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# GUIDANCE NOTES FOR REQUEST FOR AMENDMENT OF A PREVIOUSLY APPROVED RESEARCH STUDY

## INTRODUCTION

The FHREB policies/procedures correspond to, and therefore comply with, the current version of the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans (TCPS 2), specifically Article 6.16 which states that "Researchers shall submit to their REBs in a timely manner requests for substantive changes to their originally approved research. REBs shall decide on the ethical acceptability of those changes to the research in accordance with a proportionate approach to research ethics review."

The Principal Investigator is responsible for ensuring all required amendments are submitted to the FHREB and approved prior to implementation. Changes to the study design, procedures, or documents are implemented prior to FHREB approval are considered protocol deviations. A Protocol Deviation Form must be submitted in such cases where study changes were implemented without appropriate approval.

Amendments should only be submitted for review AFTER the study has received initial approval from the FHREB. Changes to study documents prior to initial approval are permitted as part of a response to a modifications or deferral notice. Such changes are required to be listed and explained in the Researcher Response Form

The following guidance notes are intended to ensure the applicant has the necessary information to complete the Amendment request section of the Integrated Post-Approval Application Form.

## GUIDANCE NOTE #1: WHEN IS AN AMENDMENT REQUIRED?

New study documents must be submitted as a study amendment and approved prior to use. Similarly, changes to the previously approved study documents must be approved by the FHREB prior to implementation, including changes to:

1. The protocol/proposal
2. The consent form(s)
3. The data collection tool(s)
4. Recruitment materials
5. Any other documents that would be given to or read by the participants,

Other changes that must be submitted for amendment include:

1. The study design
2. Study procedures, such as recruitment or consent
3. Administration changes to contact information, funding, study sites, co-investigators, etc.

### 1.1 Exceptions to the above requirements

#### 1.1.1 Changes to eliminate immediate hazards

With respect to clinical trials, the ICH Good Clinical Practice (ICH GCP) Guidelines[1] Article 3.3.7 states:

"…no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favourable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g. change of monitor(s), telephone numbers(s))". Such changes should, however, be submitted to the FHREB as a study amendment as soon as possible.

### 1.2 Changes that do not require amendment submission

#### 1.2.1 Documents that should be submitted for acknowledgement

The following study documents that do not require an amendment submission when changed or newly issued, but should instead be submitted as a **request for acknowledgement**:

1. Updated investigator brochures or product monographs (unless these changes require and are accompanied by amendments to the protocol and/or consent forms)
2. Administrative letters from the study sponsor; and
3. Safety data reports;

Please refer to the FHREB GUIDANCE NOTES FOR ACKNOWLEDGEMENT REQUESTS for more information.

#### 1.2.2 Changes that do not require submission to the REB

Changes to study documents that are not given to/seen by the participants and not normally required for ethics review, such as clinical trial source documents, SOPs, or instructions for CRF completion, etc., do not require submission for amendment.

#### 1.2.3 Changes that should be submitted as new initial submissions

Rollover studies, open-label extension studies, and other studies requiring a distinct protocol will general not be considered as an amendment and should instead be submitted as new submissions.

## GUIDANCE NOTE #2: HOW TO SUBMIT AN AMENDMENT

The Principal Investigator or designate must complete Section A (Amendments) of the Integrated Post-Approval Form for Amendments, Renewals, Close-Outs, Acknowledgements of Previously Approved Research, and submit to REB@fraserhealth.ca, along with all new and/or revised study documents.

New documents must be clearly identified as such in the application form, and be labeled with a version number and date. Revised documents must have an updated revision number and date and all changes must be clearly highlighted or tracked in some fashion.

Incomplete submissions or submissions in which the changes to revised documents are not clearly highlighted will be returned to the Principal Investigator.

All study documents should be closely inspected prior to amendment submission to ensure that all necessary documents are appropriately revised. E.g., if the study procedures have been amended in the protocol, the consent forms should also be amended to include this information.

Major Amendments for industry-sponsored studies submitted for initial review on or after January 1, 2021 are subject to a review fee of $250.

## GUIDANCE NOTE #3: MAJOR VERSUS MINOR AMENDMENTS

Major amendments are defined as the following: any change to the study design and documentation that impacts the assessment of potential risk to participants. The following are considered major amendments:

- Changes that require review at a full board meeting as they are funded or supported by the US Federal government or are subject to the regulations of the US Food and Drug administration (21 CFR Part 56 Subpart C, Section 56.110);
- Any amendment that requires notification of and/or approval from Health Canada;
- Addition of genetic testing, new genetic tests, or tissue banking where genetic testing may/or will be performed;
- Changes to the design or methodology of the study, or to background information affecting its scientific value;
- Changes to the procedures undertaken by participants;
- Any change relating to the safety or physical or mental integrity of participants, or to the risk/benefit assessment for the study;
- Significant changes to study documentation such as participant information sheets, consent forms, questionnaires, letters of invitation, letters to GPs or other clinicians, information sheets for relatives or careers;
- A change of sponsor(s) or sponsor's legal representative;
- A change to the insurance or indemnity arrangements for the study;
- Appointment of a new principal investigator at a trial site in a clinical trial of investigational medicinal product;
- Temporary halt of a study to protect participants from harm, and the planned restart of a study following a temporary halt;
- A change to the definition of the end of the study;
- Any other significant change to the protocol or the terms of the REB application.

Minor amendments include the following:

- Addition of or changes to the Co-Investigator(s);

- Changes to contact details for the sponsor, PI, or other study staff member;
- Changes in funding arrangements;
- Changes in the logistical arrangements for storing or transporting samples;
- Extension of the study beyond the period specific in the application form; and
- Inclusion of new sites and investigators in a clinical trial of investigational medicinal product;
- Minor administrative changes to the protocol or other study documentation, e.g. correcting errors, updating contact points;
- Changes to the research team at trial site(other than PI);
- Other materials given to participants (bags, birthday cards, expense forms, coffee mugs, newsletters, dosing diary, etc.);
- Changes in the documentation used by the research team for recording study data.

## GUIDANCE NOTE #4: LEVEL OF REVIEW

Any amendment must be submitted using the Integrated Post-Approval Application form. The FHREB will decide on the ethical acceptability of substantive changes to the originally proposed research in accordance with a proportionate approach to research ethics review.

Amendments that do not substantially increase the level of risk will normally be reviewed under the delegated review process. Timelines vary in accordance with current volumes.

### 4.2 Full Board Review

Amendments that increase the level of risk or that meet the criteria for full board review in accordance with the FHREB Guidance Notes for Initial Ethical Review, will be referred to full board review. The FHREB reserves the right to refer any amendment to full board review for any reason.

If full board review of a study amendment is required by a regulatory body or sponsor, it is the Principal Investigator's responsibility to indicate this on the amendment application form.

#### 4.2.1 Health Canada regulated studies:

Health Canada requires the following types of amendments to regulated clinical trials [drug, device, natural health product] be referred to the Full Board for review:

1. Addition of genetic testing, new genetic tests or tissue banking where genetic testing may or will be performed;
2. Emergency amendments that arise because of safety concerns and that are submitted after implementation as a result, and;
3. amendments to the protocol that affect the selection, monitoring or dismissal of a clinical trial participant;
4. amendments to the protocol that affect the evaluation of the clinical efficacy of the drug;
5. amendments to the protocol that alter the risk to the health of a clinical trial subject;
6. amendments to the protocol that affect the safety evaluation of the drug;

7. amendments to the protocol that extend the duration of the clinical trial; and
8. amendments to the chemistry and manufacturing information that may affect the safety or quality of the drug.

### 4.2.2 Studies sponsored by the United States Department of Health and Human Services

Studies sponsored by the United States Department of Health and Human Services (DHHS) (e.g. NIH and its related institutes including NCI, U.S. Centre for Disease Control) may require Full Board Review under 45 CFR 46.109 (e) and 46 CFR 110 (Code of Federal Regulations).

### 4.2.3 Studies sponsored by other United States federal agencies

Studies that are funded by other American federal agencies (e.g. United States Department of Defence) may require Full Board Review under 21 CFR 56.110.

Refer to the following link for guidance on the interpretation of 21 CFR 56.110 as it applies to studies with this funding source.

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm.

## GUIDANCE NOTE #5: CHANGE OF PRINCIPAL INVESTIGATOR

In order to change the Principal Investigator, the amendment section of the Integrated Post-Approval Application Form (section A) should be submitted, along with the Change of Principal Investigator Application Form, and any other documents that require amending (e.g., consent form, recruitment materials, etc.).

**The Integrated Post-Approval Application Form must be signed by the original Principal Investigator, and must list all changes to the study and study documents.**

The new Principal Investigator must sign the Change of Principal Investigator Form, as well as the new Principal Investigator's Administrative Supervisor. This form is required to provide the appropriate contact information for the new Principal Investigator, document the new Principal Investigator's attestation to abide by the Tri-Council Policy, and declare any conflict of interest that may arise from assuming this role.

## GUIDANCE NOTE #6: CHANGES AFFECTING PARTICIPANT SAFETY

Changes that affect participant safety, such as changes to the study risks, eligibility criteria, monitoring procedures, etc., should be detailed in section 2.a of the Amendment section of the Integrated Post Approval Application Form. The rationale for these changes should also be provided in this section.

## GUIDANCE NOTE #7: CHANGES AFFECTING SCIENTIFIC INTERPRETABILITY

Changes that affect the scientific interpretability of the study, such as changes to research objectives, sample size, analysis plans, etc., should be detailed in section 2.b of the Amendment section of the Integrated Post Approval Application Form. The rationale for these changes should also be provided in this section.

## GUIDANCE NOTE #8: ADMINISTRATIVE CHANGES

Administrative changes, such as changes to the investigative team or funder, changes to the study title, new recruitment materials, minor wording changes in questionnaires, and any other changes that do not affect the safety or scientific interpretability of the study should be listed in section 2.c of the Amendment Section of the Integrated Post Approval Application Form. The rationale for these changes should also be provided in this section.

N.B. that changes to the funding agency or sponsor, including name changes, and to the investigator listings, require amendment to the consent form.

## GUIDANCE NOTE #9 PRINCIPAL INVESTIGATOR'S SIGNATURE

The Principal Investigator or designate must sign the Integrated Post Approval Form. Amendment submissions that do not include this signature will be returned to the Principal Investigator and/or main contact.

## GUIDANCE NOTE #10: NOTICE OF DECISION

All Certificates and Notices will be issued to the Principal Investigator and main contact. The current main contact should be listed on the Integrated Post Approval Application Form to ensure this information is up to date.
Approved amendments will be issued a certificate of approval. All new or amended study documents will be listed on this certificate.

If the FHREB requires changes to the study prior to the approval of the amendment, a modifications memo or deferral notice will be issued to the Principal Investigator and main contact.

## GUIDANCE NOTE #11: RE-CONSENT

For amendments that require changes to the study consent form, the amendment application must indicate whether already-enrolled participants will be re-consented. A justification of the decision whether to re-consent should be provided. If participants will not be re-consented, a justification of this decision and explanation of how participants already enrolled in the study

will be informed of the changes must be provided in section 1.c of the Amendment Section of the Integrated Post-Approval Application Form.

### 11.1 Additional Information About Risks

The notification of a new risk(s) must be documented in a revised consent form for new participants. Depending on the nature of the risk the FHREB may require that participants already enrolled in the study be re-consented.

### 11.2 Change in Industry Sponsor

The FHREB may request that participants already enrolled are asked to re-consent when significant changes are made in the sponsorship of the research.

Re-consenting participants may be considered by the FHREB for studies that involve tissue/DNA banking when the sponsor has changed or a different storage facility is used to store the participants' specimens.

## GUIDANCE NOTE #12 AMENDMENTS SUBMITTED WITH A REQUEST FOR ANNUAL RENEWAL

If necessary, amendments may be submitted at the same time as the request for renewal, using the Integrated Post-Approval Application Form. However, the amendment may be processed separately from the annual renewal if deemed necessary by the FHREB.

## GUIDANCE NOTE #13 APPROVAL PERIOD FOR AMENDMENTS

The term of the approval for the amendment expires at the same time as the initial approval/annual renewal for the study.