incompetent to consent to interventional research;
4. Studies that have corporate sponsorship; and
5. Studies that involve linkage of subject personal information to non-FHA databases/registries.
6. Minimal Risk Studies that recruit residents or trainees as subjects/participants.
7. Prospective studies requesting a waiver of consent.
8. Studies that collect data using MRIs or X-Rays.

2.1.4.1 Referral by the FHREB Chair

The FH co-Chairs reserve the right to refer any study for full board review for any reason.

2.1.5 Delegated Review Process

The FH co-Chairs review new applications within this category on a rolling basis. New applications may be submitted by email to REB@fraserhealth.ca. The decision will usually be sent back within 5 business days from the review.

Note: All studies receiving Delegated Approval: A summary of the approval is emailed to the FHREB members for their review. The FHREB members have 3 business days to respond with questions or concerns. If no concerns are raised, the ethics approval can be released at this time as long as all other documents (i.e. if applicable, DAR Form, Clinical Registration No., etc.) are completed.

2.2 FULL BOARD REVIEW OF NEW APPLICATIONS

All studies that do not meet the criteria described in **GN 2.1** must be submitted for full board review.

2.2.1 FHREB Meetings

The FHREB meetings are held on the second Wednesday of every month. The deadline for submitting the application and its attachments to the FH Research Ethics Board is two weeks before the meeting. All applications that meet the submission deadline are put on the agenda for the upcoming meeting on a first come/first served basis. The FHREB reserves the right to limit the number of studies reviewed at one meeting.
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GUIDANCE NOTE #3: APPLICATION FEE FOR INDUSTRY-SPONSORED STUDIES

The fee described below covers the submission of the initial request for ethical review, subsequent amendment and renewal applications, as well as the submission of serious and unexpected adverse event reports and protocol deviations in the case of clinical trials.
The fee for ethical review of industry sponsored studies is $4000.00 and applies to:

1. research that receives its funding from an industry sponsor (i.e. pharmaceutical/medical devices company or an agent thereof- also refer to Section 10

and page 4 of the Application Form);
2. research that receives funding from a grant-in-aid from an industry sponsor when there are conditions/expectations that the sponsor may sublicense the data back from the researcher, and;
3. sub-studies/extension studies that include a new protocol (i.e. not an amended protocol) and therefore require full board review as a new application.

Payment of the required fee, or a letter stating that the fee will follow and by when, must accompany the Application for Initial Ethical Review for all industry-sponsored research. It is the responsibility of the Principal Investigator to ensure that their sponsor is aware of this requirement and to submit the cheque/letter at the time of the submission to the FHREB.

The FHREB will review the research only if the fee or letter accompanies the application.

3.1 FEE WAIVER CRITERIA

The fee is waived for:
a. Studies receiving a grant-in-aid (normally an investigator-initiated study with partial funding-e.g. supply of drugs or devices or a very limited amount of funding from an industry sponsor) with NO data returned to the sponsor in any form or manner (i.e. it is permissible for the sponsor to acquire a final study report);
b. Studies that are funded by not-for-profit agencies;
c. Studies funded by CIHR, NSERC and NIH (including NIH Institutes), and;
d. Studies without funding.

3.2 MECHANISM FOR SUBMITTING THE FEE

1. Attach the cheque made payable to Fraser Health Authority to the Application for Initial Ethical Review.
2. For cheques sent to the FH Research Ethics Board AFTER the submission of the initial application: Accompany the cheque with a memo that identifies the study by citing the Principal Investigator's name, the exact study title, and if possible the FHREB #.
3. If an invoice is required, please submit a cover letter requesting it and provide details on who the invoice should be made out to. Requests for invoices sent to the FH Research Ethics Board after an application is submitted, must include the exact title of the research study, the Principal Investigator's name, and if possible the FHREB #.

3.3 REQUIREMENTS FOR FEE REFUND

3.3.1 Full Refund

The fee will be totally refunded if the associated research study is withdrawn prior to review.

3.3.2 Partial Refund

$1500.00 of the fee amount is non-refundable if the associated research study is withdrawn after the review and before the specific contract for the study is signed.

All requests must be submitted to Susan Chunick, Director, Department of Evaluation and Research Services for consideration.

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GUIDANCE NOTE #4: INSTITUTIONS

The letterhead of the subject informed consent documents must cite the Fraser Health Authority research carried out within FH. Ensure that all institutions within FH that will be involved in the research (including recruitment sites) are specified in Section 8 of the Application for Initial Ethi Review Form.

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GUIDANCE NOTE #5: DOCUMENT IDENTIFICATION

5.1 STUDY TITLES

The title given in Section 1 of the Application Form and the title of the protocol submitted should be the same and correspond to the title of any consent form(s) also submitted.

5.2 EXTENSION/SUB STUDIES

Indicate whether the study is an extension or a sub-study of a primary study. For example, in an extension study, the study period could be extended in order to give subjects/participants the opportunity to undergo an extra regimen of treatment with the experimental drug. A sub-study is a concurrent study on a sub-sample/population of the original study sample/population.

Alternatively, some sub studies may be submitted as an Amendment to the initial application while the main study is ongoing.

5.3 GRANTS COVERING A SERIES OF STUDIES

In some situations, a single grant is awarded to fund a series of studies in the same topic area or line of research over a period of several years (e.g. one study per year for three years). These studies may be sufficiently different that a full ethical review is required of each study. For these types of studies, include the specific title of the smaller study and following that, the more inclusive title of the grant. This will ensure that the FH Research Office can authorize the release the funds at the appropriate time for each specific study.
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GUIDANCE NOTE #6: REQUIRED DOCUMENTATION

Applications that are submitted without complete protocols or consent forms will be deferred by the FHREB and will have to be resubmitted to another board meeting.

Ensure that the documents submitted include all pages in the correct order.

Reference:

1. TCPS 2 Article 6.11
2. TCPS 2 Articles 10.1
3. TCPS 2 Article 10.5 (re qualitative research involving emergent design) and 9.12

Subject to the exceptions in Article 10.5, REB review is NOT required for the “initial exploratory phase (often involving contact with individuals or communities) intended to

discuss the feasibility of the research, establish research partnerships, or the design of the research proposal. In addition, there are specific submission requirements for participatory research using an emergent design as follows:

1. The initial submission must identify that an emergent design is being used AND that the specific application is for approval of the initial Phase or Phases as applicable. (note add emergent design to application form);
2. Justification of the emergent design including benefits of this approach and any potential risks with respect to viability of this type of plan;
3. Description of the proposed phases of research including development of the research design for data collection, the data collection methods and any data collection instruments;
4. If participatory design is used, then the design must clearly describe and explain the nature of the 'participation';
5. For emergent research that includes a participatory/collaborative component, submission of the plan for developing a Research Agreement or the Research Agreement as required under TCPS 9.11.
6. The Research Agreement must adhere to TCPS 2 requirements for participatory research and identify the type of consent that would be used for the study, e.g. community/individual, and explain that the Research Ethics Board(s) has the authority to NOT approve the research as an outcome of the ethical review process; and that the 'community' could be asked to respond to any requests for further information from the REB.
7. For each phase of the research, a description of expected outcomes which could lead to the next phase of design development;
8. Submission of draft instruments with specification of the plan for finalization and/or plan for ongoing refinement/amendment over the course of the study;

6.1 REQUIREMENT FOR RESEARCH PROTOCOLS FOR ALL STUDIES

POLICY #1: Requirement for Research Protocol

The FHREB requires that a research protocol/research plan be submitted for all types of studies, including pilot studies and retrospective chart reviews. The research proposal submitted to granting agencies may be used to meet this requirement; in this case, ensure that the appropriate section of the grant application is referenced. For all other studies, including those that are submitted for delegated review, investigators must submit a protocol that includes the following components; which are described in more detail in the following Guidance Notes:

1. Table of Contents,
2. Study Protocol Summary or Abstract,
3. Background Information,
4. Purpose of Study,
5. Hypothesis (if applicable),
6. Justification for Study,
7. Objectives of study,
8. Research Method (including data collection methods),
9. Sample Size,
10. Statistical Analysis Plan,
11. Justification if the study has a placebo-control (if applicable),
12. (refer to Article 11.2 of the TCPS2 for appropriate use of placebos in clinical trials in Canada),
13. Subject Inclusion Criteria,

14. Subject Exclusion Criteria,
15. Research Procedures,
16. Potential Benefits
17. Subject Safety Provisions, i.e. un-blinding, data monitoring, and stopping rules.

6.2 RESEARCH PROTOCOL/PROPOSAL

References:

1. TCPS 2 Section 11A re "clinical equipoise"
2. TCPS 2 Article 11.2 re "Placebo-Controlled Studies"
3. TCPS 2 Article 3.8 re “Research in Individual Medical Emergencies”
4. ICH GCPS Articles 6.3 and 6.4

A protocol template is available at http://research.fraserhealth.ca/research-support/research-toolkit/, and should be referred to for more detail.

The Research Protocol/Proposal should include the following information:

1. Purpose
This is the main reason that the study is being conducted (e.g. to determine efficacy, equivalence, safety, dosage levels, effectiveness, pilot a research design, understand subject perceptions to improve patient care, improve service delivery, etc.) and should include the direct implications/applications of the research. Specify whether or not optional studies that may be part of a protocol are being conducted at the local site.

2. Hypothesis or Aim
This specifies the precise research questions being evaluated in the study.

3. Justification for the study
This includes background evidence that explains the need for the study. In particular this section should explain what is unique about the study and what new research questions can be answered in order to support the ethical tenet that the proposed research has value. Note that the FHREB requires that a bibliography of references to the literature accompany the protocol.

a. Clinical Trials – The justification for clinical trials that are investigating drugs, devices, natural health products or other therapeutic information should provide evidence of *clinical equipoise*, which is defined as "...a genuine uncertainty on the part of the expert medical community about the comparative therapeutic merits of each arm of a clinical trial." The justification must include the differences between what is considered the current ‘standard of care’ and the experimental intervention.

Some clinical trials are conducted in order to satisfy requirements for Health Canada or FDA approval. This is not a sufficient ethical justification for the study. Ensure that a more precise justification is provided which explains why additional studies are needed and warranted.

4. Objectives
This includes the specific outcomes/primary and secondary endpoints of the research.

5. Research Method
This should include a description of the target population and/or sample, sample size,

sampling method (e.g. randomization, convenience sample), type of research design (e.g. experimental parallel group, cross-over design, qualitative focus groups) and the analysis plan (i.e. statistical or qualitative). It should also include a justification for the use of deception or placebo or for the need to carry out research in emergency health situations, if applicable.

If deception is proposed, explain the following:
1. Why deception is necessary to achieve the research objectives,
2. Why the benefits of the research outweigh the cost to the subjects,
3. Why there will be no permanent damage as a result of the deception,
4. Describe how subjects will be debriefed at the end of the study

Debriefing

Where partial disclosure or deception has been used, debriefing is an important mechanism to maintain the subject's/participant's trust in the research community. The debriefing referred to in TCPS 2 Article 3.7(d) should be proportionate to the sensitivity of the issue. Often, debriefing can be a simple and straightforward candid disclosure. In sensitive cases, researchers should also provide a full explanation of why subjects/participants were temporarily led to believe that the research, or some aspect of it, had a different purpose, or why subjects/participants received less than full disclosure. The researchers should give details about the importance of the research, the necessity of having to use partial disclosure or deception, and express their concern about the welfare of the subjects/participants. They should seek to remove any misconceptions that may have arisen and to re-establish any trust that might have been lost, by explaining why these research procedures were necessary to obtain scientifically valid findings.

6. Subject Enrollment
Describe local FHA enrollment and participation by other sites if the study is multi-site. Note that a multi-site trial usually applies to clinical trials.

7. Inclusion Criteria for Subjects/participants

8. Analysis Plan

9. Data Management Plan

References:

1. TCPS 2 Article 3.9 re Incompetent Subjects/Participants
2. TCPS 2 Articles 4.1 re Appropriate Inclusion
3. TCPS 2 Articles: Inappropriate Exclusion 4.2 (re women), 4.3 (re women), 4.4 (re children), 4.5 (re elderly), 4.6 (re incompetent) and 4.7 (re vulnerability)
4. TCPS 2 Chapter 9 re Research Involving the First Nations, Inuit and Métis Peoples of Canada
5. ICH GCP Article 1.61 re Vulnerable Subjects/Participants
4. ICH GCP Articles 4.8.13 and 4.8.14 re participation requirements for non-therapeutic trials

The research protocol/proposal must include inclusion criteria, which should be based on the following information:

a. Requirements for equitable selection of subjects/participants

The selection of subjects/participants must be considered equitable and should strive to achieve a demographically representative sampling, subsequent to the constraints of the research.

b. Vulnerable subjects/participants
Special consideration must be given to the potential for inclusion of vulnerable subjects/participants who are not competent to give a legally or ethically valid consent or who have relatively little social or economic power. The research must not intentionally or inadvertently increase or exploit this vulnerability, nor should these types of populations be excluded from research, which is potentially beneficial to them as individuals, or to the group that they represent.

i. Legally Incompetent Subjects/participants
The inclusion of legally incompetent subjects/participants must meet the requirement of TCPS 2 Article 4.6, which also requires that "that the research does not expose the participants to more than minimal risk without the prospective of direct benefits for them…."

Refer to **GN 20.3** for the FHREB Policy #17 on "Obtaining Assent from Subjects/participants Who Are Legally Incompetent".

9. Exclusion Criteria for Subjects/Participants

References:

6. TCPS 2 Articles: Inappropriate Exclusion 4.2 (re women), 4.3 (re women), 4.4 (re children), 4.5 (re elderly), 4.6 (re incompetent) and 4.7 (re vulnerability)

The research protocol/proposal must include all exclusion criteria, which should also be based on the following information:

a. Provide justification if subjects/participants are excluded on the basis of such attributes as culture, language, religion, race, mental or physical disability, sexual orientation, ethnicity, gender or age.
b. Note pregnancy as an exclusion criteria if applicable.

9. Research-Related Procedures

References:

1. TCPS 2 Articles 3.2 and 3.3 "Informing Potential Subjects/participants"
2. ICH GCP 4.8.10 (c) and (d)

a. Specification of Research Procedures

Specify the research procedures/interventions that will be used throughout the study.

Describe any specific interventions: type, quantity, and route of administration of drugs and radiation, operations, tests, use of medical devices that are prototypes or altered from those in clinical use; interviews, focus groups or questionnaires. Specify if the study involves hospitalized patients.

In the case of clinical trials, describe the experimental intervention and research-related procedures and how they differ from standard care. This information must be transferred to the consent form in such a way that the subject understands that the intervention received and the procedures used are experimental and therefore different from the treatment normally received with standard care.

b. Timeline Requirements

Report the exact time requirements for participation by the subject; including:

- How much time beyond standard care is required for this study (if applicable);

- How much time a control/normal subject (if any) will be asked to dedicate to the study;
- Duration of each procedure;
- Duration of overall study, and;
- Total number of visits.

c. Radiation Doses Use for Research Purposes
When the radiation doses used are "indicated for research" and are not for the medical benefit of the subject (medically indicated radiation), refer to the Canadian Nuclear Safety Commission (CNSC) "Guidelines for Research on Human Participants Using Radionuclides" (INFO - 0491).

In any research, use of radiation or radioactive materials with human subjects/participants, the study should be designed to use radiation doses that are as low as reasonably achievable (the "ALARA" principle). Radiation dose guidelines apply to the dose from all radionuclide procedures and all diagnostic radiology (x-ray) procedures related to the research study, together with doses from other research studies in which the subject may be participating or has participated in during the year. Repeated use of the same volunteers for different studies is discouraged.

Provide the following information in the study protocol/proposal:

1. The source(s) of radiation exposure, including x-ray exposure;
2. The dosage of any radionuclide in activity units (becquerels or Bq);
3. The radiation dose(s) in millisieverts (mSv) to the whole body. When the major dose administered is to a particular organ or tissue, this dose must be converted to the effective dose in accordance with the guidelines of the International Commission on Radiological Protection (ICRP).

d. Studies Using Magnetic Resonance Imaging
Include the field strength of the scanners as they relate to the possible occurrence of side effects.

e. Disclosure Of Abnormal Findings From Research-related MRI, PET, CT Scans
The consent form must specify whether scans will be referred for review by a radiologist (or other similarly qualified individual) if any unusual findings are detected or suspected and whether a report would be sent to the subject's physician. The consent form should explain that the scans are obtained for research purposes only and are not intended to be diagnostic, if that is the case.

f. Subject Safety Provisions
Specify any stopping rules for stopping the research-related procedures/treatment, un-blinding, and data monitoring provisions as applicable to the study. Refer **GN 16, 17, & 18** as well.

6.3 DEFINITIONS OF ESSENTIAL DOCUMENTS REQUIRED FOR ETHICAL REVIEW

Include the correct reference/version numbers and dates on Page 1 of the application form.

As this information will be included on the Certificate of Approval, check for accuracy against the documents submitted.

6.3.1 Specific Requirements for Clinical Trials

References:

1. TCPS 2 Articles 3.2 and 3.3 re "Informing Potential Participants"
2. ICH GCP Articles 3.1.2, and 8.2.7 re "Essential Documents for the Conduct of a Clinical Trial - Before the Clinical Phase of the Trial Commences"

Health Canada requires that all clinical trials, whether industry funded or not, comply with the ICH GCP's. The following definitions for protocol, protocol amendments, Investigator's Brochure and informed consent are adopted from the ICH GCP's Glossary. All other definitions are consistent with the TCPS.

6.3.2 Specific Requirements for Other Types of Studies

With the exception of Investigator's Brochures, tissue banking consent forms, and peer review reports, the preceding types of documents are required, where relevant, for studies that are not clinical trials.

Peer review reports are generally not required for new applications considered for delegated review.

6.3.3 List of Required Documents

1. Protocol

A document that describes the background, rationale, objective(s), design, methodology, statistical considerations and organization of a study.

2. Protocol Amendments

A written description of a change(s) to, or formal clarification of, a protocol.

3. Investigator's Curriculum Vitae (C.V.)/Resume

A current resume for the Principal Investigator is required upon submission.

4. Peer Review Reports

Refer to Section 14 of the Application Form and **GN 10** for details.

5. Investigator's Brochure (IB) – Clinical Trials only.

A compilation of the clinical and non-clinical data on an investigational product(s), which is relevant to the study of an investigational product(s) in human subjects/participants.

The Canadian Food and Drugs Act - C.05.005 (e) describes the requirement for a sponsor to file the IB as part of their REB application; however under C.05.012 (d) (g) it is not included in the documents that the FHREB must approve. The FHREB reviews IB's submitted to full board meetings to verify the information on risks included in the consent form.

6. Advertisement to Recruit Subjects

This includes any type of communication (e.g. flyer, radio/television script, poster, newspaper ad, Internet message) that is directed to potential subjects/participants for the purpose of recruitment. The purpose of submitting this documentation is to ensure that recruitment messages are appropriate and not coercive. Refer to Section 22 of the Application Form and **GN 12** for further details.

7. Letter of Initial Contact

This is a letter written to prospective subjects/participants to inform them about a research study. The letter may invite them to contact the Principal Investigator/designate for further information should they be interested in considering participation or inform them that a follow up telephone call will be made and by whom if permission to use their contact information has been obtained. Refer to **GN 12** for further details.

8. Subject Consent Form

Informed consent is normally documented by means of a written, signed, and dated consent form, following a process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Refer to the Consent Form Guide and Template for UBC Clinical REBs and Fraser Health Authority REB [Template Version: June 20, 2011].Studies approved by the FHREB before this consent form template was formally adopted are not required to adopt this new consent form at the time of the renewal application.

9. Normal/Control Subject Consent Form

This is a separate consent form for subjects/participants who participate as the controls in the research study.

10. Tissue/DNA Banking Consent Form

This is required if consent to bank tissue (including blood) or DNA is being requested in connection with a research study but is not required for the subject's participation in the main study (i.e., the subject may refuse banking, but may participate in the main study). Refer to **GN 24.4** for further specifications regarding information about tissue banking that is required in consent forms.

11. Other Consent Forms

These may include for e.g.: 1) translated versions if available, 2) Substitute Decision Maker (SDM) consent forms, 3) consent forms for the use of previously collected tissue that has not been anonymized, 4) consent to contact, and, 5) consent to screen.

12. Assent Form

TCPS 2 Article 3.10 stipulates that the assent of a subject is required in situations where free and informed consent has to be obtained from a Substitute Decision Maker, and where the legally incompetent individual substantially understands the nature and consequences of the research. Refer to Section 22 of the Application Form and **GN 20** for further clarification.

13. Data Collection Tools: Questionnaires, Tests, Interview Scripts, Data Collection/Case Report Forms etc.

Append copies of all relevant study materials. Indicate whether the questionnaire is a standardized validated instrument or whether it is in development. If the instrument is in development, send a copy of the finalized questionnaire to the FH Research Ethics Board. Ensure that qualitative data collection tools are also included, when applicable. Refer to **GN 24.1** for further specifications regarding the content of the consent form when using these types of data collection methods.

14. Wallet Card Specifications

Wallet cards are required for any study whereby the study treatment or study drug could potentially impact future medical care and must be submitted for review by the FHREB. The information on a wallet card must include at a minimum the following:

- study title,
- name of study drug clearly highlighted [if possible, use the generic name],
- name of principal investigator, and,
- 24 X 7 contact numbers.

15. Other Written Documents

These may include Patient Information Sheets for Investigational and Marketed Drugs. Institution Approval Form(s) are required when permission must be obtained from an institution (e.g. school board) to undertake the study at a particular site.

6.4 APPLICATIONS SUBMITTED FOR REVIEW

Applications for full and delegated review may be submitted by email to REB@fraserhealth.ca. Scan and email the signature page of the application form, or fax to 604-930-5425. Electronic signatures are also permitted. Please submit the following:

- Application for Initial Ethical Review Form,
- Protocol/Study Proposal,
- All other accompanying documentation [i.e. consent forms, if applicable].

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GUIDANCE NOTE #7: REQUIRED SIGNATURES

The Principal Investigator for a study is responsible for adhering to the TCPS 2 and other relevant guidelines, and indicates this by signing the Application Form in Section 3. The Principal Investigator's signature attests to the following:

"By signing this page, I certify that I have read this application and that the information provided is accurate and complete. I will conduct the proposed research in accordance with the FHA policy on the "Ethical Conduct of Research and Other Studies Involving Human Subjects/participants", the Tri-Council Policy for "Ethical Conduct for Research Involving Human Subjects/participants" and all other applicable laws, regulations and guidelines."

The Principal Investigator's Administrative Supervisor must also sign the Application Form in Section 3 to indicate that the Principal Investigator has the qualifications, experience, and resources to carry out their research. If the Principal Investigator is also the Department Head, the next administrative supervisor must sign the form.

Applications will not be reviewed by the FHREB without both of these required signatures. If not available at the time of submission, they must be received by the FH Research Office no later than the Wednesday prior to the Board meeting.

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GUIDANCE NOTE #8: MAIN CONTACT NAME

The FH Research Office will send all information arising from a FHREB review including requests for modifications, deferral notices, Certificates of Approval, acknowledgements, and any other correspondence to this contact person.

Note: The Principal Investigator will be copied on all correspondence.

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GUIDANCE NOTE #9: FUNDING SOURCE

Include the NAME of the funding source or sources in Section 10a/10b along with the other required information.

For grant-in-aid support, specify whether the grant-in-aid is for the provision of materials in kind such as drug or device.
Researchers must inform the FHREB office of any changes or additions to the funding source(s) using a separate Application for Amendment of a Previously Approved Research.

The FH Research Office can only authorize the release the funds for awards/grants when the Certificate of Approval has been updated to reflect the addition or change of a funding agency, should this occur.

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GUIDANCE NOTE #10: PEER REVIEW

Reference:

1. TCPS 2 Article 2.7 re "Relationship between Research Ethics Review and Scholarly Review"

10.1 REQUIREMENTS FOR EXTERNAL PEER REVIEW

For research with more than minimal risk, the FHREB must be satisfied about both the value and the scientific validity of the study. Under some circumstances and depending on the level of risk, the FHREB may request that a peer review be conducted as a condition of approval. The criteria for determining whether an external peer review is required are described below.

1. External peer review is defined as a scholarly review of a study conducted by an individual with academic qualifications in the area under question and who is not affiliated with the Fraser Health Authority.

2. Research that is non-invasive, for example, health services research, and which does not involve more than minimal risk shall not normally be required by the FHREB to be peer reviewed.

3. Clinical research that is deemed minimal risk, for example, observational studies, shall not normally be required by the FHREB to be peer reviewed.

4. The FHREB may choose to send the study research protocol for external review when:

    a. the methods described in the protocol are not known to the FHREB reviewers and require validation from an expert in that discipline; or,
    b. the merit of the study cannot be determined either by the study documentation or clarification provided by the principal investigator; or,

c. the magnitude/type of risks and/or risk management measures of the study require additional evaluation or clarification from a scientific, clinical and/or legal basis; or,
d. the FHREB cannot reach a majority decision on the status of the study.

10.1.1 Exception to Peer Review Requirement

Research that poses minimal risk will not usually require peer review.

10.2 INDEPENDENT PEER REVIEW INFORMATION

Peer review is considered independent when experts in the field, who are not affiliated with the institutional department carrying out the study or who are not affiliated with the company sponsoring a clinical drug/device trial, have evaluated the study for its scientific appropriateness.

The FHREB recognizes that an independent peer review may be either 'internal' or 'external'. The appropriate type of review is dependent on the nature of the study.

Peer reviews conducted by granting agencies or by Health Canada, for investigational drugs or devices, are considered to be acceptable types of 'external' peer review.

Provide a description of any independent peer review conducted in Section 14b of the Application Form, and include a copy of the peer review report, if available. This copy need not exceed two or three pages in length.

10.3 PEER REVIEW CONDUCTED BY AN INDUSTRY SPONSOR

Any review process conducted within a for-profit agency is not considered to be independent. However, describe details of any in-house review processes carried out by industry sponsors in Section 14b of the Application Form.

10.4 PEER REVIEW NOT CONDUCTED

If a peer review has not been conducted, explain why this is the case. Do not use 'not applicable' to complete Section 14b since there are no categories of research which are automatically exempted from peer review.

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GUIDANCE NOTE #11: OBTAINING REGULATORY APPROVAL FOR CLINICAL TRIALS

This GN is applicable only to those investigators carrying out clinical trials as regulated by Health Canada.

11.1 OBTAINING REGULATORY APPROVAL FROM HEALTH CANADA FOR CLINICAL TRIALS

Investigators conducting clinical trials involving either investigational drug(s), device(s), or natural health products formulated for therapeutic purposes OR involving a drug/device/natural health product used for an indication outside those specified in a

Health Canada Drug Identification Number, Notice of Compliance or Medical Device License must submit the appropriate application for regulatory approval to Health Canada before research can begin.

The Clinical Trial Application (CTA) for drugs/radiopharmaceuticals/natural health products or the Investigational Testing Authorization (ITA) for devices must be filed with the appropriate directorate within the Health Protection and Food Branch of Health Canada:

1. Clinical trials for either drugs or devices - Therapeutics Product Directorate.
   Refer to: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/index-eng.php

2. Clinical trials for either biologics or radiopharmaceuticals - Biologics and Genetic Therapies Directorate.
   Refer to: http://www.hc-sc.gc.ca/dhp-mps/brgtherap/index-eng.php

3. Clinical trials involving natural health products formulated for therapeutic purposes -
   Refer to: http://www.hc-sc.gc.ca/dhp-mps/prodnatur/index-eng.php

11.1.1 Compliance With The Food And Drug Act Regulations For Investigational Drugs

All investigators conducting clinical trials must be familiar with the details of the 'Regulations Amending the Food and Drug Act Regulations (1024 - Clinical trials) which were effective September 1, 2001. Refer to http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/reg/1024_tc-tm-eng.php for the amendments and to http://laws-lois.justice.gc.ca/eng/regulations/c.r.c.,_c._870/index.html for the complete set of Food and Drug Act Regulations.

Several of the important new regulations are summarized below:

- These regulations apply to clinical trials for both new investigational drugs and some marketed drugs. The use of a marketed drug outside of its approved indication now requires Health Canada approval for use in a clinical trial (whether investigator or industry initiated).

- A 'Sponsor' is defined in the Regulations as an individual, corporate body, institution or organization that conducts a clinical trial.

- All clinical trials, including Phase IV trials, must be conducted in accordance with good clinical practices as specified by http://www.fda.gov/cder/guidance/959fnl.pdf. However Phase IV clinical trials are not subject to the Clinical Trial Application filing requirements with Health Canada.

- Each clinical trial must have a 'Qualified Investigator' who is responsible to the sponsor for the conduct of the trial and who has appropriate medical qualifications (see the definition under C.05.001).

- All information collected in a clinical trial must be stored in accordance with C.05.012, which includes the requirement for the sponsor to store records for 25 years.

- C.05.001 of the Regulations empowers the Research Ethics Boards to review, approve and conduct periodic reviews of biomedical research involving human subjects/participants to ensure the protection of their rights, safety and well-being.

11.1.2 Compliance With The Regulations for Medical Devices

The Medical Devices Regulations are applied under the authority of the Food and Drug Act and regulate the use of medical devices for investigational purposes. The obligations of the sponsor and qualified investigator are covered under these regulations.
Refer to: Part 3 of the Medical Devices Regulations at:
http://laws-lois.justice.gc.ca/eng/regulations/sor-98-282/page-18.html#h-54

11.1.3 Compliance With The Regulations for Natural Health Products

The Natural Health Products Regulations Part 4 – Clinical Trials Involving Human Subjects/participants came into force on 01 January 2004 and regulate the use of natural health products that are formulated specifically for therapeutic purposes. The obligations of the sponsor and qualified investigator are covered under these regulations.

Refer to: Part 4 of the Natural Health Product Regulations at:
http://www.hc-sc.gc.ca/dhp-mps/prodnatur/index-eng.php

11.2 HEALTH CANADA LETTER OF NO OBJECTION FOR INDUSTRY SPONSORED AND INVESTIGATOR-INITIATED CLINICAL TRIALS

It is the duty of the principal investigator to be certain that Health Canada has issued a NO OBJECTION LETTER before the study begins enrollment.

Specify the date of the application to Health Canada in Section 13e and the Health Canada control number for all clinical trials. The Health Canada "No Objection Letter (NOL)" must be submitted to the FH Research Ethics Board once obtained if not available at the time of initial submission to the FHREB.

11.3 HEALTH CANADA AUDIT

The Health Products and Food Branch Inspectorate of Health Canada is conducting inspections of clinical trials to ensure that good clinical practices are met, data are of good quality and that the trials comply with the Food & Drug Act Regulations.
Refer to the following link for details of Health Canada inspection reports:
http://www.hc-sc.gc.ca/dhp-mps/pubs/compli-conform/index-eng.php

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GUIDANCE NOTE #12: RECRUITMENT OF SUBJECTS/PARTICIPANTS: IDENTIFICATION AND INITIAL CONTACT

Reference:

1. TCPS 2 Chapter 5

The FHREB requires information on how subjects/participants are identified and initially contacted to participate in a research study. In particular, this information should include a description of:

1. the source (i.e. its original purpose, if relevant) of the contact information;

2. who will collect the contact information;
3. who will make the initial contact with the prospective subject;
4. how the prospective subject will be initially contacted;
5. when the prospective subject will be initially contacted, and;
6. the Investigator's relationship, if any, to the subjects/participants (e.g., treating physician, teacher).

In addition, include copies of any recruitment materials, such as letters, advertisements, flyers, radio or television scripts, or Internet messages.
Provide this information in the study protocol/proposal or as an appendix to the study protocol/proposal, see section 22 of the application form. Refer to the following sections for details on methods approved by the FHREB for conducting these types of activities.

12.1 OBTAINING ACCESS TO PERSONAL INFORMATION FROM THIRD PARTY RECORDS FOR INITIAL CONTACT

The use of personal information for contacting subjects/participants must comply with the current version of the FH Policy on "The Collection, Use and Disclosure of Personal Information for Research-related Purposes". Refer to http://research.fraserhealth.ca/about_us/research_policies/research_policies

The B.C. Freedom of Information and Protection of Privacy Act (FOIPPA) applies to public sector institutions. These include health care (e.g. hospitals, the Provincial Health Services Board, and regional health boards), governmental (e.g. provincial government ministries, Medical Services Commission, Pharmanet, WCB) and educational (e.g. school boards, universities) bodies.

Amendments made to Section 35 of the Act on 28 March 2003 limit the uses of information collected by such bodies such that the public body cannot release this information for contact purposes.

The amendment states: *"35 - A public body may disclose personal information or may cause personal information in its custody or under its control to be disclosed for a research purpose, including statistical research, only if (a.1) the information is disclosed on condition that it not be used for the purpose of contacting a person to participate in the research."*

Updated 2016 November 16: A further amendment which came into force on 2009 June 30 provides an exception to this article which permits the B.C. Privacy Commissioner to approve contact with prospective research subjects under certain conditions. Refer to FIPPA at http://www.bclaws.ca/EPLibraries/bclaws_new/document/ID/freeside/96165_00

The following procedures for identifying and making initial contact with prospective subjects/participants are acceptable to the FHREB.

12.1.1. Identifying And Contacting Prospective Subjects/participants From Primary Health Care Providers

a. Obtaining Personal Contact Information
In some situations, an investigator may request contact information from a primary health care provider (i.e. family doctor or other health care professional) who retains

patient/client personal contact information for clinical purposes. In this case, the health care provider must first obtain permission from their patients/clients (i.e. the prospective subjects/participants) before their name and contact information can be given to an Investigator for recruitment purposes. The primary care physician may, in person when the prospective subject attends for a visit, ask the prospective subjects/participants' permission to release their names to the Investigator.

Note that private practice physicians fall under the provisions of the British Columbia Personal Information Protection Act (PIPA), which was enacted on 06 October 2003. Section 21 of the Act regulates the disclosure by physicians of personal information for research or statistical purposes.

Refer to: http://www.leg.bc.ca/37th4th/3rd_read/gov38-3.htm

b. Contact of Prospective Subjects/participants Under Special Care by Other Care Providers

A Treating physician/care provider who has patients/clients under their specialized care at particular points in time may be asked by other Investigators to approach these patients/clients for recruitment purposes. Patients such as these are in a very dependent and vulnerable position and so the possibility of coercion must be minimized. In this type of situation, the possibility of coercion is minimized if the treating physician/care provider simply asks the prospective subject whether they might be interested in participating in a research study and, if so, gives them a copy of an introductory letter or recruitment flyer, so that the individual can decide if they wish to contact the Investigator or not.

In contrast, a prospective subject/client who is asked to provide contact information (i.e. either verbally or using a consent to contact form) directly to the treating physician/care provider so that it can be passed onto the investigator, may find it difficult to refuse a request of that nature because they are in a dependent relationship with that physician/care provider.

In order to minimize the possibility that a prospective subject/client may feel coerced, the FHREB prefers that the first approach be used to recruit subjects/participants under the special care of other care providers.

12.1.2 Information Held by Disease Specific Registries

Subjects/participants who have previously consented to be included in a registry for research purposes and this consent included contact for future research studies must first be contacted by mail vis a vis the contact information included in the Registry. The letter must explain how their contact information was obtained in addition to the purpose of the contact.

12.1.3 Identifying and Contacting Prospective Subjects/participants Using the FH Outlook Global Email List

This is only permissible if the study is being conducted for the purposes of program evaluation or quality improvement since the study is primarily being conducted for business purposes. It is not permitted for the recruitment of study subjects/participants for research purposes.

Exception: Fraser Health employees with managerial responsibilities may use outlook to notify his/her department/unit that a research study may be conducted in their

department /unit and if interested employees can contact the study's principal investigator or study contact. If the Principal Investigator is in a managerial position, then he/she must ensure that a statement be included in all recruitment documents to avoid coercion.

12.2 INITIAL CONTACT WITH PROSPECTIVE SUBJECTS/PARTICIPANTS UNDER THE INVESTIGATOR'S CARE OR AUTHORITY

12.2.1 Ensuring Non-coercive Contact

Special care needs to be taken during the initial contact when the Investigator is in a fiduciary relationship with prospective research subjects/participants (i.e. also providing medical care to the prospective subject). For example, the prospective subject may feel obliged to participate because they believe that participation will ensure that they still receive good medical care and/or that they 'owe' the investigator/care-giver participation in exchange for care.

Similarly coercion is a factor when participation in a research study is being solicited from students taught by the Investigator or from employees by management.
In order to mitigate the possibility of prospective subjects/participants participating in research studies as a result of a coercive relationship, non-coercive means for inviting participation should be used. A typical example of the latter would be posting notices to invite volunteers from the entire group concerned, for example, in the waiting room of the medical clinic, or for the entire school rather than one particular class. This also leads to the recommendation that a treating physician/care provider who is also an investigator (principal investigator or co-investigator) not be the person making initial contact with subjects/participants unless this is absolutely necessary.

12.2.2 Direct Initial Contact By Study Nurses

The FHREB permits study nurses/co-ordinators who co-ordinate studies out of a specialized medical clinic/unit to make direct initial contact with a prospective subject who is attending that clinic for patient care or for research purposes. The study nurse must identify him/herself and the relationship to the clinic/medical department at the time of contact with the prospective subject.

12.2.3 Recruitment of Students from School Populations

School districts vary in their requirements for approaching and involving teachers, staff, or students in research. It is the responsibility of the Investigator to know and comply with these local regulations.

A generally acceptable approach involves contacting the principal of the school in order to obtain permission to contact the teacher directly to obtain his/her assistance to recruit students. This may not be sufficient in all districts.

Documentation of approval from the school district(s) affected by the proposed research must be included with the study submission for ethical review.

12.3 INITIAL CONTACT WITH PROSPECTIVE SUBJECTS/PARTICIPANTS WHO PROVIDE PERSONAL DATA TO SPONSORS' CALL CENTRES

Subjects/participants may choose to contact a call centre directly to indicate that they would like to participate in a clinical trial and to provide their contact information. The local study centre, upon receiving this information from the call centre, may contact

the prospective subject directly by phone, explaining how their name and phone number were obtained. A description of this procedure must be included in the Application Form along with the script used by the call centre to receive calls and all screening scripts.
The FHREB is concerned about how personal information (including contact information) given to central screening agencies is handled by these agencies. Researchers are required to describe the planned disposition of the information by the call centre. For example, the FHREB would not permit this information to be provided to the sponsor for possible use in marketing or for contacting patients for reasons unrelated to the research project.

12.4 IDENTIFICATION AND CONTACT OF SUBJECTS/PARTICIPANTS BY THIRD PARTIES

The FHREB does not permit investigators to ask their subjects/participants to invite other people (e.g. family members) to participate in a proposed research study. While recruitment of subjects/participants by subjects/participants may be methodologically desirable and convenient, it may put the index subject and the people they contact in a variety of potentially uncomfortable and coercive situations and is therefore not permitted. At no time should there be any obligation placed on the subject to recruit subjects/participants for the investigator.
In some situations (with FHREB approval) it is permissible for subjects/participants to distribute an invitation letter and/or consent to contact to the potential subject (e.g. a family member). The invitation letter should contain the contact details of the investigator so that if the subject is interested in participation, he/she can contact the investigator directly. If the consent to contact is used, a self-addressed, pre-stamped envelope should be provided for the prospective subject to use.

12.5 RECRUITMENT FOR FOLLOW-UP/EXTENSION STUDIES

Subjects/participants who have consented to participate/have participated in a prior study may be contacted directly [i.e. by phone] by the investigator/designate for the purpose of inviting them to participate in a follow up [i.e. extension] to this main study, only if the main study has a current valid certificate of ethical approval.

12.6 RECRUITMENT METHODS AND MATERIALS

12.6.1 Letter of Initial Contact

If prior consent-to-contact (refer to **GN 12.6.4.e)** has been obtained from the prospective subject, letters used for initial contact purposes may be followed by a telephone call or email. In this situation, the letter must explain when the telephone call/email will occur, such that there is a reasonable length of time between receiving the letter of invitation by mail and the follow up telephone call/email. It is preferred that the initial contact letter be accompanied by the full consent form so potential subjects/participants can be more informed and prepared for the subsequent telephone/email contact.

12.6.2 Initial Contact By Telephone For Obtaining Consent in Emergency Situations

Reference:

1. ICH GCP 4.8.15

Any proposal to make initial contact with a potential subject by telephone should include a detailed description of the procedure and provide adequate justification.

POLICY #2: Telephone Contact For Obtaining Consent in Emergency Situations

The FH REB does not allow initial contact by telephone, except under unusual circumstances where timely consent is required, but no Substitute Decision Maker (SDM) can be present in that time-frame.

1. This consenting procedure may be used only when the principal investigator or designate cannot speak to the SDM in person. Telephone contact may be allowed if the SDM has not arrived with the potential study subject and is not expected at the hospital within the time limit of the study initiation.
2. The principal investigator or designate will present the information in the consent form over the phone and provide any clarification required.
3. Once the SDM of the patient has been fully informed of the patient's medical condition by the attending physician, the study will be discussed by one of the Investigators. The Principal Investigator or Co-investigator will read the entire consent form over the telephone and provide any clarification requested by the SDM.
4. When all questions have been answered to the satisfaction of the SDM, the call will be terminated to provide an opportunity for the SDM to consider the study. Once a minimum of 30 minutes have passed, the Investigator (and witness) will again contact the individual for their decision (This is done so the family does not have to bear the costs of long distance charges).
5. A witness to the telephone consent, in addition to the Investigator reading the consent form, will be on the telephone line to hear the reading of the consent form and the verb granting or refusal of consent by the SDM.
6. The identity of the witness will be disclosed to the SDM prior to the reading of the conse form.
7. The date and time that the telephone consent is obtained, the names of the SDM, the Investigator (reader), and the witness will be entered into the original consent form.
8. Whenever possible the consent form will be emailed/faxed to the SDM prior to the readi of the form, enabling them to follow along as it is read to them. If the TSDM agrees to participate they will be instructed to sign the form and fax it back to the principal investigator. If the SDM does not have access to a fax, the DSM may send an email acknowledging that he/she has received and read the consent form and is agreeing to allow the subject to participate in the study. Following the email, the signed consent for should be sent to the principal investigator by mail.
9. Written evidence of consent will subsequently be obtained in a timely manner after obtaining verbal consent.

12.6.3 "Negative" Marketing to Prospective Research Subjects/participants

Negative marketing to prospective research subjects/participants occurs when an individual receives a direct invitation (e.g. by email) to participate in a research study BECAUSE they failed to 'unsubscribe' to this recruitment strategy when visiting a sponsor's website.

The use of negative marketing for the purposes of recruitment is strictly prohibited by the FHREB on the basis that it:

- is an invasion of privacy without consent;
- has the potential to cause psychological harm to individuals who may be in

the earlier stages of diagnosis for a particular disease/condition, and;
- is coercive.

12.6.4 Recruitment Materials

a. Inclusion of Information

In general, a recruitment flyer/poster/pamphlet should include at a minimum FH letterhead, study title, a very brief description of the study purpose, general inclusion criteria such as age and diagnosis, type of intervention, duration of study and time required, and a contact name and number. The latter may be the principal investigator or designate. Information stating that expenses are reimbursable is also acceptable. Every effort must be made to avoid using language that may come across as coercive.

b. Statement of Remuneration in Recruitment Materials

The FHREB feels that inclusion of the monetary value of the remuneration for participation in recruitment materials is dependent on the level of risk that the study involves and that the subject could expose themselves to.

i. experimental interventions – The exact amount of the remuneration should not be disclosed in recruitment materials aimed at recruiting subjects/participants into experimental therapeutic trials. The exclusion of specific details about remuneration at this phase mitigates the possibility of inducing subjects/participants to trade accepting potential risks for financial gain. In addition, a prospective subject may not realize that participation can only occur if they meet the conditions of the study's inclusion and exclusion criteria. In which case, the promise of remuneration in the recruitment materials may unintentionally mislead some prospective subjects/participants into thinking that they will automatically be enrolled into the study. A particular need to include an exact amount of remuneration in recruitment materials would have to be justified to the FHREB in the initial submission for ethical review.

Policy #3: Remuneration In Recruitment Materials

Recruitment materials that are used for the purpose of recruiting subjects/participants, such as letters, advertisements, flyers, radio or television scripts, or internet messages, must not include any information about the value of the remuneration for participation.

Minimal risk studies – The FHREB believes that it is acceptable to advertise the details of reasonable remuneration for participation in minimal risk studies that involve interviews, focus groups or the completion of questionnaires or other types of non-invasive data collection given the understanding that there is no expected benefit from this type of research. Refer to **GN 15** for guidance on the acceptable value of the remuneration.

c. Inclusion of Information Relating to Provision of Medical Supplies in Recruitment Materials

Recruitment materials may include the information that medical supplies required for the study will be provided free of charge; the value of these supplies must not be included in the material.

d. Consent Form

The value of the remuneration must be included in the consent form.

e. Consent to Contact Form

The B.C. Freedom of Information and Protection of Privacy (FOIPP)Act Section 35(1) has been amended as of **June 30, 2009**. The amendment is the result of section 30 of Bill 24-2008: the *E-Health (Personal Health Information Access and Protection of Privacy) Act* being passed. The Bill is available at http://www.leg.bc.ca/38th4th/3rd_read/gov24-3.htm

Previously, Section 35 of the FOIPP Act permitted the disclosure of personal information for research purposes as long as certain conditions were met, including if the personal information was not being used for the purpose of contacting a person to participate in the research. The amendment has changed this by allowing such contact for research in relation to health issues, as long as the Information and Privacy Commissioner approves the research purpose, the use of the disclosed information for the purposes of contacting a person to participate in the research, and the manner in which the contact is to be made.

Therefore the Fraser Health Authority will only permit FH researchers to use FH health records to obtain contact information from FH patients/clients for recruitment purposes if the research study has received approval from the Information and Privacy Commissioner.

If approval from the Information and Privacy Commissioner is not given or not requested, the consent to contact form can be used to obtain consent from the subject for future contact for research purposes.

The template for this consent to contact template is available at: http://research.fraserhealth.ca/approvals_%26_ethics/forms_and_guidance_notes/

12.7 ALLOWING SUFFICIENT TIME FOR PROSPECTIVE SUBJECTS/PARTICIPANTS TO CONSIDER PARTICIPATION

Reference:

1. TCPS 2 Article 3.2

Recruitment must be done in such a way that prospective subjects/participants have adequate time between the time of initial contact to the actual consent phase to consider whether or not they wish to participate. For example, prospective subjects/participants who are attending a clinic for elective or scheduled procedures should not be approached and asked to consent to participate in a study at that time. They may be invited to participate in the study and if interested, given the consent form, which they can return, should they decide to participate.

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GUIDANCE NOTE #13: HARMS

References:

1. TCPS 2 Articles 3.4, 11.4 (re clinical trials) and 13.2 (re genetic research)
2. ICH GCP 4.8.10 (g)

13.1 SPECIFICATION OF HARMS

The following sections provide a classification of relevant harms. Information on harms must be included in the Application Form Section 20, and that must be consistent with the information on harms provided in the protocol and Investigator's Brochure (IB)/Product Monograph if the latter is applicable to the study. If information is not available from the protocol or IB, indicate the source of the risk data provided.

13.1.1 Minimizing Harms

The information in Section 20 should include an explanation of any strategies put in place to minimize and/or manage the harms for subjects/participants and other affected individuals (e.g., reporting side effects to the investigator, rescue medication, early withdrawal from the study).

a. Studies Where The Interaction With Other Drugs Is Unknown

Disclose whether the research necessitates that certain medication or treatments not be administered during the study so subjects/participants can evaluate this in the context of their current health.

b. Studies With Wash-Out Periods or Requirements For Stopping Medication

The consent form must explain the symptoms/signs that subjects/participants could experience from being taken off of any medication.

Advice on procedures that must be followed in special cases is included in the following sections.

13.1.2 Harms to Others

Any potential harms to others (e.g., unborn child, sexual partner, family members) that may arise from the study intervention must be explained.

13.1.3 Harms to Women and Men

The risk of any harms to pregnant women, to women who could become pregnant during the course of the research or to men with reproductive capacity must be disclosed in the consent form under the risk section.

Specific instructions regarding the prevention of pregnancy must be included in the consent form as follows:

1. specific measures to take to prevent pregnancy,
2. how to notify the researcher if a subject suspects that she is pregnant, and,
3. what would happen if a pregnancy should occur during the research.

13.1.4 Social and Psychological Harms

Note that harms to the subject may also include social harms such as breach of confidentiality, social stigmatization, threats to reputation, and psychological harm. Explain what strategies are in place to minimize and/or manage the risks for subjects/participants and other affected individuals. For studies where the research activities are likely to reveal high levels of psychological distress (e.g., EQ-5D

questionnaire), a rescue plan should be described in the protocol and consent form.

13.1.5 Harms Requiring Special Counselling and Disclosure of Material Incidental Findings

TCPS 2 Article 3.4 defines 'incidental findings' as "unanticipated discoveries made in the course of research but that are outside the scope of the research" and that have "significant welfare implications for the participant, whether health-related, psychological or social". All investigators have an obligation to inform their research subjects/participants of such findings. The FHREB requires the following if material incidental findings are likely:

a. submission of a plan indicating how these findings will be disclosed to research subjects/participants. If the investigator is uncertain in this regard, they may consult with the FHREB.
b. Consideration in the plan of provisions for counselling for the research subject/participant in order to discuss the possible implications of the incidental findings for their welfare.
c. Consideration in the plan of any legal reporting obligations (Refer to TCPS 2 5.1).

In addition, some studies (e.g. genetic tests) may intentionally provide results to subjects/participants, which identify them as belonging to a high-risk group on the basis of the result. (e.g. genetic status, biochemical and biomarker test results. A biomarker is an element that should be able to be objectively measured and evaluated so it can be used as a reliable indicator to detect the presence or extent of a disease or condition. It can also be used to evaluate the efficacy/toxicity ratio of a given treatment before it is administered. Biomakers are biological molecules found in the blood, body fluids, organic tissues or tumours.

TCPS 2 Article 13.2 requires all investigators conducting genetic research to: 1) develop a plan as part of their research proposal for managing information that may be revealed through genetic research (the plan may need to include provision for follow-up counseling if applicable); 2) submit this plan to the REB, and; 3) advise prospective subjects/participants of this plan. Refer to Article 13.2 for further detail and Article 13.3 regarding the requirement to provide research subjects/participants with the option to decide whether or not they wish to receive the information and to share it with others.

In addition, the FHREB believes that it is the Principal Investigator's responsibility to ensure that research subjects/participants experience no avoidable harm, such as psychological distress, arising from any knowledge that they could obtain as a result of their participation in any type of research study.

Overall, the FHREB expects to see evidence of measures taken to ensure that counselling services are made available to research subjects/participants if the study tests could lead to information which would have serious consequences for that individual and/or their family.

Please also see **GN 13.1.7.**

13.1.6 Harms Related to Testing for Reportable Diseases

Pre-test counselling for subjects/participants tested for reportable diseases includes the implications, some of which may be life-altering, of having a positive test. These may include the legal obligation for mandatory reporting by the investigator [Refer to

GN 26.6.1.i], medication implications for sexual partners as well as the impact of a positive test on a subject's insurance policies.

Investigators have a responsibility to inform the study subject if the laboratory test(s) show evidence that the subject has been infected with the HIV or hepatitis virus and can offer to discuss with the subject the BC Centre for Disease Control's management of a positive HIV/Hepatitis test. Refer to the link for the BC Centre for Disease Control Policy below:

Refer to: http://www.bccdc.org/download.php?item=2727

The following websites provide some information on pre-test counseling for HIV testing that can be applied to Hepatitis B and C as well.

Refer to: http://research.bidmc.harvard.edu/VPTutorials/HIV/Tclin03.htm

Policy #4: Provision of Pre- and Post-Test Counselling
If in the course of research, there are tests that might have results that impact seriously on the research subject's health or have other serious implications (e.g. HIV or some genetic tests), appropriate pre- and post-test counselling services shall be made available to that person, and, when appropriate, to his or her family.

13.1.7 Other Harms to Subjects/Participants Participating in Genetic Studies

In addition, some genetic studies may provide results to subjects/participants, which identify them as belonging to a high-risk group on the basis of their genetic status. The FHREB requires that the following information be included in the consent form should this be the case.

Policy #5: Information Required For Subjects/Participants Identified As High Risk As A Result Of Genetic Status
The consent form must include a statement that informs subjects/participants that any knowledge gained from the research study, that identifies the subjects/participants as belonging to a high-risk group, may reduce the ability of the subject to obtain health and/or life insurance.

The only reason not to tell the subject about this potential risk is if the risk of developing the disease is high based on family history and is not heightened by knowing their genetic status.

13.1.8 Other Harms to Subjects/participants Participating in Studies

A subject's improvement in health, which could have arisen from taking a study drug, may be harmed if the subject cannot afford the costs of a study drug, should it become commercially available, after the research is completed. Should this be a possibility, the FHREB requires that the following information is included in the consent form.

Policy #6: Disclosure of Reasons For Not Receiving Study Treatment After Subject Research Participation is Completed
The following statement will be required in the Consent Form for any trial involving any drug or other experimental therapy, which is of a chronic nature
"AFTER THE STUDY IS FINISHED:
You may not be able to receive the study treatment after your participation in the study is

completed. There are several possible reasons for this, some of which include: The treatment may not turn out to be effective or safe. The treatment may not be approved for use in Canada. Your caregivers may not feel it is the best option for you. You may decide it is too expensive and insurance coverage may not be available."

13.1.9 Harms to Children

"ICH Guidance: Clinical Investigation of Medicinal Products in the Pediatric Population E11" states that "protocols and investigations should be designed specifically for the pediatric population (not simply re-worked from adult protocols…" (p. 14). The FHREB requires that the protocol include measures taken to minimize the distress of children participating as research subjects/participants and that this information be included in the consent/assent form(s).

For further details refer to: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e11-eng.php

13.2 QUANTIFICATION OF HARMS TO RESEARCH SUBJECTS/PARTICIPANTS

Policy #18: Disclosure of Research-related Harms for Clinical Trials

The FHREB requires that research-related harms (i.e. attributable to the research and including cumulative risks) must be identified and quantified in the subject consent form. Any risks related to standard care must be identified and explained to the subject by their study doctor. An explanation of this must be included in the consent form when standard care is involved.

EXCEPTION: The FHREB may require the risks of standard care to be identified and quantified in comparison with those of the experimental procedure if that standard of care required in the protocol is not the standard of care currently used in the Fraser Health Authority. This decision will be made on a case by case basis and will be at the discretion of the FHREB. The principal investigator will be informed of any such decision by the FHREB.

a. Quantify the foreseeable risks of harms (side effects) or inconveniences (discomfort or incapacity) to the subject associated with each procedure (including radiation risks from X-rays), therapy, test, interview, or other aspect of the study. See the consent form template for further details regarding the inclusion of a table in the consent form to display the risk information. See http://research.fraserhealth.ca/approvals_%26_ethics/forms_and_guidance_notes/

   Quantification should include information about the seriousness and consequences of the different types of adverse events that have been observed, as well as the probability of these events occurring. Quantification of these harms should emphasize the INCREMENTAL risk with the experimental intervention as compared to placebo or no treatment, wherever possible.

b. The Board requires numerical (usually percentage) quantification of risks wherever possible. Qualitative terms such are "rare", "common", "infrequent" are not acceptable. Quantifiers such as ">5%" are similarly not acceptable since they do little to define the magnitude of risk.

   It is helpful to list risks in descending order of frequency, i.e. 50%, 30%, 5%, 1%, and/or group them according to the range of the risk, if the range is sufficiently

narrow. In addition, the severity of the side effects should be explained in the application form and in the subject consent form.

c. Where no percentages are available, specific discussion about risks encountered in case series/case reports, preclinical studies, or studies involving similar procedures are required. If absolutely no relevant data about harms of the experimental procedures is available (e.g. a Phase I trial), Investigators are required to make their **best effort** to honestly inform subjects/participants about possible risks of participating in the research, even if they can't be quantified. This quantification can be in the form of "for thirty subjects/participants, five experienced a particular side effect." This information must always be included in the consent form.

d. The consent form must include an explanation that unanticipated side effects, including severe or irreversible ones, could occur if a novel combination of drugs is being tested, even if the individual drugs are not expected to have these side effects.

e. Risks involved with standard of care should NOT be included in the consent form unless otherwise requested by the Fraser Health Research Ethics Board. Standard of care risks should be discussed with the subject by the subject's treating physician. A sentence in the consent form detailing that standard of care risks will be discussed with the subject's treating physician must be included in the consent form.

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GUIDANCE NOTE #14: BENEFITS

References:

1. TCPS 2 Articles 3.2 and 3.3 "Informing Potential Subjects/participants"
2. ICH GCP 4.8.10 (h)

Specify the benefits to the subjects/participants. If there are no benefits, state this explicitly. If any specific therapeutic benefits cannot be assured, but may be hoped for by the subject, state explicitly that the subject may or may not benefit from participation in the study.

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GUIDANCE NOTE #15: REMUNERATION

References:

1. TCPS 2 Article 3.1 re prorated payment
2. ICH GCPS Article 4.8.10 (k) and (l)

Where researchers plan to provide remuneration to subjects/participants, the FHREB will assess the value of the remuneration on a study-by-study basis. In general, remuneration should not be so substantial as to induce subjects/participants to trade accepting potential risks for financial gain. Refer to **GN 12.6.4.b** for clarification

regarding the inclusion of remuneration in recruitment materials.

For most clinical studies, remuneration that is considered reasonable is within the $25.00 to $100.00 range for participation. For socio-behavioural studies, the typical range is $5.00 to $25.00. Gift cards and randomly provided monetary remuneration (e.g. via entry into a draw) are considered acceptable forms of remuneration. This does not include reimbursement of any expenses incurred by the subject during participation in the research.

a. Include any specific details about the reimbursement of expenses related to transportation and parking and when these will be paid.

b. If the subject will not be paid for participation or reimbursed for expenses, this should be stated in the consent form.

c. Subjects/participants must be eligible for remuneration according to their actual amount/duration of participation with no rewards for completing the study or withholding of "owed" remuneration from those who withdraw. In studies where draws are the main source of remuneration, participants who withdraw must remain eligible for the draw.

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GUIDANCE NOTE #16: UNBLINDING IN THE EVENT OF AN EMERGENCY

a. For applicable research, the FHREB requires that sufficient information to reveal treatment assignment in the event of a medical emergency be held locally and that an emergency contact (24 hours, 7 days a week), who can break the code, be identified on the consent form(s). If the code cannot be held locally, the Board requires a detailed explanation of how the code can be broken in an emergency and how quickly this can occur.

b. For applicable research, the emergency contact's name and phone number must be clearly identified in the consent form.

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GUIDANCE NOTE #17: MONITORING

Reference:

1. TCPS 2 Article 11.7

In randomized clinical trials of extended duration, there are likely to be ethical reasons for interim analyses and safety monitoring (e.g. Independent Data Safety Monitoring Boards). TCPS 2 Article 11.7 requires that investigators provide the REB with "an acceptable plan for monitoring the safety of participants, including a plan for the tabulation, analysis and reporting of safety data, and the sharing of other new information in a form that permits REBs to interpret and respond appropriately".

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GUIDANCE NOTE #18: STOPPING RULES

When relevant, describe any plans for interim data monitoring (e.g. interim analysis)

and the specific stopping rules (e.g. thresholds), which will be used to determine whether the research will be allowed to proceed.

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GUIDANCE NOTE #19: PROTECTION OF PRIVACY: THE CONSENT PROCESS
References:

1. TCPS 2 Article 3.2
2. ICH GCP 4.8.8

19.1 PRIVACY LEGISLATION

Privacy is the right of an individual to exercise control over their data, its use and is disclosure. The FHREB upholds the requirements of the following three privacy Acts:

19.1.1 Freedom of Information and Protection of Privacy Act of British Columbia [FOIPPA] enacted 04 October 1993.

The FOIPPA of BC provides individuals with specific information and privacy rights with regard to information that is collected or controlled by public bodies in British Columbia. If the Act is referred to in the consent form, the following statement in the consent form is an acceptable addition to the discussion of confidentiality:
"Your rights to privacy are also protected by the Freedom of Information and Protection of Privacy Act of British Columbia. This Act lays down rules for the collection, protection, and retention of your personal information by public bodies, such as the Fraser Health Authority. Further details about this Act are available upon request."

Refer to: https://www.oipc.bc.ca/

19.1.2 Personal Information Protection Act of British Columbia (PIPA) enacted 01 January 2004.

The PIPA of BC provides individuals with specific information and privacy rights with regard to information that is collected or controlled by private organizations (e.g. physician offices) in British Columbia that do not fall under either FOIPPA, which applies to B.C. public bodies only, or under the federal Personal Information Protection and Electronic Documents Act (PIPEDA).

Refer to:
http://www.bclaws.ca/EPLibraries/bclaws_new/document/ID/freeside/00_03063_01

19.1.3 Personal Information Protection and Electronic Documents Act (PIPEDA)

Enacted 01 January 2001 and amended 01 January 2004. The PIPEDA is federal legislation which applies to private sector organizations in Canada if the province that organization operates in does not have its own privacy legislation deemed to be commensurate with PIPEDA requirements. Therefore industry sponsors of research outside of British Columbia may have to comply with the PIPEDA provisions for the collection, use or disclosure of personal information in the course of any commercial activity.

Refer to: http://www.privcom.gc.ca/legislation/02_06_01_e.asp

19.2 REQUIREMENT FOR CONSENT FOR ALL PROSPECTIVE RESEARCH

Consent must be obtained for all prospective research [i.e. there is a prior intent to conduct research which involves the prospective collection of data from subjects/participants] BEFORE subject participation in a study can begin.

For example, the collection of personal information from patients to populate a specific program based clinical database which is ALSO intended to be used for research purposes requires the patient population to consent to the use of their information for future research. In this case, the consent should also include a request for permission to contact these patients in the future if there is any intent to request their participation in specific research studies.

In addition, refer to **GN12.7** Allowing Sufficient Time for Prospective Subjects/Participants to Consider Participation.

a. Exception to Obtaining Consent

See **GN 28.3** for exceptions requiring a waiver of consent.

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19.2.1 Requirement for Consent Forms for 'Minimal Risk' Research

References:

1. TCPS 2 5D, Articles 5.5 and 5.6 re accessing data contained in records (i.e. patients' medical charts) that contain personal identifying information.
2. TCPS 12.3 – Consent is not required if the previously collected tissue had been provided by “persons who are not individually identifiable”.

Subject consent IS required for collecting prospective subject data as described above in **GN 2.1.2.1**

Subject consent is NOT required for:

- the use of previously banked anonymous tissue that is NOT linked to other sources of information;
- chart or health record review;
- disease specific registries with data collected from subjects/participants who have already consented to its use for the sort of research being done.

Note that the FH Policy “The Collection, Use and Disclosure of Personal Information for Research-related Purposes” prohibits the unauthorized use of any personal information for contact purposes.

The requirements for seeking consent are subject to federal and provincial privacy legislation and researchers are responsible for compliance with these laws, which relate to their research. The FHREB does not have the authority to authorize any procedure, which contravenes these laws. See Policy #11: Confidentiality for further detail on the privacy legislation requirements as they pertain to information which must be included in consent forms.

19.2.2 Obtaining Written Consent

Reference: TCPS 2 3.12

Written evidence of the subject's consent/assent or substitute decision maker's consent must be obtained in most cases after a face to face discussion with the subject or substitute decision maker. This documentation shall be obtained in a signed consent form or in documentation by the investigator of another appropriate means of consent, i.e. the consent process used by the investigator to obtain consent must be documented. Refer to **GN 20.2.**

a. Exceptions To Written Consent

See **Policy #2** for emergency telephone consent and **GN 24.1** and **GN 19.2.9** regarding studies using questionnaires for exceptions. Where written consent is culturally unacceptable, or where there are good documented reasons for not recording consent in writing, the procedures used to seek free and informed consent must be documented in writing by the person obtaining consent. Refer to TCPS 2 3.12 for other possible exceptions.

19.2.3 Who Can Obtain Consent

A person knowledgeable about the research study must obtain consent. This may be the principal investigator or designate.

19.2.4 Time Period For Obtaining Consent

The process of obtaining consent should not occur until a minimum of 24 hours after initial contact, except in the case of emergency situations. The FHREB requires justification of shorter periods of time. See **Policy #2** for emergency telephone consent.

19.2.5 When Consent Is Valid

The FHREB considers the consent to be valid as of the giving of it by the subject, i.e. the time it was signed or verbally provided, unless a protocol stipulates that the consent is not valid until such time as the Principal Investigator or designate signs the form.

The FHREB does not recognize consents that are obtained "after the fact".

19.2.6 Use Of Previously Collected Tissue And/Or Data Obtained From Tissue And Data Banks

a. Use of tissue or data that has been previously collected must receive authorization from the custodian of that bank or registry for its use, regardless of whether the tissue/data is anonymized or de-identified. Evidence of this authorization must be submitted with the application to the FHREB.

b. If the tissue/data is not anonymized, evidence that consent was obtained at the time of collection for use of the tissue/data must also be submitted (or a waiver of consent from the institution's REB). This may include the original consent form or an assurance from the investigator that appropriate protections were undertaken to ensure confidentiality and privacy.

19.2.7 Use Of Mailed/Faxed/Emailed Consent Forms

Consent forms with an introductory letter may be mailed or faxed to potential subjects/participants who live in areas outside of the geographical catchment area for a study as long as the researcher has previous consent to contact from the subject. In these circumstances, the Principal Investigator or designate can sign the consent form after receiving the signed consent form back from the subject, or after having obtained telephone consent.

19.2.8 Questionnaires/ Interviews Conducted By Telephone

Consent forms with an introductory letter (indicating that a follow up phone call will be made) may be mailed or faxed to prospective subjects/participants when the study involves questionnaires/interviews that must be conducted by telephone. A follow up telephone call can then be made after a reasonable period of time to the subject to obtain their verbal consent in order to proceed with the interview or questionnaire. The complete written consent form should be read to subjects/participants over the phone and their verbal consent documented prior to proceeding with the interview/questionnaire. The subject's signed written consent form must be returned to the investigator as evidence that written consent has been obtained. The investigators must maintain a verifiable record detailing when and who obtained verbal consent by phone.

N.B. Prior consent-to-contact must have been obtained.

N.B. On-line questionnaires must include a disclosure if the data collected will reside outside of Canada. For example, for studies using Survey Monkey, the data resides in a databank located in the United States. The introductory letter/consent form must include wording that states this explicitly: "Your views/opinions are considered to be personal information. Survey Monkey stores information collected in the United States for an undetermined time period, and is therefore subject to U.S. law. By participating in the survey, you are consenting to having your personal information stored in the U.S. Please indicate your understanding and provide your consent to the above by checking the appropriate selection.

19.2.9 Studies Using Questionnaires Only

Questionnaires completed independently and anonymously by subjects/participants and returned to the researcher can be taken as implied consent. The questionnaire should be accompanied by an information letter containing the components of a consent form.

N.B. On-line questionnaires must include a disclosure if the data collected will reside outside of Canada. For example, for studies using Survey Monkey, the data resides in a databank located in the United States.

19.2.10 Consent to Screen for a Specific Study

In some situations, research may be facilitated by using a consent form to obtain permission from a prospective research subject to screen their medical records for specific inclusion criteria, for example, in the case of research that requires patients who are hospitalized for very short periods of time or who are in acute care situations.

The FHREB permits the use of the "Information and Consent Form for Reviewing Health Records to Determine Patient Eligibility for Research" for this purpose when

satisfied that the justification for its use is valid.

The template for this consent to screen template is available at:
http://research.fraserhealth.ca/media/20060223ConsentScreentemplate.doc

19.2.11 Consent to Review Records & Contact for Participation in Future Research

In some situations, research may also be facilitated by using a consent form to obtain permission from a prospective research subject to screen their medical records for future contact for a research study, that is not specified at the time

The FHREB permits the use of the "Consent to Review Records & Contact for Participation in Future Research" if the following criteria is followed:

- Review of medical records is specific to the hospital admission where the consent is provided
- The consent is only valid for six months post hospital discharge.

The template for this consent to review records and contact is available at:

http://research.fraserhealth.ca/media/2008%2011%2026%20Consent%20to%20review%20records%20and%20contact%20Template.doc

19.3 SPECIAL REB AUTHORIZATION FOR A CONSENT FORM WAIVER

There are special circumstances under which a waiver of consent may be approved by an ethics board. This applies in situations where the FHREB can, under very specific circumstances, give special authorization to proceed with a study without subjects/participants' consent where they are incapable of providing it, and where substitute decision makers or others may not be able to consent on their behalf for various reasons. Refer to TCPS 2 3.7 and 3.8. The FHREB requires that the researcher justify such a request.

Researchers do however still have obligations to inform these subjects/participants about the nature of the study and their participation in it if they become competent to receive that information. The subject shall be informed that the initial investigation had prior FHREB approval.

In the event that the subject can participate in remaining part(s) of the study, a consent for the remaining part(s) of the study must be prepared that informs subjects/participants who did not consent to the initial investigation of what happened and why they are now being requested to continue to participate. The consent form shall explain that the initial investigation had prior FHREB approval.

19.4 CONSENT EXCEPTION IN EMERGENCY RESEARCH

TCPS 2 Article 3.8 outlines the criteria a REB may follow for allowing health emergency research to be conducted without the free and informed consent of the subject or of a substitute decision maker.

Researchers must promptly obtain free and informed consent for continuing participation in the study once the subject regains capacity. A subject may decline continuing participation in a study and also request that their data not be used. The researcher must uphold the wishes of the subject regardless of the concerns related to loss of data already collected. If the study included an intervention which was

already administered this cannot be taken back, but all the data collected from it can be withdrawn by the subject if he/she so wishes.

19.5 EXCEPTIONS TO THE REQUIREMENT TO OBTAIN INFORMED CONSENT

Reference:

1. TCPS 2 Article 5.5
2. TCPS 2 Article 9.20 – For special provisions that may need to be considered for Aboriginal research.

Studies that do not require informed consent include those whose data is derived solely from: 1) retrospective secondary data obtained from medical records (i.e. retrospective chart reviews), such that the research-related data are de-identified, or; 2) any anonymous source; this applies in particular to anonymous tissue from tissue banks.

Studies that prospectively collect secondary data from medical records are required to seek consent or provide a justification for an alteration of consent based on TCPS 2 article 3.7A.

Studies that collect identifiable secondary data must seek consent or provide a justification for a waiver of consent based on TCPS 5.5A.

1. TCPS 2 5.6

Consent to contact individuals for additional information that was originally obtained for the purposes of secondary research from primary sources of data is prohibited by the B.C. Freedom of Information and Protection of Privacy Act (FIPPA) unless approved by the B.C. Privacy Commissioner. Refer to the current version of the Act – Section 35. Disclosure for research or statistical purposes.
Any plan to obtain research data using this approach must be submitted to the FHREB for review and approval.
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GUIDANCE NOTE #20: COMPETENCY – Research Involving Subjects/participants with Questionable Capacity to Consent

The FHREB requires that the competency level of all prospective participants be assessed and that the researcher describe how they will determine each individual's ability to consent to participate in the study. The following typology is a guide for distinguishing these levels:

a. Unable to consent and without decision making capacity, or;
b. Unable to consent and with some decision making capacity, or;
c. Legally able to give fully informed consent. If legally able to consent, but under the age of majority in BC (i.e. 19 years of age), describe if: i) mature minor, or ii) emancipated minor.

Please refer to the following section which is intended to provide guidance on the requirements for obtaining consent or assent for research involving subjects/participants who would not be considered legally competent to give their own consent. Types of subjects/participants who may fall into this category include:

- individuals with permanent or transient cognitive impairments (e.g. subjects/participants with Alzheimer's Disease, subjects/participants who are

sedated/ventilated; subjects/participants with a variable/permanent mental illness);
- ❖ children who do not yet meet the tests for competency.

20.1 RESPONSIBILITY OF PRINCIPAL INVESTIGATOR

The determination of legal competence is the responsibility of the principal investigator or designated representative. Competency must be assessed not only at the time of obtaining initial consent but also must be assessed on an ongoing basis throughout the duration of the study. Should a substitute decision maker of the subject consent on behalf of a subject, the principal investigator or substitute decision maker is also obligated to assess that representative's competence to consent.

20.2 SUBSTITUTE DECISION MAKERS

"Until the contrary is demonstrated, every adult is presumed to be capable of giving, refusing or revoking consent to health care. If an adult is incapable, consent must be obtained from someone on the patient's behalf. The Adult Guardianship legislation sets out a ranked list of substitute decision makers.

In priority order, these substitute decision makers are:

1. A Committee, appointed under the *Patient's Property Act*;
2. A Representative, designated in a Representation Agreement under the *Representation Agreement Act;* or
3. A Temporary Substitute Decision Maker, as identified by the Health Care Team under the *Health Care (Consent) and Care Facility (Admission) Act"*

Refer to: http://www.qp.gov.bc.ca/statreg/stat/H/96181_01.htm#section16. According to the Health Care Consent Act regulations and the Representation Agreement Act, a substitute decision maker cannot consent to "experimental health care involving a foreseeable risk to the adult for whom the health care is proposed that is not outweighed by the expected therapeutic benefit". [Source: ***Health Care (Consent) and Care Facility (Admission) Act*** HEALTH CARE CONSENT REGULATION at http://www.bclaws.ca/EPLibraries/bclaws_new/document/ID/freeside/00_96181_01#section5].

References:

1. TCPS 2 Articles 3.9 and 3.10
2. ICH GCP 4.8.12, 4.8.13 and 4.8.14

TCPS 2 Article 3.9 specifies the following minimum conditions that must be met for research involving incompetent subjects/participants:

(a) the researcher involves participants who lack the capacity to consent on their own behalf to the greatest extent possible in the decision-making process;
(b) the researcher seeks and maintains consent from authorized third parties in accordance with the best interests of the persons concerned;
(c) the authorized third party is not the researcher or any other member of the research team;
(d) the researcher demonstrates that the research is being carried out for the

participant's direct benefit, or for the benefit of other persons in the same category. If the research does not have the potential for direct benefit to the participant but only for the benefit of the other persons in the same category, the researcher shall demonstrate that the research will expose the participant to only a minimal risk and minimal burden, and demonstrate how the participant's welfare will be protected throughout the participation in research; and

(e) when authorization for participation was granted by an authorized third party, and a participant acquires or regains capacity during the course of the research, the researcher shall promptly seek the participant's consent as a condition of continuing participation"

TCPS states that competence (capacity to consent) consists in "the ability of prospective or actual participants to *understand* relevant information presented about a research project, and to appreciate the potential consequences of their decision to participate or not participate." (TCPS 2 3C, emphasis added). There are thus two thresholds or tests that must be met to establish capacity to consent: capacity to understand, and capacity to appreciate, one's decision. Understanding is the ability to discern in significant measure the nature of the research and the consequences of choosing/forgoing participation in it. Appreciation is the ability to give reasons for participation that reflect, or are consistent with, the prospective subject's own fundamental values. It assumes adequately developed adult capacities for forming and revising personal values.

The Principal Investigator must judge the potential subject's ability to consent to research on his or her own behalf, in all patients, in all research projects, regardless of the prospective subject's age. Although BC health care legislation appears to use only an "understanding" test for determining capacity to consent, case law and health care practice take a broad interpretation of understanding to include "appreciation". Thus, the TCPS distinction between capacity to consent and capacity to assent is applicable in BC.

Incompetent subjects/participants should be informed and involved in decision making with respect to their participation to the extent possible. These subjects/participants may not be able to participate in research if they dissent or do not assent, even though third party consent has been obtained. See **GN 20.3** for the FHREB Policy #17 on Obtaining Assent From Subjects/participants Who Are Legally Incompetent.

20.3 OBTAINING ASSENT FROM LEGALLY INCOMPETENT SUBJECTS/PARTICIPANTS, INCLUDING CHILDREN AND THE MENTALLY IMPAIRED

In keeping with article 4.6 of the TCPS 2, individuals who lack capacity to decide whether or not to participate in research should not be inappropriately excluded from research. However, according to the TCPS 2, legally incompetent subjects/participants may be ineligible to participate in research unless they assent to participation. Refer to Appendix 1 for discussion of the TCPS assent policy and a full description of the assent requirement and procedures, including preparation of assent forms required by the FHREB.

The procedures that the researcher plans to adopt for obtaining and documenting assent must be described in the study protocol/proposal or appendix of the same. Refer to Section 22 of the application form.

POLICY # 17: OBTAINING ASSENT FROM SUBJECTS/PARTICIPANTS WHO ARE LEGALLY INCOMPETENT

The FHREB requires researchers to ascertain the willingness of individuals to participate in the research if they are legally incompetent but can nevertheless understand the nature and consequences of the research. These individuals will normally be required to assent by verbal or physical means or to sign an assent form before they can participate in research. These requirements may apply even though free and informed consent has been obtained, or is available, from an authorized third party.

GUIDANCE NOTE #21: OBTAINING ONGOING CONSENT

References:

1. TCPS 2 Articles 3.9 and 3.10 re incompetent subjects/participants who become competent ICH GCP Article 4.8.2 and 4.8.11

The FHREB believes that the consenting process is continual and requires vigilance on the part of the Principal Investigator to ensure that information that may in any way alter a subject's decision to remain in the study be conveyed in a timely manner to that subject. Information that may affect the subject's safety may be relayed to the subject verbally as quickly as possible. Refer to **GN 21.3** below.

Provisions should be made to ensure that any new information, which has the potential to change a subject's decision to continue participation, is conveyed in written form to the subject. The information may take the form of a letter or an addendum to the consent form unless it is more appropriate to administer the revised consent owing either to the special circumstances of the subject or to the importance of the new information.

Verbal confirmation of a subject's decision to continue participating may be obtained if informed by letter or verbally and should be documented accordingly. The subject should be given a copy of the consent as part of the process for deciding whether or not to continue participation in the study. Revised consents, addendums or letters must be submitted to the FHREB for approval prior to their use unless another prior arrangement is made with the FHREB.

The following sections provide information on provisions required in special cases.

21.1 INCOMPETENT SUBJECTS/PARTICIPANTS WHO BECOME COMPETENT

The informed consent of a subject who was incompetent at the time of enrolment but who becomes *competent* during the project should be sought as a condition of continuing participation. This means that although subjects/participants who were incompetent cannot give consent to receive the experimental intervention(s) after they have been administered, that the subject must consent to continue participating in the study (i.e. consent to receive any remaining procedures).

21.2 COMPETENT SUBJECTS/PARTICIPANTS WHO BECOME INCOMPETENT

In situations where a subject becomes *incompetent* during a study, and where the investigator intends to continue to include the subject in the research, the Principal

Investigator is obliged to find an appropriate substitute decision maker who will agree to monitor consent accordingly on behalf of the subject, as long as the subject remains incompetent. If a substitute decision maker does not exist, the best approach is to consult the FHREB for guidance.

In addition, refer to the FHREB **Policy #17 Appendix 1** on Obtaining Assent from Subjects/participants who are legally incompetent, as this may be relevant for some subjects/participants who become incompetent during the study and who will need to assent to the study, if they are capable of doing so.

21.3 NEW INFORMATION ABOUT HARMS

Reference:

1. TCPS 2 Article 11.8

When previously unknown/undisclosed harms of research become available, investigators are required to inform all subjects/participants/legal representatives, to whom this information may be relevant using appropriate means within an appropriate time, depending on the nature and consequences of the harm, i.e. risk = probability of harm. This may involve :

1. informing the subject(s) verbally of additional or increased likelihood of harms, or changes in procedures and ensuring that the communication of this information is documented in the study notes of the investigators and;
2. informing subjects/participants who have completed their study treatment if the newly identified harms or increase in harm could still affect them (e.g. irreversible or delayed adverse effects).

Written re-consent is required in situations when the information concerning harms has the potential to affect the subject's decision to continue participation in the study. ICH GCP 4.8.2 states that " the written informed consent form and any other written information to be provided to subjects/participants should be revised whenever important new information becomes available that may be relevant to the subject's consent".

Any revised written information or consent form (e.g. consent addenda) must be submitted to the FHREB for approval before use, using the 'Application for Amendment of a Previously Approved Study' form.

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GUIDANCE NOTE #22: PROVISIONS FOR OBTAINING CONSENT FROM SUBJECTS/PARTICIPANTS WHO REQUIRE SPECIAL ASSISTANCE

References:

1. TCPS 2 Article 3.7

22.1 TRANSLATIONS

The Principal Investigator is responsible for ensuring that for "English as a second language" (ESL) subjects/participants that either a consent form in the most

appropriate language or an appropriate translator be present during the initial informed consent process.

Policy #8: Translated Consent Forms

Translated copies of the consent form(s) will be required for acknowledgement after the FHREB has approved the English version of the consent form. A copy of the translator's signed and appropriate confirmation of the accuracy of the translation must accompany this.

Consent forms originally written in other languages must be translated into English and the back translation submitted for ethical review.

If a translator enrolling a subject is using an English consent form, the consent form must include the signature and printed name of the translator and the name of the language it was translated into.

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GUIDANCE NOTE #23: CONFIDENTIALITY: PROTECTION OF SUBJECT IDENTITY

References:

1. TCPS 2 Article 3.2 and 3.3 re "Informing Potential Subjects/participants" and Chapter 5 re "Privacy and Confidentiality"
2. TCPS 2 Articles 5.5 and 5.6 re "Secondary Use of Data"
3. FH Policy “The Collection, Use and Disclosure of Information for Research-related Purposes” [Approved 21 June 2005]

23.1 PRESERVING CONFIDENTIALITY

Preserving the confidentiality of a subject’s research records means that the subject’s personal information (which can also include tissue), which the researcher has previously established the authority to collect and use vis a vis the subject’s informed signed consent, is protected from inappropriate access and use.

Personal information is defined by FOIPPA as any recorded information about an identifiable individual other than contact information. Information can be in paper, electronic or photographic form, or as tissue about which can reasonably be said to identify an individual. (Source: Office of the B.C. Privacy Commissioner, June 2005)

The Principal Investigator is accountable for ensuring that proper protections, such as the use of unique study codes, are put into place to protect the confidentiality of the research subjects/participants' information. In addition, the Principal Investigator is responsible for ensuring that research-related information is made available only to the parties listed in the confidentiality section of the consent form. For example, FH researchers are prohibited from providing information on serious adverse events to drug companies that manufacture the drug being tested in a clinical trial if that company is not identified in the consent form.

23.2 USE OF IDENTIFIERS ON RESEARCH-RELATED RECORDS

23.2.1 Definitions

a. Directly Identifiable – Identifiable information can identify a specific individual directly. This may occur even without the subject's name when the existence of other variables (i.e. other identifiers as listed below) makes the information easy to tie to an individual.

b. De-identified/Quasi-Identifiers – Information that is indirectly identifiable or de-identified can be linked to a specific individual by way of an identifying tag or code. Quasi-identifiers can include gender and postal code as examples. (Source: **Pan-Canadian De-Identification Guidelines for Personal Health Information** Report (2007 May 14 Version 11) at http://www.ehealthinformation.ca/)

c. Anonymized/Anonymous/Non-identifiable – 'Anonymized' information was originally identified but has been permanently stripped of all possible identifiers and therefore is no longer identifiable. 'Anonymous' information is anonymous due either to the absence of tags or records such that the source has never been identifiable.

23.2.2 Permitted Identifiers

Unique study codes, which are made up of a combination of letters and/or numbers unrelated to the subject's identity, are permissible.

a. **Identifiers on Source Documents** - 'Source Document' Definition: 8.3.13 SOURCE DOCUMENTS To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject. (Reference: INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH): ICH HARMONISED GUIDELINE; INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE, E6(R2), Current Step 4 version, dated 9 November 2016, p.55)

Re Laboratory Reports: Although the type of 'source document' is not defined in the ICH GCP Essential Documents list or in the Tri-Council Policy Statement: Ethical Conducting on Conducting Research in Humans, the FHREB is including records of laboratory tests as a source document for clinical research, so that the standard of practice used by the Fraser Health laboratory for producing lab reports is also applied to the production of lab reports for research studies. This standard of practice requires the use of a unique identifier for the research participant, i.e. name, PHN, MRN, in order to also permit the automatic production of reference ranges for the particular lab value needed.

Fraser Health Lab Services will include the specified identifier on the lab report which will also be available in the Meditech system.

Updated 2017 03 13 Policy #7: Identifiers Not Permitted On Study Documents

The FHREB expects that research-related documents (except the source record(s), master randomization schedule, consent forms, or screening and enrollment logs) do not include information that would allow the subject to be identified.
Information is considered de-identified if the following conditions are met:

1. the unique study code is not derived from or related to the information about the individual;

2. the unique study code could not be translated to identify the individual, and;
3. the investigator or their institution could not use OR disclose the unique study code for other purposes OR disclose the mechanism for re-identification.

To this end, spaces/fields for subject name, the first or last three letters of a subject's name, actual initials, reversed initials, birth date, hospital medical record number, provincial personal health number, social insurance number, address or phone number are not permitted on study-related documents. Because many other people know/could access these identifiers, they provide less protection of privacy than the use of a unique study code.

Date of Birth: The FHREB will accept the use of month and year only, as an identifier. In some cases, '15' may be used as the default for 'day' of birth when the computer program required for the analysis does not accept '00' or UNKNOWN. Many databases automatically default the date of birth to the 15th of the month, in that the age is never more than 15 days over or under the subject's correct age at any given time (i.e. if defaulted to the 1st or the last day of the month, the age could be up to 30 days over or under the correct age). Confidentiality is maintained if all subjects entered into the database have the 15th as the day of birth.

It is not necessary to use a personal identifier (for example, birth date) as a secondary identifier in order to confirm the identity of the subjects/participants. This can be accomplished by using any two unique study codes.

23.2.3 Justification Required For The Use of Non-standard Identifiers

Personal information that is coded with any identifier, other than a unique study code, is considered 'identifiable'. The FHREB requires justification for the use of birth date or any other identifier when it is not possible to de-identify or anonymize research related records completely.

The following standard consent form wording is required in **bold text** if birth date or any other identifier is permitted for use by the FHREB [also refer to **GN 24.6.1.b].**

"It is unusual to include [name the non-standard identifiers, e.g. date of birth] on research records and material forwarded to others. Most studies submit information identified by code numbers or letters only."

23.2.4 Transfer of Personal Information Outside of Canada

Include information on the provisions in place to protect the confidentiality of the personal information if it is transferred to other study sites outside of the local site (e.g. countries outside of Canada, sites in other parts of Canada).

If identifiable/de-identified information is sent outside of Canada, the FHREB requires explicit informed consent describing the nature of the disclosure as per requirements under the B.C. Freedom of Information and Protection of Privacy Act if the personal information is to be transferred out of Canada as no disclosure outside of Canada of identifiable data is permitted without the consent of the individual/research subject. The FHREB requires that the consent form include the following standard consent form wording to ensure that the subject understands that their personal information is leaving Canada [also refer to **GN 19**].

"I understand that any study related data [and samples], sent outside of Canadian borders may increase the risk of disclosure of information because the laws in those countries (for example, the Patriot Act in the United States) dealing with protection of information may not be as strict as in Canada. However, all study related data [and samples], that might transferred outside of Canada will be coded (this means it will not contain your name or personal identifying information) before leaving the study site. Any information will be transferred in compliance with all relevant Canadian privacy laws. By signing this consent form, you are consenting to the transfer of your information [and samples], to organizations located outside of Canada. [Include list of organizations.]**"**

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GUIDANCE NOTE #24: CONSENT FORM REQUIREMENTS

Refer to the FHREB informed consent form templates at http://research.fraserhealth.ca/approvals-&-ethics/forms-and-guidance-notes/ for detailed information on consent form requirements. In most cases, consent forms should be written at a grade 7 level of understanding.

The following information includes specific requirements with respect to standard wording required for specific types of studies (GN 24.1 TO 24.5). Refer to **GN 25.6** for information on standard consent form requirements and for all studies.

24.1 STUDIES USING QUESTIONNAIRES

Questionnaires completed by subjects/participants which are completely anonymous and are returned to the researcher can be taken as implied consent. However the introductory letter/consent form must include wording that states this explicitly: ***"If you wish to participate in this research study and are comfortable with the procedures described in this letter/form, please complete the attached questionnaire and mail it back to us".***

Researchers may or may not choose to request that subjects/participants completing the questionnaire also sign a consent form.

N.B. On-line questionnaires must include a disclosure if the data collected will reside outside of Canada. For example, studies using Survey Monkey, data resides in a databank located in the United States. The introductory letter/consent form must include wording that states this explicitly: *"Your views/opinions are considered to be personal information. Survey Monkey stores information collected in the United States for an undetermined time period, and is therefore subject to U.S. law. By participating in the survey, you are consenting to having your personal information stored in the U.S. Please indicate your understanding and provide your consent to the above by checking the appropriate selection.*

N.B. When using SurveyMonkey researchers must change the settings so that no IP addresses can be collected. This will ensure that the data collected is completely anonymized.

Refer to the following SurveyMonkey Privacy links for more information:

- Full Privacy Policy http://www.surveymonkey.com/Monkey_Privacy.aspx
- Data Security https://www.surveymonkey.com/mp/policy/security/
- SurveyMonkey is compliant with EU Safe Harbour Privacy requirements, which are available here: http://www.ita.doc.gov/td/ecom/shprin.html
- Other Basic Info http://help.surveymonkey.com/articles/en_US/kb/HIPAA-Compliance-and-SurveyMonkey

24.2 SUB-STUDIES

The consent form for the main study must include a provision that allows the subject to decline participating in a sub-study, should the sub-study already be planned. A separate consent form for the sub-study must be submitted for ethical review.

24.3 OPEN LABEL EXTENSION STUDIES

If a study protocol includes a provision/plan for an open-label extension study, the main consent form should mention that the subject might be offered an opportunity to participate in another longer-term study after this initial study is finished.

An entirely separate informed consent process must be administered at the time of enrolment into the extension study, using a specific consent form dedicated to the extension study.

When necessary, the consent form for the open-label extension study may be submitted as an amendment.

24.4 TISSUE BANKING STUDIES

References:

1. TCPS 2 Chapter 12

The following TCPS requirements must be observed for obtaining free and informed consent for the purposes of banking tissue (n.b. tissue is defined as including blood).

a) That the collection and use of human tissues for research purposes shall be undertaken with the free and informed consent of competent donors.
b) In the case of incompetent donors, free and informed consent shall be by an authorized third party.
c) In the case of deceased donors, free and informed consent shall be expressed in a prior directive or through the exercise of free and informed consent by an authorized third party.
d) When identification is possible, researchers shall seek to obtain free and informed consent from individuals, or from their authorized third parties, for the use of their previously collected tissue.

The following FHREB policies must be applied if relevant.

24.4.1 Mandatory Tissue Banking

Policy #9: Criterion for Permitting Mandatory Tissue Banking

Tissue is defined as including blood. Mandatory tissue banking is only permitted if the tissue is being banked for purposes **directly related** to the study at hand (i.e. the tissue banking must be integral to the study, such that there would be no study if the subject did not contribute the tissue).

It is unethical to *require* that subjects/participants agree to allow their tissue to be banked for future use or experimentation that is unspecified or unrelated to the study at hand as a condition for entry into a therapeutic trial, as this could be perceived as a coercive method of obtaining tissue samples through offering a perceived therapeutic opportunity.

24.4.2 Donation of Tissue For Unspecified Uses

Policy #10: Voluntary Donation Of Tissue For Unspecified Uses

Subjects/participants *may* donate their tissue for future, unspecified uses provided:

1. this condition is made explicit in the main consent form for the study;
2. that such donation is optional, and;
3. that the Investigator discloses whether or not they plan to seek the subjects/participants' consent for future projects involving their tissue.

24.4.3 Information Required In Consent Forms For Tissue/DNA Banking

The information described below must be included in either the subject consent form for the entire study, if tissue/DNA banking is part of the study, OR in a separate consent form, if consent to bank tissue/DNA is being requested in connection with a research study but is independent of the subject's participation in that study. Include the following information in the tissue/DNA banking consent form.

a. The research purpose, and the **specific** uses of the tissue;
b. The type and amount of tissue to be taken, as well as the location(s) where the tissue is to be taken;
c. The manner in which tissue will be taken, the safety and invasiveness of acquisition, and the duration and conditions of preservation (i.e., address whether the tissue will be stored after the study is completed and, if so, why this is required);
d. The potential uses for the tissue, including any commercial uses, who the tissue might be sold to if this is known, and transfer to another institution;
e. The safeguards to protect the individual's privacy and confidentiality;
f. Access by other Investigators to banked tissue;
g. Identifying information attached to specific tissue, and its potential trace-ability;
h. How the use of the tissue could affect privacy;
i. Whether the subjects/participants will be notified of the results, and if so, the provisions for counselling of subjects/participants upon receipt of the results;
j. Whether tissue can be removed from the bank, if the subject later withdraws permission. Any options must be discussed with the research subject and disclosed in the Consent Form. (refer to TCPS 2 5.3.)

24.5 INFORMATION REQUIRED IN CONSENT FORMS FOR THE USE OF PRIMARY AND SECONDARY DATA COLLECTED USING: PERSONAL INTERVIEWS, SURVEYS, QUESTIONNAIRES, OBSERVATION TECHNIQUES, OR OTHER SOURCES OF PERSONAL INFORMATION

Reference:

1. TCPS 2 Article 3.2

The consent form(s) must specify the following types of information.

a) The specific type of data to be collected. For example, this may include:
   i. information from the subject's pre-existing personal information including medical records related to the subject's medical history and treatment prior to or during the study and that exist at a FH site or other non-FH sites;
   ii. information from the subject's personal family physician or specialist/other care provider;
   iii. information created as a result of receiving research-related procedures including testing done to determine a subject's eligibility in the study.
b) The **specific** purpose for which the data will be used;
c) Limits on the use, disclosure and retention of the data;
d) Appropriate safeguards for security and confidentiality;
e) Any modes of observation (e.g., photographs or videos) or access to information (e.g., sound recordings) in the research that may allow identification of particular subjects/participants;
f) Any anticipated secondary uses of identifiable data from the research;
g) Any anticipated linkage of data gathered in the research with other data about subjects/participants, whether those data are contained in public or personal records; and
h) Provisions for confidentiality of data resulting from the research (including observational data).

24.5.1 Consent Forms For Research Registries

Consent must be obtained from individuals for the prospective collection of their personal information for the purpose of developing a registry/database for future research. This requirement also applies to the development of registries/databases for clinical purposes when there is also intent to conduct future research.

The consent form for registry development must also include the following types of information:

a) possibility of foreseeable commercialization, if applicable;
b) who will have access to the registry;
c) linkage to other sources of data/databases/registries, if applicable;
d) period of data collection [i.e. when data collection stops] and opportunity for subject to opt out at any time;
e) notification that subject will be informed of new or expanded uses of the data set different from those originally consented to, and;
f) how long data is retained and how is data destroyed once no longer used.

24.6 CONSENT FORM STANDARD DISCLOSURES

See the FHREB consent form template for descriptions of required components of the consent form. Other specific disclosures required by the FHREB are outlined below.

24.6.1 Confidentiality

Policy #11: Confidentiality

The following requirements must be in place in order to protect subject confidentiality, but at the same time to allow monitoring of any study to occur. The consent form must include the following, as applicable, along with an explanation about the type of information that will be collected about the research subject.

a. De-identification:
An explanation of how the subject's information has been de-identified. If de-identified, the consent form must explain what type of unique code is used and an explanation that the list that links/matches the subject's name to the unique code and therefore to the subject's research-related information is kept by the principal investigator and/or designate ONLY, under secure conditions, so that it cannot be accessed by unauthorized personnel. See Standard Confidentiality Wording below.

OR

b. Use of Non-standard Identifiers
When sponsors require that identifiers other than a unique study code be used on research records, justification for such use including their intended use must be provided to the FHREB. Include details of how the subjects/participants' confidentiality will be protected despite the use of the non-standard identifiers. The following standard wording is required and should be added to the Standard Confidentiality Wording as appropriate:

- **"It is unusual to include [name the non-standard identifier(s), e.g. date of birth/reversed initials] on research records and material forwarded to others. Most studies submit information identified by code numbers or letters only."**

OR

c. Anonymization:
If the information is anonymized such that it does not include any identifiers, the consent form must explain that the research information will not identify the subject in any way. The following standard wording is required:

- **"Your research-related information will not identify you in any way because all identifying information has been removed such that the information is now anonymous and there is no possibility of linking your identity to your information."**

d. Availability of Records For Monitoring
Records must be made available to a scrutineer from an industry sponsor (in the case of sponsored clinical trials), Health Canada (in the case of regulated clinical trials), the U.S. Food and Drug Administration (in the case of American regulated clinical trials), and the Fraser Health Research Ethics Board, provided that it is done in the presence of the Principal Investigator or his or her designate and that the records are not copied or the names recorded. The consent form must explain that identifiable information from source research-related records may be inspected for regulatory, legal and ethical review requirements. See standard wording below:

e. Standard Wording for Confidentiality Disclosures:

Your confidentiality will be respected. However, research records and health or other source records identifying you may be inspected in the

presence of the Investigator or his or her designate by representatives of *[Insert here, if relevant to study, the name of the sponsoring company or cooperative group conducting the study],* Health Canada, *[Insert here, if relevant to study, the U.S. Food and Drug Administration],* and *[Insert name of your REB]* for the purpose of monitoring the research. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law. [If this is a US FDA regulated study, insert the sample paragraph noted below that describes the right of the US FDA to remove identifying information.]

You will be assigned a unique study number as a subject in this study. Only this number will be used on any research-related information collected about you during the course of this study, so that your identity [i.e. your name or any other information that could identify you] as a subject in this study will be kept confidential. Information that contains your identity will remain only with the Principal Investigator and/or designate. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to insure that your privacy is respected and also give you the right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor.

For US FDA-regulated studies only, include the following wording in separate paragraphs:

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. [This is mandatory US FDA wording and cannot be amended.]

Because this is a study that also falls under U.S. regulation, in some circumstances the U.S. Food and Drug Administration (US FDA) may seek to copy records that contain your personal information. If this occurs, you will be informed before the records are copied, but your consent may not be sought. You should be aware that privacy protections on personal information may differ in other countries.

NOTE: If there is planned disclosure of personal identifiers (e.g. names, date of birth, or initials) outside the local study site, or if such personal identifiers are used on study documents or any research-related information or are part of the unique identifier, this must be justified to the REB and, if permitted, the foregoing standard wording must be amended as necessary.

As well, placement of any research data or results in the subject's health records must be disclosed to subjects and justified to the REB.

Sample Wording (if applicable):

Your birth date will also be provided if requested by the sponsor or responsible regulatory agency.

f. Research-related Records Leaving the Research Site

For studies, which require that information be copied, or leave the FH site, include an explanation in the consent form that states specifically what information is leaving the site and where it is going. Note that this explanation should be consistent with the explanation about the use of identifiers, if any.

g. Research-related Records Sent Outside of Canada

For studies which have identifiable or de-identified information that is sent outside of Canada, the following standard wording is required:

"Any study related data [or samples], sent outside of Canadian borders may increase the risk of disclosure of information because the laws in those countries *[for example, the Patriot Act in the United States]* dealing with protection of information may not be as strict as in Canada. However, all study related data [and samples], that might be transferred outside of Canada will be coded (this means it will not contain your name or personal identifying information) before leaving the study site. By signing this consent form, you are consenting to the transfer of your information *[and samples*], to organizations located outside of Canada*. [Include list of organizations.]"*

h. Archiving Research Records
When investigators must archive research records off-site, they are responsible for the security and confidentiality of the data. The FHREB still considers the data to be "in the Investigators' offices" for the purposes of the wording used in the confidentiality statement.

i. Mandatory Disclosure of Subject's Identity: Reportable Communicable Diseases/Suspected Child Abuse
In rare instances it will not be possible to ensure confidentiality because of mandatory reporting laws (e.g., suspected child abuse, reportable communicable diseases, and knowledge of harm to others). When this is the case, the prospective research subject should be made aware of this limitation in the consent form.

The BC Health Act Communicable Disease Regulation Schedules A & B list reportable diseases. Sections 2(1), 2(2) and 2(3) require physicians/researchers to report communicable diseases (e.g. HIV, HCV) to the Medical Health Officer. Reporting includes the name, age, sex and address of the infected person.

The only exception to mandatory reporting is for persons who voluntarily submit to testing for HIV; for which a non-nominal report is permitted (i.e. the report must omit the name and address of the person if that person so chooses).

Anonymous surveys that are unlinked do not fall within the reporting requirements of the Act as the physician/researcher would not know that any particular individual was infected.

Standard wording is required for any research studies in which blood tests may reveal the presence of a communicable disease that is reportable by law. Refer to the BC Health Act Communicable Disease Regulation Schedules A & B for the list of reportable diseases at http://www.qp.gov.bc.ca/statreg/reg/H/Health/4_83.htm.

In addition, standard wording is also required for notification of suspected child abuse for studies involving children.

Required Wording: Use the standard wording for either blood tests for communicable diseases [see a below] OR studies involving children or harms to others [see b below] that is applicable to the study.
"In most cases, your personal information or information that could identify you will not be revealed without your express consent. However, if as a result of your participation in this study, facts become known to the researchers which must be reported by law to public health authorities or legal authorities, then your personal information will be provided to the appropriate agency or authority".

[a] *This requirement applies to communicable diseases which include but are not limited to, Hepatitis B or C, West Nile Virus and Human Immuno-deficiency Virus [HIV].*
[b]*Similarly, information that leads the researchers to strongly suspect that a child or others are being harmed or in danger of being harmed, may have to be disclosed by law. Also, information that leads the researchers to strongly suspect that [you/your condition/the subject] may cause serious risk of imminent bodily harm to either [yourself/themselves] or another person may result in immediate action to protect your safety and may require your information and circumstances to be disclosed. [Updated 2008 June 10]*

Except for the circumstances described above the risk of disclosure of personal information is usually very small".

j. Potential for Breach of Confidentiality
The following statement concerning the possibility of a breach of confidentiality is permissible in the consent form: ***"Your personal information may be disclosed if required by law"***. This wording means that there is an absolute obligation to keep confidentiality until such time as there is an exception arising out of a legal requirement to disclose a subject's identity. Other wording, i.e. "to the extent permitted by law" is generally not permissible as this implies that there is not an absolute obligation to keep confidentiality.

k. Photography, Video / Audio Taping
If there are any plans to use photography (including digital photographs), video or audio taping in the research, who will have access to the recordings and the methods used to protect the subject's identity must be described in the consent form. The eventual fate of the records must also be disclosed (i.e. where and for how long they will be stored and whether they will be destroyed, any plans for secondary uses of the recordings). If there are plans to use these materials for any other purpose than the research project (e.g. for teaching purposes) and subjects/participants could be identified, separate consent is required.

l. Disclosure of Inclusion of Signed Consent Form in Subject's Health Record (For Clinical Interventional Research Only)
If the subject is a patient in an institution (e.g. hospital) when the research is conducted, inclusion of the signed Consent Form in their permanent health record in Fraser Health is required and if so, this must be disclosed in the Consent Form. The requirement for inclusion of the Consent Form in the health record may vary between other non-FH institutions, and investigators should seek clarification from the institutions involved.

m. Disclosure of Test Results in Subject's Health Record
If it is the intention or a likely consequence of the research that test results which might affect treatment decisions or have important implications (e.g. HIV tests, genetic tests) will become part of the subject's health record, this must be disclosed in the Consent Form.

24.6.2 Disclosure Of Legal Rights Of Subjects In The Event Of Injury Or Illness Arising From Research Participation

References:

1. TCPS 2 Article 3.2
2. ICH GCP 4.8.4

The FHREB feels that it is important that subjects do not bear the cost of illness or injury arising from their participation in a research study. At the same time the FHREB does not have the authority to direct how such costs will or will not be covered by sponsors of research as per their respective insurance plans or those of the subjects/participants. Information about insurance coverage that is included in the Compensation for Injury section must be written to reflect the Canadian situation.

Inclusion of this standard statement in the consent form ensures that the subject is not restricted from seeking compensation through the courts for injury or illness that is related to participation in the research study, even when research sponsors place restrictions on the medical or other costs that they are prepared to cover in the event of injury or illness arising from a subject's participation in a research study.

Policy #12: Compensation for Injury (This Does Not Apply for Non-Regulated or Unfunded Studies)
The following wording will be required to appear in the subject consent form under the Compensation for Injury section:

"By signing this form, you do not give up any of your legal rights and you do not release the study doctor or other participating institutions from their legal and professional duties. *There will be no costs to you for participation in this study*[1]. You will not be charged for any research procedures. If you become ill or physically injured as a result of participation in this study, medical treatment will be provided at no additional cost to you. The costs of your medical treatment will be paid by your provincial medical plan and/*or by the study sponsor.** *[Name the Sponsor].*

[1] *include if statement is true for this study, i.e. all parking, mileage expenses are being reimbursed to the study subject.*
*Definition of "Sponsor" Refer to ICH Good Clinical Practice Guidelines (ICH GCPs)

(1997) [Updated 2008 August 08]
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

The following statements are not permitted because they may be seen to limit the circumstances under which compensation for injury is available:

"Although no funds have been set aside to compensate me in the event of illness or injury related to the study treatment or procedures" OR "While participating…through to "guarantee full coverage", OR There will be no financial compensation…" for damages (e.g. lost time from work, disability or discomfort)" OR "compensation for…. is not routinely available.".

24.6.3 Disclosure of Rights of Human Subjects/participants in Research

The standard consent form wording is as follows: ***"If you have any concerns or complaints about your rights as a research subject and/or your experiences while participating in this study, contact the Fraser Health REB co-Chairs by calling 604-587-4681. You may discuss these rights with the co-chairmen of the Fraser Health REB."***

24.6.4 Disclosure of Whom to Contact for Study Procedure Information

Provide a contact name and phone number that subjects/participants may use if they have questions about study procedures or other questions directly related to what they need to know to participate. Ensure that this information is kept separate from that required under **GN 24.6.3** above.

24.6.5 Disclosure Regarding Rights of Subject to Withdraw from Research

References:

1. TCPS 2 Article 3.2 (3)
2. ICH GCP 4.8.10 (m)

The consent form(s) must include a statement that assures the subject that their participation is voluntary and that they may withdraw at any time. For Health Canada and/or US FDA regulated clinical trials, the statement should also notify the subject that data collected up to the point of their withdrawal from the study will be kept for data analysis purposes under strict provisions of confidentiality. However, this is not a legal requirement. The retention of data after a participant withdraws from non-Health Canada and/or US FDA regulated research must be justified in the study protocol.

The following wording is recommended for Health Canada and/or US FDA regulated clinical trials:

> *"You may withdraw from this study at any time without giving reasons. If you choose to enter the study and then decide to withdraw at a later time, all information about you collected up to the point of your withdrawal [including, where applicable, information obtained from your biological samples] will be retained for analysis in order to protect the integrity of the research, which may benefit future research participants and patients. However, no further information will be collected.* ***This is not a legal requirement.****"*

If withdrawal of data is not possible, the following wording is recommended:

> *"Your participation in this research is entirely voluntary. You may withdraw from this study at any time. If you decide to enter the study and to withdraw at any time in the future, there will be no penalty or loss of benefits to which you are otherwise entitled. Please note however that there may be exceptions where the data [and/or samples] will not be able to be withdrawn for example where the data [and/or sample] is no longer identifiable (meaning it cannot be linked in any way back to your identity) or where the data has been merged with other data. If you would like to request the withdrawal of your data [and/or samples]*

For all other studies, the following wording is recommended:

> *"Your participation in this research is entirely voluntary. You may withdraw from this study at any time. If you decide to enter the study and to withdraw at any time in the future, there will be no penalty or loss of benefits to which you are otherwise entitled. If you choose to enter the study and then decide to withdraw at a later time, all data collected about you during your enrolment in the study will be destroyed."*

The subject must be permitted to request withdrawal by any means. It is not acceptable to require that the subject submit a request for withdrawal in writing. Separate consent forms for "Subject Withdrawal From Study" are not permitted.

24.6.6 Physician Notification of Subject Participation

Physician notification of a subject's participation in a clinical trial may be a requirement of the particular trial, in which case, the consent form must include a statement indicating that the subject's physician will be notified.

Alternatively, in studies where physician notification is not part of the study protocol, the FHREB may decide that it is necessary that the subject's physician be notified for safety reasons [e.g. to avoid potential for drug interactions]. In this situation, the FHREB will require that the consent form include a statement indicating that the subject's physician will be notified.

In other studies, notification of the subject's physician may be desirable but not necessary. In this situation, the consent form must include the following wording which provides a choice for the subject to either approve or not whether their physician will be notified.

> *Please indicate by checking the applicable box, whether you want us to notify your primary care physician or specialist of your participation in this study:*
>
> ☐ *Yes, I want the study investigator to advise my primary care physician/specialist of my participation in this study; his/her name and office phone number is:_____.*
> ☐ *No, I do not want the study investigator to advise my primary care physician/specialist of my participation in this study*
> ☐ *I do not have a primary care physician/specialist*
> ☐ *The study investigator is my primary care physician/specialist*
>
> *I understand that if I choose not to advise my primary care physician/specialist of my participation in this study, there are potential medical issues or consequences*

which may affect my comprehensive medical care or treatment. I agree that the study investigator will not be responsible for these consequences"

24.7 REQUIRED SIGNATURES ON CONSENT FORMS

References:

1. TCPS 2 Article 3.2
2. ICH GCP 4.8.8

24.7.1 Subject/Substitute Decision Maker Signature

The FHREB requires that the prospective subject consent to participate in a research study by signing and dating the consent form. The FHREB does not require that subjects/participants initial each page of the consent form.

24.7.2 Signature of Assenting Subjects/Participants

An Assent form, where used, must be signed and dated by the subject. A signature by a witness or Principal Investigator/ Substitute Decision Maker is not necessary and is generally discouraged by the FHREB. Refer to **Policy #17 Appendix 1** on Obtaining Assent from Subjects/Participants who are legally Incompetent

24.7.2.1 Assent Statement in Consent Forms Signed by an Authorized Third Party (e.g. Parent or Guardian)

The following standard wording is required to appear in the consent form in cases where the subject assents to participate in the research:

"The parent(s)/guardian(s)** and the investigator are satisfied that the informat was explained to the child** to the extent that he/she is able to understand it, tha answered, and that the child** assents to participating in the research."
(** Substitute appropriate wording if the research subject is not a child).

24.7.3 Witness Signature

Witness signature is not required on consent forms unless the subject/substitute decision maker is unable to read and the information in the consent form is read and explained to the subject/substitute decision maker. In this circumstance, a witness signature is required to attest that the consent form and any other written information was accurately explained to and understood by the subject or substitute decision maker and that informed consent was freely given.

Reference:

1. ICH GCP 4.8.9

a. 24.7.4 Principal Investigator/Designated Representative Signature

Investigators or their qualified designated representatives are responsible for securing free and informed consent from their subjects/participants.

The Consent Form must include the signature and printed name of the Principal

Investigator/delegated representative, and this would have to be identified as such in the Consent Form.

24.8 FHREB APPROVAL STATEMENTS IN CONSENT FORMS

Policy #13: FHREB Approval Statements in Consent Form

The FHREB accepts (but does not require) references in consent forms to the project having been reviewed and/or approved by the Research Ethics Board. When mentioning the Research Ethics Board, the FHREB accepts (but does not require) an explanation of the Board's role in terms similar to the following: "This Board aims to help protect the rights of research subjects/participants."

Note that no mention of risks will be accepted in describing the role of the REB so as to avoid the misinterpretation that the REB's oversight makes it safe for subjects/participants to participate in the research.

24.9 STATEMENTS PERTAINING TO SUBJECT'S INSURANCE COVERAGE

Statements made in the consent form that advise a subject to contact their insurer about the potential for future coverage should they choose to participate in a study are not permitted since the subject doing so may restrict their ability to seek legal recourse should they not be able to obtain insurance or if premiums were increased as a result of a subject's participation in the study.

24.10 USE OF "NEGATIVE CONSENT"/CHECK BOXES

Policy #14: Use of "Negative Consent" Check Boxes in Consent and Assent Forms

1. The use of "Yes/No" check boxes for consent is not allowed. Lack of signature on a consent form is taken as evidence of dissent, and no subject shall be required to declare in writing in any way that they do not consent to participate in a research project.

Exception to #1:

1a. Where a single consent form contains multiple optional sub-components, (e.g. tissue banking for genetic research) where subjects/participants can choose which ones they wish to participate in, the optional SUB-COMPONENTS (but not the main question of consent to participate in the main project) may employ "Yes/No" indicators to signify willingness to participate.

Lack of indication of "Yes" (or equivalent) shall be taken as evidence of DISSENT and **no requirement to check "No" (or equivalent) is allowed.**

The FHREB may require that *separate* consent forms fully describing a sub-component(s) of a project be required instead of allowing the procedure described in 1(a) where necessary.

24.11 LISTING OF CO-INVESTIGATORS ON CONSENT FORMS

Policy #15: Co-Investigators Listed In Consent Forms

1. The FHREB prefers that all co-Investigators, their institutional affiliation (i.e. use the local site in a multi-site trial) and appropriate titles be listed after the Principal Investigator on both page 1 and the Subject Consent to Participate page of the consent form. (The purpose of including all investigators names is to enable release of health records to any investigator in the study team for that subject.)
2. Where it is not practical to do so, the Board accepts that only the Principal Investigator (including their telephone number) be listed on the consent form.
3. Where a subject's "study doctor" is other than the Principal Investigator, a place must be provided in the consent form for this person to be named, and their telephone number provided.
4. Choice of listing of the Principal Investigator and co-investigators does not affect the requirement for an emergency 24 hour contact number for subjects/participants enrolled in the research.

GUIDANCE NOTE #25: DATA SECURITY

References:

1. ICH GCPS Article 5.1 re Quality Assurance and Quality Control
2. ICH GCPS Article 5.5 re Trial Management, Data Handling, and Record Keeping
3. ICH GCPS Article 5.15 re Record Access

25.1 PREVENTING UNATHORIZED ACCESS

Appendix 2 of the Initial Application collects information related to data access and security. This will be forwarded to the Fraser Health Information Privacy Office for their review and approval once the FHREB has approved the study. The Privacy Office will either authorize the data access, or request a Privacy Impact Assessment. The Principal Investigator will be notified by the Privacy Office of their decision.

25.1.1 During the Study

Include information in the protocol on what measures are taken to prevent unauthorized access to the research data during the study.

25.1.1.1 Storage During the Study

Patient Enrolment Logs, documents, databases, mobile computers and any other device which retain research data must be kept in a locked cabinet/drawer in the locked premises of the Principal Investigator/designate.

25.1.1.2 Computer Protection

Research data retained in computer files must be password protected.

Computer Validation:
The researcher must provide verification of the security level of a computer being used for the study.

In a large research site (i.e. located in hospital or large institution using a shared server), this could include information from the Information Management Department

outlining the security features (i.e. login, firewalls and back-up capability in case of fire, flood, electrical failure).

In a small research site, i.e. researcher's office, a note to file or standard operating procedure should be available detailing the security features (i.e. password protection, who has access, firewall software, etc.) and details on how the data is backed up and stored.

This information should be kept in the study research binder or a note to file stating where this information can be found.

25.1.2 After the Study is Completed

Storage of research documents after the study is completed must be in a storage facility that is dedicated to the storage of documents and that can show evidence of having security provisions in place to protect against unauthorized access to and retrieval of records.

25.2 LINKABLE DATA/TISSUE OBTAINED FROM DATABANKS OR BIOBANKS

Reference:

1. TCPS 2 Article 5.7

Personal Information Bank (PIB): Databases that include any personal information as defined in **GN 23.1** must be registered as a PIB. Contact FH Privacy Office for further information.

a. Identify who (i.e. data/biobank custodian) has authorized access to the stored data/tissue.

b. Identify who retains the key for linking coded tissue or data to a register of human subjects/participants.

c. Explain who will perform the necessary data linkage. It is preferable if the custodian of the bank holds the key to linking the data and performs the data linkage so that identifying information is not released to investigators.

25.2.1 Linking Registry Data

a. Clarify whether registry data will be linked to other sources of data/other registries.

b. If data linkage is carried out, identify who will be responsible for linkage.

c. If data linkage is carried out, provide details on what identifiable information will be used to link the data, i.e. DOB, PHN, Hospital Record Number, etc.

d. Describe how the identifiable data will be transmitted to and from Fraser Health, i.e. encrypted files, couriered, hand delivered by research staff, etc.

e. If data linkage is carried out, clarify that the identifiers will be securely destroyed prior to release of the linked database.

25.3 PROCEDURES IN THE EVENT OF A BREACH OF CONFIDENTIALITY

In situations where a breach of confidentiality has occurred the FHREB requires that the following measures be taken to inform the subject of this breach.

1. The Principal Investigator must immediately notify the Research Ethics Coordinator or the Director, Department of Evaluation and Research Services and provide details regarding the Breach of confidentiality.
2. The Research Ethics Coordinator will contact the FH Information Privacy Office and provide the details regarding the privacy breach, including the principal investigator's contact information.
3. Once the FH Information Privacy Office determines the steps that need to be taken (which will include notifying the subjects affected by the breach), the principal investigator works with the Research Ethics Coordinator and the Director to complete any necessary steps.

25.4 Traveling with Personal Information

Never travel with personal information unless you absolutely must have it with you.

If you take personal information with you, take the least amount that you need and leave the rest behind.

Electronic records of sensitive personal information when taken away from the office must be encrypted in a manner approved by the Fraser Health Information Privacy Office. For more information on this contact the Privacy Office at: privacy@fraserhealth.ca.

Records containing personal information should never be left in a vehicle unattended or overnight.

If personal information is stolen or lost, immediately notify the Research Ethics Office, and ensure the FH Managing Privacy Breaches policy is followed.

For more information, please refer to the FH Information Privacy Office Best Practices – When Your Work Requires you to Travel with Personal Information document.

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GUIDANCE NOTE #26: USES OF DATA AFTER THE STUDY IS COMPLETED

References:

1. TCPS 2 Article 3.2 (f) and (i)

26.1 INTENDED USES

Include an explanation of the intended uses for the data after the study is completed, for example, data analysis as justification for future studies.

26.2 DOCUMENT RETENTION REQUIREMENTS

Refer to the following sources for information on the document retention responsibilities of Investigators.

26.2.1 Clinical Trials

References:

1. ICH GCP 4.9.5
Refer to: http://www.fda.gov/cder/guidance/959fnl.pdf
2. Health Canada's Food and Drug Act Division 5 C.05.012 (4)
Refer to: http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/reg/1024-eng.php

Updated 2016 November 16: Health Canada requires regulated clinical trials to be retained for a period of 25 years after the study is completed. It is the responsibility of the Principal Investigator to archive all research-related documents from all relevant departments involved in the study. Documents for each studies must be archived together. For example, a laboratory department that had collected blood samples for a particular research study does not need to retain these records after the study is completed because the principal investigator delegated the lab tasks to the lab only.

26.2.2 Other Research

Research records that are of a non-clinical trial nature must be retained by the Principal Investigator for a period of 5 years.

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APPENDIX 1

POLICY #17: OBTAINING ASSENT FROM SUBJECTS/PARTICIPANTS WHO ARE LEGALLY INCOMPETENT

The FHREB requires researchers to ascertain the willingness of individuals to participate in the research if they are legally incompetent but can nevertheless understand the nature and consequences of the research. These individuals will normally be required to assent by verbal or physical means or to sign an assent form before they can participate in research. These requirements may apply even though free and informed consent has been obtained, or is available, from an authorized third party.

See below for a full description of FHREB requirements, directions on the preparation of assent forms, and a discussion of TCPS policy in this area. The procedures the researcher adopts for obtaining assent must be described in the study protocol/proposal. Please refer to section 22 of the application form

Contents:

1.0 Introduction

This FHREB policy describes procedures for obtaining assent to participate in research from certain legally incompetent individuals. It also aims to answer questions about what constitutes assent, how to assess when subjects/participants are capable of assent, how assent differs from consent, and why seeking assent from certain prospective subjects/participants is ethically important. These questions raise ethical and legal issues that require systematic discussion. Researchers must be informed about these issues. Those who already have a grasp of them or who wish to begin by reviewing the procedures for obtaining assent may skip to section 5. A summary of procedures is included in section 7.

The procedures for obtaining assent must be clearly detailed in the study protocol, including: 1) the basis for determining the potential participant's capacity to consent/assent; 2) how record of assent will be documented; 3) who will administer the assent procedures; and, 4) how prospective participants who are not legally competent but who can understand the nature and consequences of research but who neither clearly assent nor dissent will be handled.

2.0 Tri-Council Policy on Assent

The FHREB assent policy follows the Tri-Council requirements for obtaining assent, which state:

Where free and informed consent has been obtained from an authorized third party, and in those circumstances where the legally incompetent individual understands the nature and consequences of the research, the researcher shall seek to ascertain the wishes of the individual concerning participation. The potential subject's dissent will preclude his or her participation. (TCPS 2 Article 3.9)

The Tri-Council further explains the meaning and scope of this Article as follows:

Many individuals who are not legally competent are still able to express their wishes in a meaningful way. Prospective subjects/participants may thus be capable of verbally or physically assenting to, or dissenting from, participation in research. Those who may be capable of assent or dissent include: (a) those whose competence is in the process of development, such as children whose capacity for judgment and self direction is maturing; (b) those who once were capable of making an informed decision about informed consent, but whose competence is now considerably, but not completely, diminished, such as

individuals with early Alzheimer's disease; and (c) Those whose competence remains only partially developed, such as those suffering from permanent cognitive impairment.
3. Discussion of Tri-Council Assent Policy.

TCPS 2 requires researchers to determine the willingness to participate in research of prospective subjects/participants who are legally incompetent but who are nevertheless capable of understanding the nature and consequences of the research. The *dissent* of these prospective subjects/participants, by verbal or physical means, precludes their participation in the research. Furthermore, their participation is precluded even though free and informed consent has been obtained, or is available, from an authorized third party. Such a policy recognizes that (1) subjects/participants with diminished competence retain some control over decision-making, and that it is appropriate to protect their dignity in this respect; (2) it is important to preserve relations of trust between subjects/participants and health care providers; and (3) the voluntariness of health care research must be protected to preserve public trust in it and in health care generally.

For the same reasons, TCPS also clearly contemplates seeking *assent* from legally incompetent individuals who are capable of understanding the nature and consequences of the research. However, these passages and TCPS 2 fall short of requiring the explicit assent of all such prospective subjects/participants as a condition of their participation in research. The FHREB interprets this to mean that failure to assent should not necessarily be construed as dissent, and thus does not always preclude participation in research.

Thus, there are three classes of individuals who must be considered among the legally incompetent who are capable of assent:

- those who express assent,
- those who express dissent, and
- those who express neither.

The status of the first two classes is straightforward regarding participation in research: assenting individuals may participate in research with the informed consent of an authorized third party; dissenting individuals may not. Explicit direction with the third class is not given by TCPS, but it is evident that such a group exists and has a morally separate status from the other groups. For example, researchers may at least occasionally encounter an 11 year old who is legally incompetent and who understands the nature and consequences of participation in research, but who remains ambivalent regarding participation in research and does not clearly assent or dissent. Such a prospective subject may also appear to rely mainly on parents or a guardian to make a decision for him or her, and this may be appropriate in the circumstances. A policy on assent must identify procedures with respect to each of these classes of individuals.

3.1 Interpretation of Tri-Council Assent Policy

TCPS policy in interpreted as requiring that:

i) assent is normally required of prospective subjects/participants who are not legally competent but who can understand the nature and consequences of the research. Prospective subjects/participants who provide such assent, by verbal or physical means, may participate in research, subject to obtaining free and informed consent from an authorized third party (and subject to other TCPS requirements governing the participation of legally incompetent subjects/participants – see TCPS 2 Articles 3.9 and 4.6).

ii) prospective subjects/participants who are not legally competent but who can understand the nature and consequences of research and who communicate unwillingness to participate in research by verbal or physical means (i.e., who dissent) are precluded from participation., even though free and informed consent has been obtained, or is available, from an authorized third party.

iii) prospective subjects/participants who are not legally competent but who can understand the nature and consequences of research and who neither clearly assent nor dissent must be handled with caution and careful judgment must be exercised on a case-by-case basis by researchers when deciding to include these individuals in research. Authorized third party consent is required as a condition of their participation in research.

Sections 4 and 5 of this policy statement will explain how to identify capacity to assent and procedures for obtaining assent from prospective subjects/participants. Section 6 will list considerations for handling prospective subjects/participants who are technically capable of assent but who neither assent to, nor dissent from, participation in research.

4.0 Capacity to Assent Contrasted with Capacity to Consent

TCPS states that competence (capacity to consent) consists in "the ability of prospective or actual participants to *understand* relevant information presented about a research project, and to appreciate the potential consequences of their decision to participate or not participate" (TCPS 2 3C, emphasis added). There are thus two thresholds or tests that must be met to establish capacity to consent: capacity to understand and capacity to appreciate one's decision. Understanding is the ability to discern in significant measure the nature of the research and the consequences of choosing/forgoing participation in it. Appreciation is the ability to give reasons for participation that reflect, or are consistent with, the prospective subject's own fundamental values. It assumes adequately developed adult capacities for forming and revising personal values.

By contrast, capacity to assent is present if the prospective subject has not adequately developed, or has lost, an adult capacity for appreciation but nevertheless has the capacity to understand the nature and consequences of the research. Examples include prospective subjects/participants who can in significant measure understand the nature of the research and the potential consequences for them of participation but who, because of lack of maturity or cognitive impairment, do not have settled personal values, are unable to develop them, or are unable to give reasons that reflect their settled values. Assent must be sought from these prospective subjects/participants for the reasons given in section 3.0. Their dissent precludes their participation. Assent/dissent can be given by verbal or physical means.

Although BC health care legislation appears to use only an understanding test for determining capacity to consent, case law and health care practice take a broad interpretation of understanding to include appreciation. Thus, the TCPS distinction between capacity to consent and capacity to assent is applicable in BC.

See the *Infants Act, the Health Care (Consent) and Care Facility (Admission) Act, and Van Mol (Guardian ad litem of) v. Ashmore* [1999] B.C.J. No. 31. A right to assent for incompetent prospective research subjects/participants is recognized in the *World Medical Association Declaration of Helsinki (2000)*.

4.1 Children and Consent and Assent

4.1.1 Research in a child’s best interests (i.e., with a potential health benefit)

Children (18 and under) may be legally capable of consenting to participate in research if certain conditions are met under the *Infants Act*. Under that *Act*, children are apparently legally able to consent to participate in research if they are competent and if participation is “in their best interests”. The tests for competence given in the previous section must be applied to determine their capacity to consent. Children who have the legal capacity to consent must sign the consent form in order to participate in research, and their assent is therefore unnecessary.

In all cases where a child is legally competent to consent to participate in research, parental consent cannot be sought on behalf of the child. However, the FHREB may permit researchers to make parental agreement an inclusion condition for the competent child’s participation in the research, particularly if parental support is required to assist the child’s participation (e.g., transportation, assisting/overseeing taking of therapy, etc.).

4.1.2 Research not in a child’s best interests (i.e., with no potential health benefit)

4.1.2.1 Where the risk is more than minimal

Where participation in the research is not in the child's best interests, it would appear that the child cannot be legally competent to give consent, and consent must be sought from an authorized party until the child is 19 years old. However, wherever a legally incompetent child has the capacity to assent, the assent policy described in this appendix must be observed.

4.1.2.2 Where there is minimal risk and the child wishes to participate in the research

If a child is competent according to the tests described in section 4.0 and if s/he is a prospective subject in research that offers no benefit but poses minimal risk, the FHREB takes an "ethics first" position that s/he is competent to consent to participate in the research. The FHREB takes this position because (1) the best interests of the child are unlikely to be undermined by such participation; and (2) competent people are normally thought to be entitled to make their own decisions, to be the best judges of what is in their own best interest and should be presumed to have their own reasons for participation in research even if there is no potential benefit to them. Hence, the FHREB believes that competent children in these situations should be permitted to judge for themselves whether they will participate in this type of research by consenting on their own behalf.

NOTE: *Currently, the law is unsettled regarding whether children who are mature enough to have the capacity to consent can be legally competent to actually consent to no-benefit/minimal risk research. If investigators believe strongly that the competent child's consent should NOT be sought (i.e., that their parent/guardian should solely consent on their behalf), they may petition the FHREB for this.*

5.0 Procedures for Obtaining Assent

Researchers must determine the willingness to participate in research of prospective subjects/participants who are legally incompetent but who have the capacity to assent. This must always involve a face-to-face interview and dialogue between the prospective subject and the principal investigator or his or her delegate. This interview must convey the main information contained in the consent form using concepts and terms that are developmentally and cognitively appropriate. In many circumstances, it will be appropriate to supplement this discussion by giving a prospective subject a written assent form to review. Sections 5.1 and 5.2 include guidelines and procedures for preparing

assent forms. These also serve as a checklist for information that is to be conveyed verbally to prospective assenting subjects/participants, including those who cannot meaningfully review a written assent form.

These assent guidelines and procedures are in addition to the procedures for obtaining informed consent. As discussed above, authorized third party consent is a condition of permitting an assenting legally incompetent person's participation in research (see section 3.1).

5.1 Preparation of Assent Forms

Preparation of a separate written assent form will often be required for legally incompetent prospective subjects/participants who are able to review information in this medium. An assent form is recommended for children aged 7-13. An assent form is not normally required for legally incompetent minors who are aged 14-18, since they will usually be cognitively mature enough to read the consent form. A separate procedure for this group is described below. An assent form is not normally required for children under the age of 7 who have the capacity to assent.

An assent form must not be merely a bureaucratic device but must be part of a meaningful process of seeking assent that describes the aims and procedures of the research using concepts and terms that are developmentally and cognitively appropriate. It should explain the research in such a manner that a prospective subject can provide meaningful assent. This must include, in language that the prospective subject can understand:

i) a description of the purpose of the research.

ii) a description of the research procedures and the potential risks, discomforts, and hoped for benefits of participation, including possible benefits to others. The FHREB recognizes that it will often be appropriate to give this information summarily and with less precision than is normally found in a consent form. Nevertheless, the information should not be so scant that subjects/participants are surprised by aspects or consequences of their participation.

iii) a statement of the amount of time that participation in the study will take.

iv) a statement that the subject's confidentiality will be respected (e.g. that the subject's involvement will be kept private and that everyone who is connected with the study is required not to reveal the subject's name or involvement in the study to others.)

v) statements that participation is voluntary, that the subject may refuse to participate at any time without giving reasons, that no one connected with the study will be angry if a decision to leave the study is made after giving assent, and that all other health care will remain available.
vi) statements that the prospective subject has had the opportunity to ask questions, is encouraged to discuss his or her participation with relatives (parents or guardians for children) or friends, and that all questions have been answered.

vii) a statement that questions are encouraged and may be asked at any time.

viii) a place for the prospective subject to sign and date his or her assent. (The principal investigator, witness, and authorized third party are not required to sign the assent form. There will be an assent statement in the consent form that eliminates the need for this. See section 5.5.)

Phrases such as "will you help me?" or "we would like your help with this" are not permitted in an assent form since children are unlikely to refuse. It is best simply to ask the child if he or she would like to participate.

Prospective subjects/participants who dissent from participation must not be required to sign any document stating that they refuse to participate in research.

The assent form should be as brief as reasonably possible, and no longer than two pages using at least a 12-point font. Merely technical information, such as the name of the sponsor, disclosure of an investigator's financial interests, advice that legal rights are not limited by participating, etc., can typically be omitted. The subject must receive a copy of the assent form and have had adequate time to review it and to discuss it with relatives or friends and the principal investigator (or delegate) prior to assenting.

5.2 Special Requirements for Preparing Assent Forms for Children Aged 7-13

When preparing assent forms for children it is especially important to convey information that is sensitive to their perspectives on the procedures, risks, discomforts, and inconveniences that they will encounter. For example, it may be appropriate to explain to children what they will experience simply by being in a hospital, for example, that they will be in a room with other children, that they will have to spend most of their time in a hospital bed and will not be able to get up and walk around without immediate supervision (or that they will be able to walk around unsupervised), that their parents will not be able to be with them all the time, that they will spend a certain number of nights away from home, that they will be looked after by nurses and doctors, etc. Also, it will typically be appropriate to describe how the research procedures will change how they feel or look, for example, that a medication will make them dizzy or itchy, or that they will be connected by tubes to a machine, or that they will have a scar and what it will look like.

5.3 Obtaining Assent from Children under 7

Children who are under 7 years old and who are capable of assent will not normally be capable of reviewing an assent form. However, the guidelines described in sections 5.0, 5.1, and 5.2 should be observed in seeking their assent.

5.4 Obtaining Assent from Legally Incompetent Subjects/participants Aged 14 and Above

Consent forms are supposed to be written for approximately a grade 7 level of reading comprehension. In practice, this is often optimistic. However, many prospective incompetent subjects/participants who are 14 years and older should not have difficulty reading the consents that are prepared for competent subjects/participants to sign. Where this is the case, it is not necessary to provide a written assent. A separate page where the legally incompetent subject can sign and date his or her assent is required to be added to the consent form. The signature should appear beneath the following standard, required text:

I have had the opportunity to read this consent form, to ask questions about my participation in this research, and to discuss my participation with my parents/guardians. All my questions have been answered. I understand that I may withdraw from this research at any time, and that this will not interfere with the availability to me of other health care. I have received a copy of this consent form. I assent to participate in this study.**

(**Substitute appropriate wording if the subject is 19 or older.)

The FHREB does not require this statement to be signed by the authorized third party, a witness, and the principal investigator or delegate, since they must sign the consent form as a condition of the legally incompetent assenting subject's participation in research, and the consent form will contain an acknowledgement that the subject assents.

5.5. Standard Wording For Assent Statement in Consent Forms Signed by an Authorized Third Party (e.g. Parent or Guardian)

The following paragraph is required to appear in the consent form in cases where the subject assents to participate in the research:

The parent(s)/guardian(s) and the investigator are satisfied that the information contained in this consent form was explained to the child** to the extent that he/she is able to understand it, that all questions have been answered, and that the child** assents to participating in the research.**

(**Substitute appropriate wording if the research subject is not a child.)

Inclusion of this statement in the consent form places the obligation on the authorized third party, who is providing consent, and on the investigator to ensure that the subject/child assents and understands the information in the consent form to the extent that he/she is able.

A separate assent document with wording aimed at the level of the potential subject may also be appropriate and is not precluded by the addition of this statement to the consent form.

6.0 Prospective Subjects/participants Capable of Assent But Who Neither Assent Nor Dissent

The FHREB recognizes that in some circumstances prospective subjects/participants may technically have the capacity to assent, but they may not clearly express a preference in favour of or against participating in the research after the procedures described in section 5.1 have been administered. Such prospective subjects/participants should not automatically be precluded from participation, but caution and special care must be exercised to ensure that there are sufficient grounds to include these participants in the research. Some guidelines include:

(i) an attempt must be made to determine what the subject would have chosen when he or she was competent (if relevant). If the subject when competent would have dissented, this is sufficient to preclude participation.

(ii) consideration of what is in the subject's best interests.

(iii) consideration of the degree of risk and prospect of benefit from participation for the prospective subject.
(iv) consideration of whether the intervention involved in the research holds a prospect of an important benefit to the health or well-being of the subject and is only available in the context of the research.

(v) authorized third party consent is required in all such cases, as per TCPS 2 Article 3.9, 3.10, and 4.6.

(vi) where the subject clearly expresses his or her dissent after being included in the

research, this must be respected. The subject must be informed of this continuing right to dissent as soon as possible after a decision is made to include him or her in the research.

(vii) where the prospective subject is included in the research, the principal investigator or his or her delegate shall document the assent procedures that were followed, the prospective subject's responses, and the rationale for including the subject in the research.

(viii) prospective subjects/participants shall not be required to sign any document stating that they do not assent or dissent.

(ix) the assent statement referred to in section 5.5 shall be struck from the consent form, if it is previously included there, where these individuals are included in the research.

7.0 Summary of Procedures under This Policy

Obtaining Assent from Children under 7	**Obtaining Assent from Children Aged 7-13**	**Obtaining Assent from Individuals Aged 14 and above**	**Individuals Capable of Assent Who Neither Assent Nor Dissent**
- follow guidelines from section 5.0, 5.1 and 5.2 for verbal interview with prospective assenting subject. - assent form not normally required. - assent statement to be included in consent form (see section 5.5)	- follow guidelines from section 5.0, 5.1, and 5.2. for verbal interview with prospective assenting subject. - assent form normally required in conformity with section 5.0, 5.1, 5.2. Subject should have sufficient opportunity to read, digest, and discuss this document with family and the PI or delegate prior to assenting. The assent	- assent form not normally required. - prospective assenting subject is given standard opportunity to read the consent form and to review it with family or friends and the PI or delegate. - assenting subject signs assent statement that is attached to the consent form (see section 5.4). - assent statement to	- effort has been made to obtain assent as per this policy. - follow guidelines from section 6.0.

	form accompanies the verbal interview. - assent statement to be included in consent form (see section 5.5).	be included in consent form (see section 5.5).	

A *reminder*: This table summarizes procedures for obtaining assent from different classes of legally incompetent subjects/participants. It is based on standard, but defensible, presumptions about age-related levels of cognitive ability and development. As such, the table cannot be followed rigidly. It may be appropriate, for example, to provide a written assent for prospective subjects/participants over the age of 14 who lack the cognitive ability to meaningful review a consent form (for example, certain mentally impaired persons); or there may be cases where a prospective subject between 7 and 13 years old, or over the age of 14, is incapable of meaningfully reviewing an assent form (for example, illiterate or mentally impaired persons); or there may be the rare case of a 6 year old who can meaningfully review an assent form. In all instances, the assent procedures to be followed are determined by the prospective subject's level of cognitive development and ability.