Standard Operating Procedures
Research Ethics
Researcher / Research Team Manual

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SECTION 1: Preparatory Activities for the Conduct of Clinical Research

SOP-01 Organizing a Site for Clinical Research

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Appendix 1 –Essential Documents for the Conduct of a Clinical Study

1. Policy
   In accordance with the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonisation (ICH), this standard operating procedure (SOP) provides a general overview of the necessary organizational elements and of the planning of clinical studies conducted by a research team.

   This SOP concerns all institutional personnel working in clinical research and should be followed by all those working on clinical studies involving human participants.

2. Objective
   The objective of this operating procedure is to describe procedures to be followed to ensure proper organization of the clinical study site.

3. Procedures
   When organizing a clinical study site, elements to take into account are: personnel related to clinical studies, location, protocol-related budgets and contracts, location and management of study medication and instrumentation, interactions with other departments and with the Ethics Committee and the use of outside resources.

3.1 Research Team Creation
3.1.1 The investigator should ensure that each clinical study is conducted according to GCP and should possess the knowledge, training and expertise required to properly complete the study (ICH 4.1.1). Moreover, should ensure that each person participating in the study is adequately trained regarding the protocol, investigational products and study-related tasks (ICH 4.2.4 & SOP 03).

3.1.2 In preparation for a clinical study, it is advisable that the investigator or his/her delegate:

I. Appoints, before submitting research proposal to the Ethics Committee, members of the research team who will be involved in the study;

II. Determines, at the beginning of the study, each team member’s roles and the availability of relief personnel;

III. Identifies team members who need GCP training;

IV. Schedules training in protocol content and application;

3.1.3 The investigator or his/her delegate should maintain a list of appropriate qualified persons to whom he has delegated significant study-related duties (ICH 4.1.5 & SOP 02).

3.2 Study Protocol Feasibility Assessment

3.2.1 In the case of clinical studies initiated by a sponsor or sponsor-investigator, a confidentiality agreement between the sponsor or sponsor-investigator and the investigator/qualified investigator, should be signed and dated. This document confirms the commitment of the investigator/qualified investigator and the research team regarding the confidentiality of study information. This document is generally signed prior to receiving the protocol. The institution/investigator often requires review of the confidentiality agreement by a legal advisor, before signing. A signed and dated copy of this agreement should be kept with the study-related essential documentation.

3.2.2 An assessment of the feasibility of a protocol should be completed in order to determine the organizational needs of the study site. The main issues to consider are the technical and ethical feasibility of the protocol, compatibility with local medical practice, access to the target population, time required and availability of the research team. In order to conduct the study, some other factors may need to be taken into account (SOP 05).

3.2.3 The investigator should also make certain that systems and procedures are implemented to ensure the quality of all aspects of the clinical study.

3.2.4 Before beginning each clinical study, the investigator should obtain approval from a Research Ethics Committee (SOP 07 and 08).
3.3 Research Team Location and Needs

3.3.1. A sufficient number of facilities should be available to interview and examine study participants and securely store study material, medication and instrumentation if necessary (SOP 17).

3.3.2. A secure space with restricted access should be provided in order to ensure the confidentiality of study-related data and documents as described in SOP 22, 23 and 25.

3.3.3. Procedures for the archiving of study-related documentation should be discussed and defined from the start.

3.3.4. When evaluating study protocols, liaison with other institutional services such as radiology, laboratories, pharmacy or outside services, if necessary, should be planned. The research team should have access to a list of contacts or replacements, for those services.

3.3.5. The research team should have access to a list of contacts for the Research Ethics Committee for study-related submissions or questions.

3.3.6. In the case of clinical studies involving investigational products (drugs) their storage must be at the pharmacy. A pharmacist responsible for their management should be appointed. Procedures for the destruction of investigational products (drugs) should also be evaluated if this is to take place within the institution.

3.3.7. In the case of clinical studies involving medical devices, biological products or radiopharmaceuticals, secure and adequate space for their storage and conservation should be allocated. A person responsible for their management should be appointed. Procedures for the destruction of medical devices, biological products or radiopharmaceuticals should also be evaluated if this is to take place within the institution.

3.3.8. If applicable, secure space for local data management should be set up as described in SOP 23 and 25.

3.4 Budget and Financial Contract

The health institution should be aware of the financial implications of any research in which it is participating. The institution should also agree to cost-sharing rules between budgets allocated to research and their own.

It is the institution’s responsibility to specify its own guidelines regarding contracts and the reimbursement of direct and indirect costs associated with the use of their facilities. The institution is required to comply with the Ministerial decree regarding indirect costs to be reimbursed and management of the resulting funds (Translated from, FRSQ, part 1, section 1, Extracted from the Code of Conduct for Research and Scientific Integrity, 1.3 – Research Management, 1.3.4 and 1.3.5).
Many contractual documents have to be completed during clinical studies. For example:

3.4.1 Document confirming that the investigator will be conducting the clinical study according to the protocol approved by the sponsor or sponsor-investigator and to which the Research Ethics Committee along with, if necessary, regulating authorities have given their approval or a favourable opinion. The investigator/institution as well as the sponsor or sponsor-investigator should sign the protocol, or any other contract, to confirm the agreement (ICH 4.5.1).

3.4.2 Document confirming the sponsor investigator’s responsibility to respect the Declaration of Helsinki and the ICH GCP.

3.4.3 Documents regarding agreements between sponsor, investigator/qualified investigator, institution, CRO and authorities on the financial aspects of the clinical study, if required. These documents should be signed and dated prior to each clinical study and kept with the study-related essential documentation (ICH 8.2.4).

These documents may include the following details:

I. Fees for the sponsor-investigator, investigator/qualified investigator or other research team members;
II. Payment per research participant or visit;
III. Payment for research participants having completed the study;
IV. Payments schedule;
V. Reimbursement of expenses to research participants.

3.5 Study-Related Essential Documentation Management

Essential documents are documents that, separately or with others, allow evaluation of the conduct of a clinical study and of the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of GCP and with all other applicable regulatory requirements (ICH – 8.1, Introduction).

There is a link between the management of documentation and efficient study management. Some of the documents included in the list of study-related essential documents of ICH sections 8.2., 8.3 and 8.4 will be used for the submission of the study to different regulatory authorities or will be examined by regulatory organizations within the framework of the study validation process. Therefore, these documents should be available for this purpose.

Study-related essential documents should be provided for each clinical study (with or without investigational product or instrumentation) submitted to the Research Ethics Committee. These documents are organized in three sections.
according to the time they have to be produced: before, during and at the end of the study. {See Appendix 1, Clinical Study Related Essential Documentation, ICH 8.2, 8.3 and 8.4.}

4. References


Fonds de la recherche en santé du Québec (FRSQ), Guide d’éthique de la recherche et d’intégrité scientifique, Standards en éthique de la recherche et en intégrité scientifique du FRSQ (2e édition), août 2003

SOP 02, Research Team: Role Definitions, Responsibilities and Task Delegation

SOP 03, Site Research Team: Competence, Knowledge and Training

SOP 05, Study Feasibility Assessment

SOP 07, Protocol and Protocol Amendment, Submission for Review by the Research Ethics Committee

SOP 08, Consent Process and the Informed Consent Document

SOP 17, Managing Investigational Products, Biological Products, Medical Devices and Radiopharmaceuticals Under Study

SOP 23, Clinical Data Management, Paper or Electronic Format

SOP 25, Security and Confidentiality of Data
8.2 **Before the Clinical Phase of the Study Commences**

During this planning stage, before the study formally starts, the following documents should be generated and filed.

<table>
<thead>
<tr>
<th>Document Title</th>
<th>Purpose</th>
<th>Located in Files of</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.2.1 Investigator's Brochure (if applicable)</td>
<td>To document that relevant and current scientific information about the investigational product has been provided to the investigator</td>
<td>X</td>
</tr>
<tr>
<td>8.2.2 Signed protocol and modifications, if any, and sample case report form (CRF)</td>
<td>To document investigator and sponsor agreement to the protocol / modification(s) and CRF.</td>
<td>X</td>
</tr>
<tr>
<td>8.2.3 Information given to study subject</td>
<td></td>
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<tr>
<td>- Informed consent form (including all applicable translations)</td>
<td>To document the informed consent</td>
<td>X</td>
</tr>
<tr>
<td>Any other written information</td>
<td>To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent</td>
<td>X</td>
</tr>
<tr>
<td>Advertisement for subject recruitment (if used)</td>
<td>To document that recruitment measures are appropriate and not coercive</td>
<td>X</td>
</tr>
<tr>
<td>8.2.4 Financial aspects of the study</td>
<td>To document the financial agreement between the investigator /institution and the sponsor or sponsor-investigator for the study</td>
<td>X</td>
</tr>
<tr>
<td>8.2.5 Insurance statement (where required)</td>
<td>To document that compensation to subject(s) for study-related injury will be available</td>
<td>X</td>
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<tr>
<td>8.2.6 Signed agreement between involved parties, e.g.:</td>
<td>To document agreements</td>
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<td>- Investigator /institution and sponsor or sponsor -investigator</td>
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<td>- Investigator/Institution and CRO</td>
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<td>- Sponsor or sponsor -investigator and CRO</td>
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<td>X</td>
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<tr>
<td>- Investigator/ Institution and authority(ies) (where required)</td>
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<td>X</td>
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<tr>
<td>Document Title</td>
<td>Purpose</td>
<td>Located in Files of</td>
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<td><strong>8.2.7</strong> Dated, documented approval/favourable opinion of institutional Review Board (IRB) /independent Ethics Committee (IEC) of the following:</td>
<td>To document that the study has been submitted to IRB/IEC review and given approval/ favourable opinion. To indicate the version number and date of the document(s).</td>
<td>Investigator &amp; Institution: X  Sponsor &amp; Sponsor - Investigator: X</td>
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<tr>
<td>o Protocol and any modifications</td>
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<td>o CRF (if applicable)</td>
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<tr>
<td>o Informed consent form(s)</td>
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<tr>
<td>o Any other written information to be provided to the subject(s)</td>
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<td>o Advertisement for subject recruitment (if used)</td>
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<td>o Subject compensation (if any)</td>
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<td>o Any other documents given approval/ favourable opinion</td>
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<td><strong>8.2.8</strong> Institutional review board/ independent ethics Committee composition</td>
<td>To document that the IRB/IEC is constituted in agreement with GCP</td>
<td>Investigator &amp; Institution: X  Sponsor &amp; Sponsor - Investigator: X</td>
</tr>
<tr>
<td><strong>8.2.9</strong> Regulatory authority (ies) authorisation/ approval/ notification of protocol</td>
<td>To document that appropriate authorisation/ approval/ notification by the regulatory authority (ies) has been obtained prior to initiation of the study in compliance with the applicable regulatory requirement(s)</td>
<td>Investigator &amp; Institution: X  Sponsor &amp; Sponsor - Investigator: X</td>
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<td>(where required)</td>
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<td><strong>8.2.10</strong> Curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and sub-investigator(s)</td>
<td>To document investigators qualifications and eligibility to conduct study and/or their competence to provide medical supervision of subjects</td>
<td>Investigator &amp; Institution: X  Sponsor &amp; Sponsor - Investigator: X</td>
</tr>
<tr>
<td><strong>8.2.11</strong> Normal value(s)/range(s) for medical/ laboratory/ technical procedure(s) and/or test(s) included in the protocol</td>
<td>To document normal values and/or ranges of the tests</td>
<td>Investigator &amp; Institution: X  Sponsor &amp; Sponsor - Investigator: X</td>
</tr>
<tr>
<td><strong>8.2.12</strong> Medical /laboratory/ technical procedures /tests</td>
<td>To document that the Investigator/Institution have access to adequate facilities to perform required test(s), and support reliability of results</td>
<td>Investigator &amp; Institution: X  Sponsor &amp; Sponsor - Investigator: X</td>
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<tr>
<td>o Certification or</td>
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<td>o Accreditation or</td>
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<td>o Established quality control and/or external quality assessment or</td>
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<td>o Other validation (where required)</td>
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<tr>
<td><strong>8.2.13</strong> Sample of label (s) attached to investigational product container(s) (where required)</td>
<td>To document compliance with applicable labelling regulations and appropriate instructions were provided to the subjects</td>
<td>Investigator &amp; Institution</td>
</tr>
<tr>
<td><strong>8.2.14</strong> Instructions for handling of investigational product(s) and study-related materials (if not included in protocol or Investigator's Brochure)</td>
<td>To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and study-related materials</td>
<td>Investigator &amp; Institution, Sponsor &amp; Sponsor - Investigator</td>
</tr>
<tr>
<td><strong>8.2.15</strong> Shipping records for investigational product(s) and study-related materials (where required)</td>
<td>To document shipment dates, batch numbers and method of shipment of investigational product(s) and study-related materials. Allows tracking of product batch, review of shipping conditions, and accountability</td>
<td>Investigator &amp; Institution</td>
</tr>
<tr>
<td><strong>8.2.16</strong> Analysis certificate(s) of shipped investigational product(s) (where required)</td>
<td>To document identity, purity, and strength of investigational product(s) to be used in the study</td>
<td>Investigator &amp; Institution</td>
</tr>
<tr>
<td><strong>8.2.17</strong> Decoding procedures for blinded studies (where required)</td>
<td>To document how, in case of an emergency, identity of investigational product can be revealed without exposing the treatment to the remaining participating subjects.</td>
<td>Investigator &amp; Institution, (third party if applicable)</td>
</tr>
<tr>
<td><strong>8.2.18</strong> Master randomisation list (where required)</td>
<td>To document method for randomisation of study population</td>
<td>Investigator &amp; Institution, (third party if applicable)</td>
</tr>
<tr>
<td><strong>8.2.19</strong> Pre-study monitoring report</td>
<td>To document that the site is suitable for the study (may be combined with 8.2.20)</td>
<td>Investigator &amp; Institution</td>
</tr>
<tr>
<td><strong>8.2.20</strong> Study initiation monitoring report</td>
<td>To document that study procedures were reviewed with the investigator and the investigator's study staff (may be combined with 8.2.19)</td>
<td>Investigator &amp; Institution, Sponsor &amp; Sponsor - Investigator</td>
</tr>
</tbody>
</table>
8.3 **During the Clinical Conduct of the Study**

In addition to having on file the above documents, the following should be added to the files during the study as evidence that all new relevant information is documented as it becomes available

<table>
<thead>
<tr>
<th>Document Title</th>
<th>Purpose</th>
<th>Located in Files of</th>
</tr>
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<tbody>
<tr>
<td>8.3.1 Investigator’s brochure updates (if required)</td>
<td>To document that investigator is informed in a timely manner of relevant information as it becomes available</td>
<td>Investigator &amp; Institution</td>
</tr>
<tr>
<td>8.3.2 Any revision to: Protocol/modifications(s) and CRF</td>
<td>To document revisions of these study related documents given effect during the study</td>
<td>Investigator &amp; Institution</td>
</tr>
<tr>
<td>8.3.3 Documented approval/ favourable opinion of institutional review board (IRB)/ independent ethics Committee (IEC) of the following:</td>
<td>To document that the modification(s) and/or revision(s) have been submitted to IRB/IEC review and were given approval/favourable opinion. To identify the version number and date of the document(s).</td>
<td>Investigator &amp; Institution</td>
</tr>
<tr>
<td>8.3.4 Regulatory authority (ies) authorisations/ approvals/ notifications where required for:</td>
<td>To document compliance with applicable regulatory requirements</td>
<td>Investigator &amp; Institution</td>
</tr>
<tr>
<td>8.3.5 Curriculum vitae for new investigator(s) and/or sub-investigator(s)</td>
<td>(See 8.2.10)</td>
<td>Investigator &amp; Institution</td>
</tr>
<tr>
<td>Document Title</td>
<td>Purpose</td>
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</table>
| **8.3.6** Updates to normal value (s)/range(s) for medical/laboratory/technical procedure(s)/test(s) included in the protocol | To document normal values and ranges that are revised during the study (see 8.2.11) | Investigator & Institution: X  
Sponsor & Sponsor - Investigator: X |
| **8.3.7** Updates of Medical / laboratory / technical procedures/tests | To document that tests remain adequate throughout the study period (see 8.2.12) | Investigator & Institution: X  
Sponsor & Sponsor - Investigator: X |
| o Certification or  
o Accreditation or  
o Established quality control and/or external quality assessment or  
o Other validation (where required) | | |
| **8.3.8** Documentation of investigational product(s) and study-related materials shipment | (See 8.2.15) | Investigator & Institution: X  
Sponsor & Sponsor - Investigator: X |
| **8.3.9** Certificate (s) of analysis for new batches of investigational products | (See 8.2.16) | Investigator & Institution: X |
| **8.3.10** Monitoring visit reports | To document site visits by, and findings of, the monitor | Investigator & Institution: X |
| **8.3.11** Relevant communications other than site visits:  
o Letters  
o Meeting notes  
o Notes of telephone calls | To document any agreements or significant discussions regarding study administration, protocol violations, study conduct, adverse event (AE) reporting | Investigator & Institution: X  
Sponsor & Sponsor - Investigator: X |
| **8.3.12** Signed informed consent forms | To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in study. Also to document direct access permission (see 8.2.3) | Investigator & Institution: X  
Sponsor-Investigator: X |
| **8.3.13** Source documents | To document the existence of the subject and substantiate integrity of collected study data. To include original documents related to the study, medical treatment and subject’s history | Investigator & Institution: X  
Sponsor-Investigator: X |
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<tr>
<th>Document Title</th>
<th>Purpose</th>
<th>Located in Files of</th>
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</thead>
<tbody>
<tr>
<td>8.3.14 Signed, dated and completed case report forms (CRF)</td>
<td>To document that the investigator or authorised member of the investigator's staff confirms the recorded observations.</td>
<td>Investigator &amp; Institution: X (Copy)</td>
</tr>
<tr>
<td>8.3.15 Documentation of CRF corrections</td>
<td>To document all changes/additions or corrections made to CRF after initial data recording.</td>
<td>Investigator &amp; Institution: X (Copy)</td>
</tr>
<tr>
<td>8.3.16 Notification by originating investigator to sponsor of serious adverse events and related reports</td>
<td>Notification by originating investigator to Sponsor/Sponsor-Investigator of serious adverse events and related reports in accordance with Item 4.11</td>
<td>Investigator &amp; Institution: X</td>
</tr>
<tr>
<td>8.3.17 Notification by sponsor and/or sponsor-investigator, where applicable, to regulatory authority (ies) and IRB (s)/IEC (s) of unexpected serious adverse drug reactions and of other safety information</td>
<td>Notification by sponsor/sponsor-investigator and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 5.16.2 and 4.11.2</td>
<td>Investigator &amp; Institution: X (where required)</td>
</tr>
<tr>
<td>8.3.18 Notification by sponsor/sponsor-investigator to investigators of safety information</td>
<td>Notification by sponsor/sponsor-investigator to investigators of safety information in accordance with 5.16.2</td>
<td>Investigator &amp; Institution: X</td>
</tr>
<tr>
<td>8.3.19 Interim or annual reports to IRB/IEC and authority (ies)</td>
<td>Provided interim or annual reports to IRB/IEC in accordance with 4.10 and to authority (ies) in accordance with 5.17.3</td>
<td>Investigator &amp; Institution: X (where required)</td>
</tr>
<tr>
<td>8.3.20 Subject screening log</td>
<td>To document identification of subjects who entered pre-study screening</td>
<td>Investigator &amp; Institution: X (where required)</td>
</tr>
<tr>
<td>8.3.21 Subject identification code list</td>
<td>To document that investigator/institution keeps a confidential list of names of all subjects allocated a study number on enrolling in the study. Allows investigator/ institution to reveal identity of any subject</td>
<td>Investigator &amp; Institution: X</td>
</tr>
<tr>
<td>8.3.22 Subject enrolment log</td>
<td>To document chronological enrolment of subjects by study number</td>
<td>Investigator &amp; Institution: X</td>
</tr>
<tr>
<td>8.3.23 Investigational products accountability at the site (if required)</td>
<td>To document that investigational product(s) have been used according to the protocol</td>
<td>Investigator &amp; Institution: X</td>
</tr>
<tr>
<td>8.3.24 Subject enrolment log</td>
<td>To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs</td>
<td>Investigator &amp; Institution: X</td>
</tr>
<tr>
<td>8.3.25 Record of retained body fluids/ tissue samples (if any)</td>
<td>To document location and identification of retained samples if tests need to be repeated</td>
<td>Investigator &amp; Institution: X</td>
</tr>
</tbody>
</table>
8.4 After Completion or Termination of the Study

After completion or termination of the study, all documents identified in sections 8.2 and 8.3 should be filed together with the following:

<table>
<thead>
<tr>
<th>Document Title</th>
<th>Purpose</th>
<th>Located in Files of</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>8.4.1 Investigational product(s) accountability at site (if required)</strong></td>
<td>To document that the investigational product(s) have been used according to the protocol. To document the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor/sponsor-investigator.</td>
<td>Investigator &amp; Institution: X, Sponsor &amp; Sponsor - Investigator: X</td>
</tr>
<tr>
<td><strong>8.4.2 Documentation of investigational product destruction (if required)</strong></td>
<td>To document destruction of unused investigational products by sponsor/sponsor-investigator or at site (If discarded at site)</td>
<td>Investigator &amp; Institution: X, Sponsor &amp; Sponsor - Investigator: X</td>
</tr>
<tr>
<td><strong>8.4.3 Complete subject identification code list</strong></td>
<td>To permit identification of all subjects enrolled in the study in case follow-up is required. List should be kept in a confidential manner and for an agreed upon time</td>
<td>Investigator &amp; Institution: X, Sponsor - Investigator: X</td>
</tr>
<tr>
<td><strong>8.4.4 Audit certificate (if available)</strong></td>
<td>To document that an audit was performed</td>
<td>Investigator &amp; Institution: X</td>
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<td><strong>8.4.5 Study close-out final monitoring report</strong></td>
<td>To document that the study close-out went according to prescribed requirements, and copies of essential documents are held in the appropriate files</td>
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<td><strong>8.4.6 Treatment allocation and decoding documentation (if required)</strong></td>
<td>Document sponsor with any treatment decoding that may have occurred</td>
<td>Investigator &amp; Institution: X</td>
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<td><strong>8.4.7 Final report by investigator to IRB/IEC where required, and where applicable, to the regulatory authority (es) (if required)</strong></td>
<td>To document study completion</td>
<td>Investigator &amp; Institution: X</td>
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<td><strong>8.4.8 Clinical study report</strong></td>
<td>To document results and data study interpretation</td>
<td>Investigator &amp; Institution: X, Sponsor &amp; Sponsor - Investigator: X</td>
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SECTION I: Preparatory Activities for the Conduct of Clinical Research

SOP-02 Research Team: Role Definitions, Responsibilities and Task Delegation

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1. Policy
2. Objective
3. Procedures
   3.1. Role Definitions
   3.2. Description of Responsibilities
   3.3. Tasks Delegation or Role Assignment Descriptions
4. References
5. Appendices

Appendix 1 – Tasks Delegation or Assignment of Responsibilities Form

1. Policy
   Within the framework of the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH), this standard operating procedure (SOP) describes the roles and responsibilities of every member of the research team. It also describes the process of delegation of tasks and responsibilities.

   This SOP concerns all institutional personnel working in clinical research and should be followed by all those working on clinical studies involving human participants.

2. Objective
   The objective of this operating procedure is to identify all members of the research team, to define their roles and responsibilities as well as to document via written procedures, the delegation of tasks and responsibilities.

3. Procedures
   3.1 Role Definitions
   An investigator should be designated for each clinical study. This designated investigator is responsible for the well-being of research participants, the conduct of the study, administration of the investigational product (overall responsibility, management), if applicable, team and space requirements, conformity with the requirements of the Research Ethics Committee and GCP team training. Some of these tasks may be delegated to another team member.
3.1.1 Organization and Management of a Clinical Study:

a) The **Sponsor** is an individual, company, institution or organization which takes responsibility for the initiation, management or financing of a clinical study (ICH 1.53).

b) The **Sponsor-Investigator** is an individual who initiates and conducts (alone or with others) a clinical study, and under whose immediate direction the investigational product is administered to the research participants. The term does not include any person other than an individual (it does not include a corporation or an agency). The obligations of a Sponsor-Investigator include both those of a Sponsor and those of an investigator (ICH 1.54).

3.1.2 Person responsible for the conduct of a clinical study:

a) An **Investigator** is a person responsible for the conduct of the clinical study at a study site. The investigator is the responsible leader of the team and may be called the “principal investigator” (ICH 1.34).

b) A **Qualified Investigator** means the person responsible to the sponsor for the conduct of research at a clinical study site, who is entitled to provide health care under the laws of the province where that clinical study site is located, and who is:

I. In the case of a clinical study respecting a drug to be used for dental purposes only, a physician or dentist and a member in good standing of a professional medical or dental association;

II. In any other case, a physician and a member in good standing of a professional medical association (Health Canada, Food and Drug Regulations, C.05.001).

3.1.3 Roles Delegated in the Course of a Clinical Study:

a) A **Sub-investigator** is any individual member of the clinical study team designated and supervised by the investigator at a study site to perform critical study-related procedures and/or to make important study-related decisions (associate, residents, research fellows, nurses) (ICH 1.56).

b) A **Study Coordinator** is a member of the clinical study team who assumes mainly administrative responsibilities and establishes a liaison between the study site, the Sponsor/Sponsor-investigator and the Research Ethics Committee. Examples of the coordinator’s activities:

I. Ensures the well-being of research participants by providing them with all pertinent information regarding the clinical study;

II. Performs study follow-up and insures compliance with regulations;

III. Prepares the protocol for submission to the Research Ethics Committee;

IV. Coordinates research participant appointments;
V. Coordinates monitoring visits;

VI. Fills in case report forms (CRFs) and makes sure that source documents correspond to CRF entries;

VII. With the authorization of the principal investigator, executes clinical study-related procedures;

VIII. Ensures liaison with hospital departments (laboratory, pharmacy, radiology, etc.).

c) During a clinical study, an active role should be played by the pharmacist. Study medication must be prepared, distributed and stored in the pharmacy according to the product description. Moreover, if necessary, disposal of the study medication can all be managed by the pharmacist.

The investigator (or a person designated by the investigator/institution) should explain the correct use of the investigational product(s), biological product(s), medical device(s) and radiopharmaceutical(s) to each research participant. In addition, verification that each research participant is following the instructions properly should be evaluated at intervals appropriate for the study (ICH 4.6.6).

d) Other parties may be involved in generating clinical study data (e.g., research and testing laboratories, etc.). Some clerical tasks, such as communication with the Research Ethics Committee, may be carried out by office staff. At the request of the investigator/researcher, these parties should be added to the Task Delegation or Assignment of responsibilities form, Appendix SOP03#1 of the present document.

3.2 Description of Responsibilities

3.2.1 The Sponsor, Sponsor-Investigator shall ensure that a clinical study is conducted in accordance with good clinical practices (GCP) and without limiting the generality of the foregoing, shall ensure that:

a) The clinical study is scientifically sound and clearly described in a protocol;

b) The clinical study is conducted, and the research product, if applicable, is used, in accordance with the protocol;

c) Systems and procedures that assure the quality of every aspects of the clinical study are implemented;

d) For each clinical study site, the approval from the Research Ethics Committee is obtained before the clinical study begins at the site;

e) At each clinical study site, there is no more than one qualified investigator;

f) At each clinical study site, medical care and medical decisions, in respect of the clinical study, are under the supervision of the qualified investigator;
g) Each individual involved in the conduct of the clinical study is qualified by education, training and experience to perform his or her respective tasks;

h) Written informed consent, given in accordance with the applicable laws governing consent, is obtained from every person before that person participates in the clinical study AND only after that person has been informed of:

   I. The risks and anticipated benefits to his or her health arising from participation in the clinical study; and

   II. All other aspects of the clinical study that are necessary for that person to make the decision to participate in the clinical study;

i) The requirements respecting information and records set out in section C.05.012 of the Health Canada, Food and Drug regulations are met;

j) If applicable, the drug is manufactured, handled and stored in accordance with the applicable good manufacturing practices under the titles 2 to 4, except for the items articles C.02.019, C.02.025 and C.02.026, (Health Canada, Food and Drug Regulations, C.05.010). The drug must be stored in the pharmacy.

3.2.2 The **Investigator/ Principal Investigator** is ultimately responsible for conducting the clinical study on site. He/she should:

a) Be qualified by education, training, and experience to assume responsibility for the proper conduct of the study, meet all the qualifications specified by the applicable regulatory requirements and provide evidence of such qualifications through up-to-date curriculum vitae and all other relevant documentation requested by the sponsor/sponsor-investigator, the Research Ethics Committee, and the regulatory authorities (ICH 4.1.1);

b) Be thoroughly familiar with the appropriate use of the investigational products, biological products, medical devices and radiopharmaceuticals as described in the protocol, in the current Investigator’s Brochure, in the product information and in other information sources provided by the sponsor/sponsor-investigator (ICH 4.1.2);

c) Be aware of and should comply with, GCP and the applicable regulatory requirements (ICH 4.1.3);

d) Permit monitoring for the clinical study and auditing by the sponsor/sponsor-investigator, and inspection by the appropriate regulatory authorities (ICH 4.1.4);

e) Make certain that:

   I. All persons assisting with the study, are adequately informed about the protocol, investigational product(s), biological product(s), medical device(s) and radiopharmaceutical(s) and their study-related tasks and roles (ICH 4.2.4, SOP 02);

   II. All study related medical decisions are taken (ICH 4.3.1);
III. Adequate medical care is provided to research participants in the case of any adverse event (ICH 4.3.2);

IV. A written and dated approval/favourable opinion from the Research Ethics Committee for the study protocol, written informed consent form, consent form updates, research participant recruitment procedures (e.g., advertisements) and any other written information to be provided to research participants (ICH 4.4.1, SOP 14);

V. The protocol approved by the sponsor/sponsor-investigator and Research Ethics Committee is abided to (ICH 4.5.1, SOP 07);

VI. All accuracy, completeness, legibility, and timeliness of the data are reported to the Sponsor/sponsor-investigator in the CRFs and in all required reports (ICH 4.9.1 & SOPs 22, 23, 24 and 25);

VII. All study documents are maintained up to date as specified in Essential Documents for the Conduct of a Clinical Study (BPC, ICH section 8) and as required by the applicable regulatory requirements (ICH 4.9.4, SOP 01);

VIII. Necessary measures are taken to prevent accidental or premature destruction of essential study documents for a clinical study (ICH 4.9.4, SOPs 22, 23);

IX. All serious adverse events are immediately reported to the sponsor/sponsor-investigator, applicable authorities, as well as to the Research Ethics Committee (ICH 4.11.1, SOP 16).

3.3 Tasks Delegation or Role Assignment Descriptions

3.3.1 To permit an evaluation of the conduct of the clinical study and the quality of the data, the signatures and initials of all persons authorized to make entries and/or corrections on CRFs, should be recorded (ICH 8.3.24).

3.3.2 The investigator should maintain a list of appropriately qualified persons to whom he has delegated significant study-related tasks (ICH 4.1.5).

3.3.3 To meet points 4.3.1 and 4.3.2 of written documentation requirements, the documents used should include:

a) Name of team members in block letters;
b) Sample complete signature and initials of each team member;
c) Tasks specification or roles delegated;
d) Start and end dates of delegation.

Appendix SOP02#1, Tasks Delegation or Assignment of Responsibilities Form, is an example that can be used to meet documentation requirements.
3.3.4 **Investigational Products, Biological Products, Medical Devices and Radiopharmaceuticals Specifications:**

Responsibility for investigational product(s), biological product(s), medical device(s) and radiopharmaceutical(s) accountability at the study site rests with the investigator/institution (ICH 4.6.1);

The investigator should ensure that the investigational products, biological products, medical devices and radiopharmaceuticals are used only in accordance with the approved protocol (ICH 4.6.5);

Where required, the investigator/qualified investigator or institution, should assign the investigational product(s) (drug(s)) accountability at the study site to an appropriate pharmacist (ICH 4.6.2);

In compliance with section 6 – Item 16 of the Ministerial action plan on Research Ethics and Scientific Integrity of the Ministère de la Santé et des Services Sociaux du Québec concerning Experimental Drugs, experimental drugs should be submitted to the same type of control as prescription drugs, in compliance with sections 116 and 117 (Appendix 1) of the Health and Social Services Act.

4. **References**


Ministère de la santé et des services sociaux (MSSS), Plan d’action ministériel en éthique de la recherche et en intégrité scientifique – A6, Les médicaments d’expérimentation, Québec, 1998. (Ministerial action plan on Research Ethics and Scientific Integrity – A6, Experimental Drugs- no translation available).

Quebec, An act respecting health services and social services (R.S.Q., c. S-4.2).

SOP 01, Organizing a Site for Clinical Research.

SOP 07, Protocol and Protocol Amendment, Submission for Review by the Research Ethics Committee

SOP 14, Research Ethics Committee (REC): Ongoing Communications.

SOP 16, Management of Adverse Events – Serious Adverse Events and Adverse Reactions

SOP 22, Source Data and Document Management

SOP 23, Clinical Data Management, Paper or Electronic Format

SOP 24, How to Fill In a Case Report Form and Modify Data

SOP 25, Security and Confidentiality of Data
SOP 2 - Appendix 1
Tasks Delegation or Assignment of Responsibilities Form

Clinical Study Name/Protocol: ___________________________________________________________
Clinical Study Number/ Protocol:_____________________________________________________

Type of tasks or responsibilities:
1. Case report form signature (CRF)
2. Physical exam
3. Subject recruiting
4. CRF entries and corrections
5. CRF process
6. Investigational product administration
7. Other __________________________
8. Other __________________________
9. Other __________________________

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SECTION I: Preparatory Activities for the Conduct of Clinical Research

SOP-03 Site Research Team: Competence, Knowledge and Training

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   3.2. Training
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   Appendix 1 – Training Documentation

1. Policy

Within the framework of the Declaration of Helsinki and in accordance with the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH), this standard operating procedure (SOP) describes the competency and training requirements of personnel involved in conducting a clinical study.

This SOP concerns all institutional personnel working in clinical research and should be followed by all those working on clinical studies involving human participants.

2. Objective

The objective of this operating procedure is to inform all members of the research team of the requirements concerning competence, knowledge and training. This SOP outlines how these requirements are to be documented.

3. Procedures

3.1 Competence and knowledge – Curriculum vitae

It is the duty of the physician in medical research to protect the life, health, privacy and dignity of the human subject (Declaration of Helsinki, B10, 2002).

Medical research involving human participants should conform to generally accepted scientific principles. It should be based on a thorough knowledge of the scientific literature, other relevant sources of information and on adequate laboratory and, where appropriate, animal experimentation (Declaration of Helsinki, B11, 2002).
In agreement with the Declaration of Helsinki, all medical research involving human participants should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human participant must always rest with a medically qualified person and never rest on the research participant, even though the research participant has given consent (Declaration of Helsinki, B15, 2002).

In agreement with ICH principle 2.8, each individual involved in conducting a study should be qualified by education, training and experience to perform his or her respective tasks.

In accordance with ICH principle 4.1.1, the investigator should be qualified by education, training, and experience to assume responsibility for the proper conduct of the study, meet all the qualifications specified by the applicable regulatory requirements and provide evidence of such qualifications through up-to-date curriculum vitae and other relevant documentation requested by the sponsor/sponsor-investigator, the Research Ethics Committee, or the regulatory authorities.

In agreement with ICH principle 4.1.5, the investigator should maintain a list of appropriately qualified persons to whom he has delegated significant study related tasks.

3.1.1 The investigator/qualified investigator, sub-investigators (ICH 8.2.10) and every other person to whom the investigator has delegated related study tasks listed in “Research Team: Roles definition, Responsibilities and Tasks Delegation” (ref. SOP 03) should provide a complete curriculum vitae, dated and signed, available for submission. It is recommended that the curriculum vitae be updated every 2 years.

3.1.2 The submitted curriculum vitae should be kept with the essential documents and be available for verification or inspection.

3.1.3 The curriculum vitae should be up-to-date and include a record of employment, education, experience, professional qualifications, training received including clinical study, e.g. GCP, seminars attended, involvement in clinical studies and, if applicable, teaching experience and publications participation.

While getting ready for the study, the sponsor or sponsor-investigator may often require a proof of the right to practice medicine from the investigator/qualified investigator (license). If applicable, this license may be required annually.

3.2 Training

In agreement with ICH principles, it is required that:

- The investigator know and comply with GCP and regulatory requirements (ICH 4.1.3);
- The investigator be able to rely on an adequate number of qualified employees and adequate facilities for the foreseen duration of the clinical study, in order to conduct it in a safe and appropriate manner (ICH 4.2.3);
• The investigator ensure that all persons assisting with the study are adequately informed about the protocol, investigational product(s), biological product(s), medical device(s), radiopharmaceutical(s) and study related tasks and functions (ICH 4.2.4);

• The investigator ensure that training of the study team in GCP of ICH is documented;

• Training documentation should be kept with the essential study documents and be available for verification or inspection;

• All training related to qualification of research team members involved in the conduct of clinical studies should be documented and kept with the essential study documents; and

• Training documentation should include the title of the training, duration, participant name and training date, the person or organization that provided the training and a summary of the training. The training documentation can be filed individually for every participant or for the whole group. To document group training, an example form is presented in Appendix 1.

4. References


SOP 03, Site Research Team: Competence, Knowledge and Training
## SOP 03 - Appendix 1
### Training Documentation

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**Standard Operating Procedures**

Research / Research Team Manual

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SOP-04 Preparing the Team for a Study

1. Policy

Within the framework of the Declaration of Helsinki and in accordance with the principles inherent with the Good Clinical Practice (GCP) of the International Conference on Harmonisation (ICH), this standard operating procedure (SOP) describes the requirements that the research team should meet in setting up a clinical study.

This SOP concerns all institutional personnel working in clinical research and should be followed by all those working on clinical studies involving human participants.

2. Objective

The objective of this operating procedure is to explain to the research team the processes involved and the requirements that should be met in setting up a clinical study.

3. Procedures

3.1 Preparation – Confidentiality Agreement

In the case of clinical studies initiated by a sponsor or sponsor-investigator, a confidentiality agreement between the sponsor or sponsor-investigator and the investigator, should be signed and dated. This document confirms the commitment of the investigator and the research team regarding the confidentiality of study information. This document is generally signed prior to receiving the protocol. The institution as well as the investigator often request legal advice in the review of the confidentiality agreement, before signing.

3.1.1 A copy of the signed and dated confidentiality agreement should be kept with the essential study documentation.
3.2 **Preparation – Protocol and Investigator’s Brochure**

In agreement with ICH principle 2.2, it is required, before a study is initiated, to evaluate foreseeable risks and inconveniences in relation to the anticipated benefit for the individual study participant and society. A study should be initiated and continued only if the anticipated benefits justify the risks.

3.2.1 **Risk (TCPS, C1):**

3.2.1.1 **Minimal Risk:** no greater than those encountered by the participant in those aspects of his or her everyday life.

3.2.1.2 **Therapeutic risk:** when interventions are required to treat patient’s illness.

3.2.1.3 **Non-therapeutic risk:** arise from actions that go beyond the needs of a patient, and that are incurred only for the needs of the research.

In agreement with ICH principle 5.6.2, the sponsor or sponsor-investigator is required to provide the investigator/institution with the protocol and an up-to-date Investigator’s Brochure and should provide sufficient time for the investigator/institution to review the protocol, and the information provided.

3.2.2 The investigator and the research team should undertake a complete review of the protocol and, in the case of a study with investigational medication, of the Investigator’s Brochure prior to the study initiation.

3.2.3 It is the sponsor/sponsor-investigator’s responsibility to provide the investigator with the above documents. The investigator should verify that the latest versions of these documents have been provided.

3.2.4 According to ICH 5.6.3 principle, the investigator/institution should sign the protocol or another document supplied by the sponsor/sponsor-investigator confirming their commitment to:

a) Conduct the study in compliance with GCP, the applicable regulatory requirements and with the protocol agreed to by the sponsor and given approval/favourable opinion by the Research Ethics Committee;

b) Comply with procedures for data recording/reporting;

c) Permit monitoring, auditing and inspection;

d) Retain the study related essential documents until the sponsor/sponsor-investigator informs the investigator/institution these documents are no longer needed.

3.2.5 A copy of this agreement should be kept with the essential documentation related to the study.
3.3 **Initiation Visit**

In accordance with ICH principle 5.6.1, the sponsor/sponsor-investigator should select the investigators/institutions who will be conducting the clinical study. All investigators should be qualified by training and experience and have adequate resources to properly conduct the study for which the investigator is selected.

3.3.1 In accordance with ICH principle 4.2.4, the investigator should ensure that all persons assisting with the study are adequately informed about the protocol, the investigational products, biological products, medical devices, radiopharmaceuticals and their study-related tasks and functions.

3.3.2 The investigator and all research team members who will be assuming delegated responsibilities should be present during the initiation visit. A written report describing involvement in the initiation visit should be completed and kept with the documentation essential to the study.

3.3.3 In the course of an initiation visit, familiarity with the protocol, objectives and procedures, eligibility (inclusion and exclusion) criteria, knowledge of the investigational products, biological products, medical devices and radiopharmaceuticals, if applicable, GCP and legal obligations of the research team should all be assured. The following specific items can also be discussed during these visits:

a) Management of adverse events and serious adverse events and management of adverse reaction and serious adverse reaction;

b) Investigational products, biological products, medical devices and radiopharmaceuticals management, if applicable;

c) Monitoring and inspection activities;

d) Case report forms;

e) Management of study essential documents;

f) Informed consent process procedures;

g) Data management;

h) Management of biological samples;

i) Any other protocol-specific item.

3.3.4 As described in ICH division 8, *Essential Documents for the Conduct of a Clinical Trial*, sub-section 8.2.19 and 8.2.20, a monitoring report should be filed proving that the facilities are suitable for the conduct of the study and that study procedures have been reviewed with the investigator and personnel responsible for the study.

A copy of this monitoring visit report, written by the sponsor/sponsor-investigator or delegate should be kept with the essential study documentation.
4. References

Health Canada, Guidance for Industry, Good Clinical Practice: Consolidated guideline, ICH Topic E6, 1997

Health Canada, Food and Drug Act– Part C, Division 5, Drugs for clinical trials involving human subjects, August 31 2004


SOP 01, Organizing A Site for Clinical Research, Study Related Essential Documentation Section
SECTION I: Preparatory Activities for the Conduct of Clinical Research

SOP-05 Study Feasibility Assessment

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Appendix 1 – Clinical Study Feasibility Check List

1. Policy

There are no specific directives concerning the feasibility assessment of a clinical study. Common sense and experience should guide our understanding of the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) related to this standard operating procedure (SOP). This SOP is designed to help the research team evaluate a protocol prepared by a sponsor or sponsor-investigator thus allowing them to make a decision regarding the feasibility of the study and whether or not to participate.

This SOP concerns all institutional personnel working in clinical research and should be adhered to by all personnel working on clinical studies involving human participants.

2. Objective

The objective of this operating procedure is to provide the research team with some tools with which to evaluate the feasibility of a clinical study in order to:

- Obtain information about the local feasibility of the study;
- Identify the environment in which the clinical study will be conducted;
- Confirm the study operations schedule;
- Make an informed decision concerning distribution of clinical sites;
- Understand and focus on the target population being recruitment into the clinical study.

3. Procedures

3.1 Clinical Study Assessment
Assessment of study feasibility can be based on a list of questions, the answers to which will allow the investigator to make an informed decision regarding the feasibility of the study at his/her site. The questions, listed in Appendix 1, Clinical Study Feasibility Check List, are the following:

3.1.1 Is this protocol scientifically, technically and ethically feasible?

a) My medical practice field permits me to fulfill my responsibilities according to the requirements of the protocol;

b) This protocol can be conducted in compliance with the local authorities and the requirements of my site;

c) Research participant eligibility criteria are realistic and well defined in the protocol;

e) If required, the comparative investigational product is available in my area;

f) This protocol is consistent with local ethical practices.

3.1.2 Do we have the population targeted by this protocol?

a) Availability of the population targeted for this protocol, has been verified at my site;

b) Competing clinical studies, targeting the same population (same population, same type of study, same time period as other studies, etc.) have been evaluated in my institution;

c) The capacity to recruit the required number of appropriate research participants, within the established time limits, has been checked;

d) According to the protocol, and if required, the number of potential research participants recruited outside my site has been discussed (type of advertisement, etc.) This means an informal discussion has taken place in this regard prior to the initiation of the study;

e) Protocol requirements which have an impact upon the consent of research participants have been evaluated (number of visits, number of hours per visit, etc.);

f) Test or treatment periods have been evaluated taking the calendar and potential holiday periods into account.

3.1.3 Do we have the time?

a. The investigator has sufficient time to personally see and treat (when applicable) research participants;

b. The investigator has sufficient time to supervise the research team;

c. The investigator has sufficient time to ensure that the data recorded in the case report forms (CRFs) and all other required reports are
accurate, complete, legible and submitted rapidly to the sponsor/sponsor-investigator;

d. The investigator has sufficient time to interact with the sponsor, sponsor-investigator and the research team;

e. The investigator has sufficient time to conduct and complete the study appropriately within the established timeframe (ICH 4.2.2).

It is important not to underestimate the involvement of the investigator in the conduct and supervision of a clinical study for which he/she is ultimately responsible.

3.1.4 Are there sufficient resources within the research team?

a. The investigator can delegate some of the medical aspects of the study to sub-investigators;

b. The investigator can delegate a number of significant aspects of the study to coordinators;

c. The investigator should be able to rely on a sufficient number of qualified employees for the anticipated duration of the study in order for it to be properly and safely conducted (ICH 4.2.3);

d. The list of technical and professional personnel required for the study undertaking has been established and all are qualified and available.

e. The budget for the research team has been assessed and is acceptable.

3.1.5 ICH principle 4.2.3 stipulates that the investigator should be able to count on adequate facilities for the expected duration of the study. Do we have access to the necessary facilities and equipment or do we need specific equipment?

a. The working space required for study personnel has been evaluated.

b. The space required for participant recruitment and follow-up has been verified.

c. The space to securely store participants’ study records and clinical study material has been evaluated.

d. All material necessary to the study is available on site.

e. Available medical materials on-site have been verified.

f. Space for storage of the investigational product (pharmacy, etc.) has been coordinated.

g. Local laboratory facilities or other services necessary to the requirements of the protocol have been verified.

h. Communications and/or written agreements with other services, if necessary, have been verified.
i. It is suggested to keep these communications and/or written agreements with the essential study documents as described in SOP 01.

j. The space required for monitoring, auditing or inspecting has been evaluated.

4. References


Quebec, An act respecting health services and social services (R.S.Q., c. S-4.2).

SOP 01, Organizing a Site for Clinical Research.
### Clinical Study Feasibility Check List

<table>
<thead>
<tr>
<th>Protocol Title:</th>
<th>Protocol Number:</th>
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<tr>
<th>Questions</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
<th>Commentaries</th>
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<tr>
<td><strong>Part 1 – Science, technique and ethics</strong></td>
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<tr>
<td>The institution Scientific Committee will evaluate the protocol.</td>
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<td>The protocol is technically feasible.</td>
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<td>The protocol is compatible with the medical field, local authorities and site requirements.</td>
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<td>The protocol admissibility criteria are realistic and well defined in the protocol.</td>
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<td>The comparative product is available in my region.</td>
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<tr>
<td>The protocol is compatible with the local ethical practices.</td>
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<td><strong>Part 2 – Research participants</strong></td>
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<tr>
<td>The targeted population is present at my site</td>
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<tr>
<td>Competitive studies at my site</td>
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<tr>
<td>The number of available subjects to recruit within the time limits is confirmed (medical files, computerized listing)</td>
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<td>Subjects’ availability outside my site (advertising)</td>
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<td>The evaluation of the subjects’ participation agreement vs. the protocol requirements has been completed.</td>
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<td>Treatment or tests period acceptable</td>
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<td><strong>Part 3 – Personnel Availability</strong></td>
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<td>Investigator: available time to see and treat the patients.</td>
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<tr>
<td><strong>Questions</strong></td>
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<td><strong>Commentaries</strong></td>
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<tr>
<td>Investigator: available time to supervise his team</td>
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<td>Investigator: available time to generate, review and submit the study data.</td>
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<td>Investigator: available time to interact with the sponsor.</td>
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<td>Evaluation of the study required qualified personnel.</td>
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<td><strong>Part 4 – Resources</strong></td>
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<td>Evaluation of tasks delegations</td>
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<td>Evaluation of the available personnel vs. the study duration</td>
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<tr>
<td>List of required technical and professional personnel</td>
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<td>Evaluation of the budget (team remuneration)</td>
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<td><strong>Part 5 – Facilities and equipment</strong></td>
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<td>Evaluation of the personnel working space</td>
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<tr>
<td>Evaluation of the subjects’ recruiting and follow-up space</td>
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<td>Evaluation of the space for (secure) storing of the subjects’ study records</td>
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<td>Evaluation of the space for secure storing of the clinical study material</td>
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<td>Available material in line with the protocol requirements</td>
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<td>Available medical equipment in line with the protocol requirements</td>
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<td>Secure preserving space for the investigational product (pharmacy or other)</td>
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<td>Local laboratory compatibility</td>
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<td>Commentaries</td>
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<tr>
<td>Other services compatibility</td>
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<td>Written agreement confirmation with other site services</td>
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<td>Evaluation of the space for monitoring activities or others</td>
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<td><strong>Part 6 – Others</strong></td>
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SECTION I: Preparatory Activities for the Conduct of Clinical Research

SOP-06 Conducting a Study in the Context of a Clinical Trial Application (CTA) in Canada

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1. Policy

This standard operating procedure (SOP) describes Health Canada requirements when submitting an application for a clinical trial involving an investigational product.

This SOP is specifically for the sponsor-investigator who is submitted to the same obligations as the sponsor as described in ICH (principle 1.54). A sponsor-investigator is responsible for implementing, managing and/or financing a clinical trial.

2. Objective

The objective of this SOP is to guide the sponsor-investigator in the conduct of a clinical trial when the trial is the subject of a Clinical Trial Application (CTA) to Health Canada.

Detailed information and forms to be used for a CTA are available on Health Canada’s web site at the following address: http://www.hc-sc.gc.ca
3. Procedures
3.1 Information

Health Canada, Food and Drugs Act and Regulations, controls the sale and importation of drugs for clinical trials in human subjects. Division 5 of Regulations Section C depicts the requirements concerning applications submitted by sponsors-investigators who want to conduct clinical drug trials in humans.

Two important points to remember:

3.1.1 The start date of the trial, which appears on the Clinical Trial Site Information Form is, once the clinical site is chosen, the date when recruitment of research participants is ready to begin.

3.1.2 Prior to starting a study, the sponsor-investigator should establish that Health Canada and the Research Ethics Board did not raise any objections to the CTA. In the case of Phase I to III studies, the notice of conformity from Health Canada (No Objection Letter (NOL)) as well as final written approval from the Research Ethics Committee should have been received before starting the recruitment of clinical trial participants.

3.2 Requirements

In Canada, a Clinical Trial Application (CTA) should be filed before initiating a clinical trial. Health Canada reviews the application and if any deficiencies are detected, should inform the sponsor-investigator within 30 days.

CTAs are required from sponsors-investigators for:

3.2.1 All Phase I to III studies on drug development;

3.2.2 Bioavailability comparison studies;

3.2.3 Clinical trials of marketed drugs whose use exceeds the parameters of the notice of compliance (NC) or the drug identification number (DIN);

3.2.4 If no deficiency is detected and the CTA is considered acceptable, within 30 days, Health Canada issues and sends a notice of compliance (No Objection Letter “NOL”) to the sponsor-investigator. This letter should be kept with the study related essential documentation as described in SOP 01;

3.2.5 Before initiating the clinical trial or clinical trial amendments, the sponsor-investigator should fill out and submit a Clinical Trial Site Information Form. **This form should be filled out for each clinical trial site.**

3.3 Clinical Trial Amendment Application

Amendments to a CTA (CTAM) are requests by which the sponsor-investigator provides information in support of a pre-approved request for modifications (C.05.008). CTA modifications may deal with changes to the clinical trial drug supply (i.e. drug manufacturing process modification), approved protocol amendments (i.e. revised dosage regimen), or both.
Health Canada should approve of the CTA before implementing the modifications (C.05.008).

3.3.1 Should a sponsor-investigator wish to modify a CTA under review, he should withdraw the active CTA and submit another one.

3.3.2 Should a sponsor-investigator have to immediately initiate one or more of the amendments described in paragraph (2) of section C.05.008, because the clinical trial or use of the drug within the study framework of the clinical trial is endangering the health of a research participant or someone else, he/she may do so without waiting for Health Canada’s review. However, he/she should provide Health Canada with the required information, within 15 days of the date of the amendment, according to paragraph (2) of section C.05.008.

3.3.3 The sponsor-investigator should present a CTAM when:
   I. An amendment to the protocol affects the selection, selection criteria, follow-up or withdrawal of a clinical trial participant;
   II. Protocol amendment affects the evaluation of the clinical efficacy of the drug;
   III. Protocol amendment alters the risk to the health of a clinical trial participant;
   IV. Protocol amendment affects the drug safety assessment;
   V. Protocol amendment that extends the duration of the clinical trial;
   VI. Amendments about drug chemistry and manufacturing information that affects the safety or quality of the drug.

3.4 Notification to Health Canada

For amendments to an already approved CTA and CTAM Health Canada should be notified within the following 15 working days even though the amendments may be implemented right away. The following changes warrant a notification:

3.4.1 Changes to the protocol that do not compromise the safety of clinical trial participants and that are not viewed as amendments according to 3.3;

3.4.2 Information about a site closure or completion of a clinical trial;

3.4.3 Premature discontinuation of a trial, at one or all of the study sites, for reasons other than the safety of the trial participants (i.e. administrative, reasons, recruiting problems, etc.);

3.4.4 Changes in data quality (chemistry and manufacturing) that do not affect drug quality or safety, such as:
   I. Pharmaceutical products: increase in production without any change in process;
   II. Narrowing of actual test specifications;
   III. Changes related to research laboratories under contract;
IV. Changes in packaging material;
V. Pharmaceutical products: extension of shelf life;
VI. Pharmaceutical products: all changes to the chemistry and manufacturing of the drug which do not affect its quality or safety according to the criteria described in 3.3.

3.5 Evaluation of a Clinical Trial Amendment Follow-up or Discontinuation

3.5.1 Following regulatory approval of a CTA or CTAM, the sponsor-investigator should present in notification format, all information regarding refusals by other regulatory authorities or Research Ethics Boards.

3.5.2 In the case of discontinuation, at one or all of the selected sites, of a clinical trial for which a CTA or CTAM has been submitted in Canada, the sponsor-investigator should notify the authorities concerned as soon as possible, within 15 days following the date of discontinuation (C05015).

The notification should include the following information:

I. A detailed report of the reasons for discontinuation;
II. A description of the effect of discontinuation on projected or ongoing trials of the drug in Canada;
III. A statement confirming that each qualified investigator has been duly notified of the trial discontinuation and the reasons thereof, and that they have been sent a written notice regarding the potential health risks to research participants or others;
IV. Confirmation that the sale or importation of the drug at each involved trial site has been discontinued;
V. Confirmation that reasonable measures will be taken to ensure the return of all unused drug.

3.5.3 The sponsor-investigator should also notify the appropriate authorities’ of the discontinuation of a clinical trial outside Canada when equivalent trials are being conducted in Canada.

3.5.4 The sponsor-investigator should promptly report to Health Canada any serious, unexpected adverse drug reactions. **Serious but foreseeable reactions, as well as serious adverse events observed in the course of a clinical trial but not considered product related do not require immediate reporting whether expected or not. For more details regarding adverse reactions declaration (SOP 16).**

3.5.5 Once a year or less, the sponsor-investigator should submit an updated Investigator’s Brochure including complete safety data and a general overview of the situation. Additional information and all modifications included in the Brochure should be highlighted. If the Investigator’s Brochure is updated more often it should be submitted accordingly.
3.6 **Records Related to the Clinical Trial Amendment or Clinical Trial Amendment Modification**

3.6.1 The sponsor-investigator should record, manage and preserve all clinical study related information so that complete and accurate reports may be presented, interpreted and audited.

3.6.2 The sponsor-investigator should keep complete and accurate records in order to demonstrate that the clinical trial is conducted in compliance with Good Clinical Practice (GCP) and Health Canada, *Food and Drug Regulations* and to offer guidelines for sponsors of clinical trials who file CTAs.

3.6.3 The sponsor-investigator should keep complete and accurate records on the use of a drug during a clinical trial as describe in ICH section 8.

3.6.4 The sponsor-investigator should retain records for a period of twenty-five years. At Health Canada’s request, these records should be available within 2 days if the use of a drug in the course of a clinical trial causes concern and endangers the health of trial participants. Otherwise, records should be provided within 7 days of receipt of the request.

3.6.5 The retention period for clinical trial related documents (25 years) starts with the document creation date. For practical reasons, it is **strongly recommended that the retention period of the study related documents start on the study completion date**. However, it is important to check with the sponsor, sponsor-investigator, institution or Research Ethics Committee if any specific additional study related requirements exist (i.e. pediatric studies).

3.7 **Research Ethics Committee**

Prior to starting a clinical study or a CTAM at a site, the proposed protocol and the Informed Consent Form should be reviewed and approved by the Research Ethics Committee (REC) as described in Health Canada *Food and Drugs Act*.

3.7.1 The sponsor-investigator should submit to Health Canada the name of the REC that has approved the trial or amendment before the trial or amendment can begin at the selected site. Section C, of the Clinical Trial Site Information form should be completed to that effect.

3.7.2 The sponsor-investigator should keep in the files a statement issued and signed by the Research Ethics Committee which has approved the protocol and according to which he undertakes to fulfill his functions in compliance with *Good Clinical Practices*. The Research Ethics Committee may elect to use Health Canada *Research Ethics Board Attestation* form or create a similar one that meets the conditions of the *Food and Drug Regulations*, Division 5. At the Jewish General Hospital, the REBA is not used, instead all required information in compliance with the conditions outlines by the *Food and Drug Regulations*, Division 5 is included in the approval letter.
3.7.3 The sponsor-investigator should provide Health Canada with specifics regarding any refusal of a protocol or protocol amendment by an REC for any reason whatsoever (C.05.008 par. 1c [II]).

3.7.4 The notice of compliance from Health Canada to a CTA (No Objection Letter “NOL”) must be submitted to the Research Ethics Committee, when applicable.

3.8 Investigators

For each protocol and its clinical trial sites, there is only one qualified investigator per site. Qualified investigators should use the Qualified Investigator Undertaking form or create a similar one that meets the conditions of the Food and Drugs Act, Division 5.

Prior to each clinical study in Canada, the sponsor-investigator should complete:

3.8.1 The Clinical Trial Site Information form. This form should be completed for each clinical trial site and submitted to Health Canada.

3.8.2 The Research Ethics Board Attestation form. The Research Ethics Committee may elect to use this form or create a similar one that meets the conditions of the Food and Drug Regulations, Division 5. This form is to be provided to Health Canada only upon their request.

3.8.3 The Qualified Investigator Undertaking form. The qualified investigator may elect to use this form or create a similar one that meets the conditions of the Food and Drugs Regulations, Division 5. This form is to be provided to Health Canada only upon their request.

4. References


SOP 01, Organizing a Site for Clinical Research

SOP 16, Management of Adverse Events - Serious Adverse Events and Adverse Reactions – Serious Adverse Reactions
Section II  Research Ethics Review Process

SOP 07 - Protocol and Protocol Amendment, Submission for review by the Research Ethics Committee

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5. Appendices
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1. Policies
Within the framework of the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonisation (ICH), this standard operating procedure (SOP) describes the preparation, submission for review of a clinical study protocol or protocol amendment to the Research Ethics Committee. It also describes the obligations to follow ICH GCP as well as applicable national or international regulations.

This SOP concerns all institutional personnel working in clinical research and should be followed by all those working on clinical studies involving human participants.

2. Objectives
One of the objectives of this operating procedure is to ensure that all clinical study protocols or amendments implemented within the institution are in compliance with ICH GCP and any applicable regulations.
A second objective is to ensure that all institutional personnel working in clinical research comply with the protocol or protocol amendment.

Furthermore, this operating procedure is designed to help the sponsor-investigator or investigator prepare and submit a clinical study protocol or a protocol amendment to the REC.

3. Procedures

Flow Chart

**Sponsor**
- Protocol Writing or Protocol Amendment
  - Submission to HPFB/FDA (according to applicable studies)
- Protocol Approved

**Investigator / Qualified Investigator**

**Sponsor-Investigator**
- Writing of Protocol or Protocol Amendment
  - Submission to HPFB/FDA (according to applicable studies)
  - Approval
  - Refusal

**Approval of the Protocol by the REC**

**Submission of the Protocol or Protocol Amendment** to the Research Ethics Committee (REC)

**Refusal of the Protocol by the REC**

**Approved Protocol or Protocol Amendment**
- Study Begins

**New Information Available for Study Participants or for Study Conduct**
- Request for Revision or Protocol Amendment
3.1 Submission of a Protocol by a Sponsor to an Investigator

3.1.1 In preparing to submit the protocol to the REC, the investigator can use Appendix 1, Reference for verification of protocol or protocol amendment and Appendix 2, Confirmation of verification of protocol or protocol amendment in order to ensure that the content of the clinical study protocol or protocol amendment is in compliance with ICH GCP, Section 6. If the Appendices are used, it is recommended that these documents be kept with the essential study documentation as described in SOP 01.

3.1.2 The investigator is responsible for submitting the clinical study protocol or amendment to the REC. This task may be delegated to another clinical study team member. It is recommended that this task delegation be documented as described in SOP 02.

3.1.3 When a clinical trial protocol or amendment has been submitted to Health Canada, FDA, it is strongly recommended that the sponsor be asked to provide the notice of compliance issued by these regulatory authorities. This document should be submitted to the REC (SOP 08).

3.1.4 The investigator is responsible for submitting to the sponsor, all modifications to the protocol required by the REC.

3.2 Writing of a Protocol

3.2.1 The sponsor-investigator is responsible for writing the clinical study protocol or clinical study protocol amendment according to ICH GCP, Section 6. This task may be delegated to another team member and should be documented as described in SOP 02. To facilitate verification, Appendix 1, Reference for verification of protocol or protocol amendment and Appendix 2, Confirmation of verification of protocol or protocol amendment can be used. It is recommended that this verification documentation be kept with the essential study documentation as described in SOP 01.

3.2.2 If the clinical study protocol or protocol amendment is written by another member of the clinical study team or by an external person, the sponsor-investigator is responsible for reviewing the content of the protocol or protocol amendment according to ICH GCP, Section 6. This task may be delegated to another team member and should be documented as described in SOP 02.

3.2.3 In the framework of Phase I, II and III studies with medication or with Class II, III and IV medical instruments, the sponsor-investigator is responsible for submitting the protocol or protocol amendment to national and international authorities, if required. This task may be delegated to another team member and should be documented as described in SOP 02.

3.2.4 The sponsor-investigator is responsible for the incorporation into the protocol, of all modifications or additions required by local or national regulatory authorities.
3.2.5 The sponsor-investigator is responsible for submitting the clinical study protocol or protocol amendment to the REC. This task may be delegated to another team member and should be documented as described in SOP 02.

3.2.6 When a clinical study protocol or protocol amendment has been submitted to Health Canada, FDA, the sponsor-investigator should obtain the notice of compliance issued by these regulatory authorities. This document should be submitted to the REC (SOP 06).

3.2.7 The sponsor-investigator is responsible for the incorporation into the protocol or protocol modification all modifications or additions required by the REC.

3.3 Preparation and Revision of a Protocol or Protocol Amendment

The contents of a study protocol or protocol modification should be in compliance with ICH GCP, Section 6, Study Protocol or Protocol Amendment.

For a Protocol Written by a Sponsor-Investigator

3.3.1 The date and version should be clearly indicated on each page of the protocol or protocol amendment.

3.3.2 Should protocol modifications be introduced or new information become available, a protocol amendment should be written to include this new information. Should that be the case, validated versions of the study protocol or study protocol modification should be retrieved.

3.3.3 Should a third party be required (medical expert) to give an opinion on the study protocol or amendment, the expert’s comments should be kept.

3.4 Submission of a Study Protocol or Protocol Amendment

The sponsor or investigator should submit the study protocol or protocol amendment to be used at the site to the REC.

During the Study:

3.4.1 A protocol amendment dealing with a logistical or administrative change (i.e. change of phone number, auditor, etc.) should be submitted to the REC for informational purposes. However, in these specific cases approval from the REC is not required to continue the study.

3.4.2 Comments (i.e. omissions or additions) from regulatory authorities or the REC should be returned to the principal investigator - the author of the protocol or protocol amendment.

3.4.3 The investigator may add a variation or modification to the protocol in order to eliminate any immediate danger to research participants in the clinical study without the REC’s prior approval. The reason for the variation or modification, and if required, proposed protocol amendments should be presented as soon as possible.

I. To the REC for review and approval;
II. To the sponsor for acceptance;

III. To regulatory authorities by the sponsor-investigator, if required (ICH/GCP 4.5.4).

Safety of Participants

3.4.4 Over the course of a clinical study, it is the responsibility of the sponsor-investigator or investigator, according to the information obtained and possibility of immediate danger to research participants, to stop recruitment until approval is granted by the REC and regulatory authorities, if required.

3.4.5 In case of termination or premature interruption of the clinical study by the sponsor or sponsor-investigator, the investigator/institution is responsible for rapidly informing research participants and ensuring that appropriate treatment and follow-up is provided to them. The investigator/institution should notify the REC and in the case of the sponsor-investigator, if required, the regulatory authorities, providing them with detailed reasons why the clinical study has been interrupted or terminated (ICH/GCP 4.12).

3.5 Approval of a Study Protocol or Protocol Amendment

In the case of a sponsor-investigator

3.5.1 Within the framework of Phase I, II and III clinical studies with medication or with Class II, III and IV medical instruments, the protocol or protocol amendment should first be submitted to national and international authorities. If required, the protocol or protocol amendment is revised according to the requirements of these authorities.

In the case of a sponsor-investigator or an investigator

3.5.2 For each clinical study, the protocol or protocol amendment should be submitted to the REC. The REC’s requests should be sent by the investigator to the sponsor or sponsor-investigator for consideration and validation. The sponsor-investigator revises the protocol or protocol amendment according to the requirements of the REC.

3.5.3 Should protocol modifications be introduced, or new information become available, the protocol or revised protocol should be submitted to regulatory authorities by the sponsor-investigator and to the REC by the investigator.

3.5.4 The sponsor-investigator or investigator should keep the original version of the protocol as well as any protocol amendments. It is suggested that the sponsor-investigator keep and archive every draft of the protocol.

3.5.5 All versions of the protocol or protocol amendments approved in the course of a study should be kept with the study essential documentation according to SOP 01.
4. References

Health Canada, Guidance for Industry, Good Clinical Practice: Consolidated guideline, ICH Topic E6, 1997

Health Canada, Food and Drug Act– Part C, Division 5, Drugs for clinical trials involving human subjects, August 31 2004


Fonds de la recherche en santé du Québec (FRSQ), Guide d’éthique de la recherche et d’intégrité scientifique, Standards en éthique de la recherche et en intégrité scientifique du FRSQ (2e édition), août 2003.

SOP 01, Organizing a Site for Clinical Research

SOP 02, Research Team: Role Definitions, Responsibilities and Task Delegation

SOP 06, Conducting a Study in the Context of a Clinical Trial Application (CTA) in Canada
# Protocol or Investigational Product:

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<th>Version Date:</th>
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<tbody>
<tr>
<td># Amendment Version:</td>
<td>Version Date:</td>
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## Audit Date:

| Quality Auditor: (name in block letters) | Quality Auditor: (signature) |

## ITEMS TO BE INCLUDED ACCORDING TO CHAPTER 6 OF THE ICH GCP

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<td>Protocol title, protocol identifying number and, if applicable, date and number of all protocol modifications (amendments) should also be indicated. ** Add development phase</td>
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<td>Name and address of Sponsor/Sponsor-investigator and Monitor (if other than Sponsor/Sponsor-investigator, ex.: CRO)</td>
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<td>Name, title, address and phone number (s) of the qualified physician who will be responsible for all study related medical decisions</td>
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<td>Name, address and phone number of clinical study site</td>
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<td>1.8</td>
<td>Name (s) and address (es) of clinical laboratory (ies) and other technical department (s) or institution (s) involved in the clinical study</td>
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<td>** List of Abbreviations and Terminology ** Make sure that this list is complete by checking text versus list of abbreviations and list of abbreviations versus text</td>
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<td>Summary of known and potential risks and benefits if any for human subjects</td>
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<td>2.4</td>
<td>Description and explanation of administration route, posology, dosage regimen and treatment period</td>
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<td>Description of target population</td>
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<td>2.7</td>
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<td>Description of treatment, posology and investigational product dosage regimen</td>
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<td>Description of dosage form, investigational product packaging and labelling</td>
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<td>Expected duration of subject participation and description of stages and duration of all study periods, especially the follow-up, if any</td>
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<td>Description of “stopping rules” or “proceeding criteria” regarding the subjects partial or total participation to the study</td>
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<td>Description of investigational product accountability procedures including placebos and comparators, if any</td>
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<td>List of codes used for treatment randomization and code key retention</td>
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<td>When and how to withdraw research participants or cancel investigational product treatment</td>
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<td>5.6</td>
<td>Way of replacing research participants, if required</td>
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<td>Treatment periods including follow-up of each subject part of a group or sub-group treated with the investigational product or participating to the study</td>
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<td>The Sponsor/Sponsor-Investigator should ensure that it is specified in the protocol or any other written agreement that the investigators/institutions will allow study related monitoring, audit, IRB/IEC review and regulatory inspections, providing a source data/documents direct access.</td>
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<td>The complete protocol or protocol modification audit includes proof of reading and compliance to governing regulation and <em>good clinical practices</em>. Protocol and protocol modification should include some space dedicated to the proof of reading by the investigator (signature and date)</td>
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SOP 07 - Appendix 2

Confirmation of Verification of a Protocol or Protocol Amendment

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<th>Version Date: dd/mmm/yyyy</th>
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DATE OF THIS AUDIT: ____________________________

dd/ mmm / yyyy

REVIEWED BY:

________________________    ___________________  _________________________
Name in block letters    Signature   Title

Appendix 1 – Reference of audit, included □ or comments:

____________________________________________________________________________
____________________________________________________________________________
____________________________________________________________________________

Protocol or protocol amendment approved □    Modifications required □

PLEASE identify the included comments with study number and protocol version date

Protocol or Protocol Amendment to Submit

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Approved Protocol Versions

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<th>No of Pages</th>
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SECTION II - Ethics Review Process
# SOP 08 – Consent Process and the Informed Consent Document

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3) Procedures  
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   3.2 Informed Consent Form Prepared by a Sponsor-Investigator or his delegate  
   3.3 Content and Adaptation of the Informed Consent Form  
   3.4 Revision of the Informed Consent Form  
   3.5 Informed Consent Process  
4) References  
5) Appendices  
   Appendix 1 – Informed Consent Form Verification List  
   Appendix 2 – Confirmation of the Informed Consent Form Verification List

## 1. Policy

Within the framework of the principles inherent in the International Conference on Harmonization (ICH) Good Clinical Practice (GCP), this standard operating procedure (SOP) defines the content of the participant informed consent form and explains the process involved in its preparation, review and approval. It further describes the procedures which should be followed in the consent process of the ICH GCP (section 4.8.). It also integrates applicable national and international regulations.

This SOP applies to all clinical studies involving human subjects conducted in an institution, as described in the ICH Guideline for GCP. This SOP addresses all institutional personnel working in clinical research and should be observed by all those involved in clinical studies with human participants.

## 2. Objectives

One of the objectives of this SOP is to ensure the compliance of all informed consent forms (ICF) being used in the institution, with ICH GCP standards, as well as with applicable provincial and federal legislation. This SOP also aims to ensure that the consent process used in the institution follows applicable ethical standards in order to ensure the safety and protection of study participants.
3. Procedures

Flow Chart

**Sponsor**
- Drafting of the source ICF according to the protocol
- Submission of the ICF to Health Canada/FDA (if applicable) +
- Translation of the ICF (if applicable)

**Sponsor-investigator or delegate**
- Drafting of the informed consent form (ICF)

- Original version of the ICF according to the protocol
- Submission of the ICF to Health Canada/FDA (if applicable)

**ICF not approved**
- Investigator/qualified investigator or delegate
  - Adaptation of the ICF
  - Verification of the translation/applicable regulation

**ICF approved**
- Sponsor-investigator or delegate - Translation/applicable regulation

- Submission of the ICF to the Research Ethics Board

**ICF not approved**
- ICF approved
  - Translation of the ICF (if applicable)
  - Use of the approved ICF

**During the study – new information becomes available**
- Concerning study conduct / subject participation
3.1 ICF Submitted by a Sponsor to the Investigator

The investigator or his delegate is responsible for:

3.1.1 Verifying the content of the ICF as outlined in GCP, section 4.8 of ICH. In order to conduct this verification, Appendix 1, *ICF Verification List* and Appendix 2, *Confirmation of the ICF Verification List*, may be used. It is recommended that the results of the verification be kept with the essential study documentation, as described in SOP 01;

3.1.2 Checking and adapting the content to languages used at the site;

3.1.3 Advising the sponsor of any changes to the ICF before submission to the Research Ethics Committee (REC);

3.1.4 Submission of the ICF to the REC - This task may be delegated to another member of the clinical research team;

3.1.5 Incorporating revisions or additions to the ICF required by the REC;

3.1.6 Sending the version of the ICF approved by the REC to the sponsor.

3.2 ICF Prepared by the Sponsor-Investigator or his delegate

The sponsor/sponsor-investigator is responsible for:

3.2.1 Drafting the initial version of the ICF. This task may be delegated to another qualified member of the clinical research team. The delegation of this task should be documented on the Tasks Delegation form (SOP 02). This form is to be kept with the other essential study documentation.

3.2.2 Checking that the contents of the ICF are in agreement with the protocol and GCP, section 4.8 of the ICH Guideline. This ICF verification should be documented. In order to fulfill this requirement Appendix 1, *ICF Verification List*, and Appendix 2, *Confirmation of the ICF Verification List*, can be used. It is recommended that the documentation be kept with the essential study documents as described in SOP 01;

3.2.3 Translation of the ICF by an individual qualified or certified in the appropriate language, when required;

3.2.4 Revision of the ICF if the study protocol is modified or if any new information becomes available that may be pertinent to the participant and might affect his/her willingness to participate in the clinical study. This task may be delegated to another member of the clinical research team;

3.2.5 Submission of the ICF to regulatory authorities, when applicable. This task may be delegated to another member of the clinical research team. The delegation of this task should be documented on the tasks delegation form as referenced in SOP 02. This form is to be kept with the essential study documentation.
3.2.6 Incorporation of any changes or additions to the ICF as required by local or national authorities, when applicable.

3.2.7 Submission of the initial ICF to the REC, as well as any amendments to versions previously approved by the REC. This task can be delegated to another member of the clinical research team. The delegation of this task should be documented on the tasks delegation form as referenced in SOP 02. This form is to be kept with the essential study documentation.

3.2.8 Incorporation of any changes or additions to the ICF as required by the REC.

3.3 Content and Preparation of the ICF

3.3.1 The ICF describes all elements of the study protocol as described in SOP 07.

3.3.2 If by participating in a clinical study a participant is at risk, a copy of a summary of the research and the ICF will be included with the participant’s medical record. The participant should have agreed to this procedure, as stated in the FRSQ Standards on Research Ethics and Scientific Integrity (par. 2.26). When applicable, this element should be added to the ICF.

3.3.3 The language used in the ICF should not be technical and should be easily understood by the participant. The form cannot include explicit or implicit terms that could lead the participant or the participant’s legal representative to renounce his rights or that release or appear to release the sponsor, the sponsor-investigator, the investigator, the institution or their delegates from their responsibilities in case of negligence (ICH 4.8.6).

3.3.4 Translation of the ICF to another language should be carried out by qualified or certified personnel. This version should be validated by the sponsor-investigator or by the investigator prior to submission to the REC.

3.3.5 Each version of the ICF should be clearly identified with the number and date of the version on each page.

3.3.6 Identification of the ICF, i.e., the footer, should be coherent and appear uniformly throughout the entire document.

3.4 Revision of the ICF

3.4.1 If changes to the protocol or new information (i.e. serious adverse event), are liable to influence the participant’s decision to continue in the study, the sponsor-investigator or the investigator or their delegate, should make sure that the ICF contains this new information and that this information is submitted to the REC. All validated versions of the ICF used during the study should be kept with the essential study documents, as described in SOP 01.

3.4.2 Comments (i.e., omissions or additions) made by the regulatory authorities or by the REC, should be communicated to the sponsor or the sponsor-investigator for discussion, if necessary, with the proper authorities and incorporated into the
ICF. The sponsor-investigator or the investigator should revise, authorize and submit to the REC, the ICF that will be used on site.

3.5 The Consent Process

Civil Code of Quebec, L.Q., 1991, C. 64:

A person of full age who is capable of giving his consent may submit to an experiment provided that the risk incurred is not disproportionate to the benefit that can reasonably be anticipated (a.20. 1991, c. 64, a. 20).

Where it is ascertained that a person of full age is incapable of giving consent to care required by his or her state of health, consent is given by his or her mandatory, tutor or curator. If the person of full age is not so represented, consent is given by his or her married, civil union or de facto spouse or, if the person has no spouse or his or her spouse is prevented from giving consent, it is given by a close relative or a person who shows a special interest in the person of full age (a.15. 1991, c.64, a.15; 2002, c.6, a.1).

A minor or a person of full age who is incapable of giving consent may not be submitted to an experiment if the experiment involves serious risk to his health or, where he understands the nature and consequences of the experiment, if he objects.

Moreover, a minor or a person of full age who is incapable of giving consent may be submitted to an experiment only if, where the person is the only participant of the experiment, it has the potential to produce benefit to the person’s health or only if, in the case of an experiment on a group, it has the potential to produce results capable of conferring benefit to other persons in the same age category or having the same disease or handicap. Such an experiment should be part of a research group approved and monitored by a REC.

Consent to experimentation may be given, in the case of a minor, by the person having parental authority or the tutor and, in the case of a person of full age incapable of giving consent, by the mandatory, tutor or curator. Where a person of full age suddenly becomes incapable of consent and the experiment, insofar as it should be undertaken promptly after the appearance of the condition giving rise to it, does not permit, for lack of time, the designation of a legal representative, consent may be given by the person authorized to give consent to any care the person requires; it is incumbent upon the competent REC to determine, when examining the research project, whether the experiment meets that condition.

Care considered by the REC to be innovative care required by the state of health of the person concerned does not constitute an experiment (a. 21; 1991, c. 64, a.21; 1998, c, 32, a. 1).

FRSQ, Guide d’éthique de la recherche et d’intégrité scientifique. Standards en éthique de la recherche et en intégrité scientifique (translated from):

If a participant is unable to read or if a legal representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to participants,
is read and explained to the participant or the participant’s legal representative, and after the participant or the participant’s legal representative has orally consented to the participant’s participation in the study and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant or the participant’s legal representative, and that informed consent was freely given by the participant or the participant’s legal representative (part 3, B, 11.3.4, BPC art 4.8.9).

“Assent to”: in addition to the legal representative consent, the minor or the incapable major must signify their assent to the research if they understand its nature and consequences (part 20).

“Assent to” may be defined as an agreement of an incapable person or:

- A minor to take part in a research project
- Certain persons legally incapable or certain minors, around 8 years and up, may also be able to indicate if they wish to take part or not in a research project and this, even if they are incapable to give a free and informed consent. In these circumstances, the researcher must obtain the assent from the participant. This assent alone is insufficient to allow participation to a research project. On the other hand, if the minor or the incapable refuse to participate, this refusal must restrain his/her participation in the research project (CRIR).

**Tri-Council Policy Statement, Research Ethics with Respect to Human Participants:**

The requirement for free and informed consent should not disqualify research participants who are not proficient in the language used by the researchers from the opportunity to participate in potential research. Such individuals may give consent providing that one or more of the following are observed to the extent deemed necessary by the REC, in the context of a proportionate approach to the harms envisaged in the research and the consent processes that are to be used:

- An intermediary not involved in the research study, who is competent in the language used by the researchers as well as that chosen by the research participant, is involved in the consent process.
- The intermediary has translated the consent document or approved an existing translation of the information relevant to the prospective participant.
- The intermediary has assisted the research participant in the discussion of the research study.
- The research participant has acknowledged in his or her own language, that he or she understands the research study, the nature and extent of his or her participation, including the risks involved, and freely gives consent (Chapter 2, rule 2.1, indent b).
3.5.1 The ICF should provide the participant all necessary pertinent information with ample time and opportunity to inquire about the details of the study and to decide whether or not to participate in a specific clinical study. All questions about the study should be answered to the satisfaction of the participant or the participant’s legal representative (ICH 4.8.7).

3.5.2 During the course of discussion concerning the informed consent, all the elements which should be included in the ICF and any other written information provided to the participant should be explained to the participant (ICH 4.8.10).

3.5.3 Only the version of the ICF that has been approved by the REC should be used and provided to the participant for the duration of the study.

3.5.4 Prior to the participant’s participation in the study, and before any procedure referred to in the protocol, the approved version of the ICF should be read, understood, signed and personally dated by the participant or the participant’s legal representative, and by the person who conducted the informed consent discussion (ICH 4.8.8).

3.5.5 The original ICF, signed and dated by the participant and the designated signatories, should be kept with the essential study documents.

3.5.6 Neither the investigator nor the study staff should coerce or unduly influence a participant when recruiting or re-consenting (continue) into a research study (ICH 4.8.3).

3.5.7 If new information becomes available during the clinical study that may be relevant to the participant’s willingness to continue to participate in the study, a new ICF should be written (ICH 4.8.2). This new version, approved by the REC, should be read, understood, signed and personally dated by all participants who remain active in the study, as well as by all new participants or their legal representatives. This new version should be signed by the person who conducted the discussion.

3.5.8 The investigator or his delegate should inform the participant or, if the participant is unable to provide informed consent, the participant’s legal representative, of all pertinent aspects of the study including the written information given approval by the REC (ICH 4.8.5).

3.5.9 If the participant or his/her legal representative is unable to read the ICF, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information has been provided, read and explained to the participant or participant’s legal representative, and after the participant or participant’s legal representative has orally consented to participate in the study and, if capable of doing so, has signed and personally dated the consent form, the witness should also sign and personally date the ICF.
By signing the ICF, the witness attests that the information included in the consent form and any other written information was accurately explained to and apparently understood by the participant or participant’s legal representative, and that the informed consent was freely given by the participant or participant’s legal representative (ICH 4.8.9).

3.5.10 Before taking part in the study, the participant or participant’s legal representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the participant. The participant or the participant’s legal representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to the participant for the duration of the study (ICH 4.8.11).

It is advised to provide commentary for the participant’s basic document on the transfer of these documents.

3.5.11 In a clinical study (therapeutic or non-therapeutic) that includes participants who can only be enrolled in the study with the consent of the participant’s legal representative (persons who are unfit or vulnerable), the participant should be informed of the study to the extent that it is compatible with their understanding and, if capable, the participants should sign and personally date the written informed consent form (ICH 4.8.12). A space should be provided on the ICF for this type of situation. Even if the participant has a legal representative, you have to inform the participants about the study in a way he can understand (Assent is required).

3.5.12 Except as described in 4.5.13 above, a non-therapeutic study (i.e., a study in which there is no anticipated direct clinical benefit to the participant), should be conducted using individuals who personally give their consent and who sign and date the informed consent form (ICH 4.8.13).

3.5.13 Non-therapeutic studies may be conducted in participants with the consent of a legal representative provided the following conditions are fulfilled:

I. The objectives of the study cannot be met by means of a study with participants who can give informed consent personally.

II. The foreseeable risks to the participants are low.

III. The negative impact on the participant’s well-being is minimized and low.

IV. The study is not prohibited by law.

V. The approval/favorable opinion of the REC is expressly sought on the inclusion of such participants, and the written approval/favorable opinion covers this aspect.

Such studies, unless an exception is justified, should be conducted in persons having a disease or condition for which the investigational product is intended. Those participating in these studies should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed (ICH 4.8.14).
3.5.14 In the case of pediatric clinical studies (persons under the age of 18), the investigator should obtain the consent from the parents or authorized legal representative, and, if possible, the assent of the child according to local regulations.

4. References


Health Canada, Food and Drug Act– Part C, Division 5, Drugs for clinical trials involving human subjects, August 31 2004

Québec, Civil Code of Québec, L.Q. 1991, C64.

Fonds de la recherche en santé du Québec (FRSQ), Guide d’éthique de la recherche et d’intégrité scientifique, Standards en éthique de la recherche et en intégrité scientifique du FRSQ (2e édition), août 2003


SOP 01, Organizing a Site for Clinical Research

SOP 02, Research team: Role Definitions, Responsibilities and Task Delegation.

SOP 07, Protocol and Protocol Amendment, Submission for Review by the Research Ethics Committee
## SOP 08 - Appendix 1
Informed Consent Form Verification List

<table>
<thead>
<tr>
<th># Study, project or research product</th>
<th>Number of verified version</th>
<th>Date of verified version</th>
</tr>
</thead>
</table>

### 1. Information concerning the informed consent procedure

<table>
<thead>
<tr>
<th>No</th>
<th>Items that require verification</th>
<th>Yes</th>
<th>No</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Participant freely gave his consent.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1.2</td>
<td>Participant had ample time and opportunity to find out about the details of the study.</td>
<td></td>
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<tr>
<td>1.3</td>
<td>Participant will have ample time and opportunity to decide whether or not to participate</td>
<td></td>
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</tr>
<tr>
<td>1.4</td>
<td>Participant understands the volutary nature of the study</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1.5</td>
<td>Participant’s understands that refusal to participate will not result in any penalty or loss of benefits to which he/she is entitled.</td>
<td></td>
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<tr>
<td>1.6</td>
<td>Participant understands his/her right to withdraw at any time without prejudice.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1.7</td>
<td>Description of the foreseeable circumstances or reasons for terminating his/her participation in the study.</td>
<td></td>
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<tr>
<td>1.8</td>
<td>Participant will receive a written explanation and a copy of the signed and dated consent form for future reference.</td>
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</tr>
</tbody>
</table>

### 2. Study information

<table>
<thead>
<tr>
<th>No</th>
<th>Items that require verification</th>
<th>Yes</th>
<th>No</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Explanation that the study involves research.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2.2</td>
<td>Purpose of the study.</td>
<td></td>
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</tr>
<tr>
<td>2.3</td>
<td>Experimental vs. standard treatments (medications or devices).</td>
<td></td>
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</tr>
<tr>
<td>2.4</td>
<td>The study procedures description including all invasive procedures.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2.5</td>
<td>Description of the study’s experimental aspects.</td>
<td></td>
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<tr>
<td>2.6</td>
<td>Description of the comparative study treatment (active treatment vs. placebo-controlled).</td>
<td></td>
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<tr>
<td>2.7</td>
<td>Explanation on randomization procedure and the probability for assignment to different treatment.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Items that require verification</td>
<td>Yes</td>
<td>No</td>
<td>Comments</td>
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<tr>
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<td>-----------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>2.8</td>
<td>The expected duration of the study</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2.9</td>
<td>Description of consequences of the decision by the participant to withdraw from the study and the methods to end their participation</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2.10</td>
<td>The approximate number of participants in the study (total participants), as well as for the site.</td>
<td></td>
<td></td>
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<tr>
<td>2.11</td>
<td>Description of what the participants will be expected to do should they choose to take part.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2.12</td>
<td>It is suggested to specify the approximate duration of each visit (time involved).</td>
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</tr>
</tbody>
</table>

### 3. Information concerning foreseeable risks and benefits

<table>
<thead>
<tr>
<th>No</th>
<th>Items that require verification</th>
<th>Yes</th>
<th>No</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>The reasonably foreseeable risks or inconveniences to the participant and, when applicable, to the embryo, the fetus or the nursing infant.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3.2</td>
<td>Procedure or treatment may involve potential risks to the participant or, when applicable, to the unborn child.</td>
<td></td>
<td></td>
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<tr>
<td>3.3</td>
<td>Description of the anticipated benefits; if no benefits are forthcoming, the participant should be informed.</td>
<td></td>
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</tr>
<tr>
<td>3.4</td>
<td>Description of the alternative treatment that may be available to the participant and their potential risks and benefits.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3.5</td>
<td>Participant or the participant’s legal representative will be informed in a timely manner if new information becomes available that may be relevant to their willingness to continue to participate in the study.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.6</td>
<td>Explanation on the compensation or treatment that is available to the participant in the event of study-related loss or injury.</td>
<td></td>
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</tr>
<tr>
<td>3.7</td>
<td>Explanation on the availability of alternative treatment in the event of study-related loss or injury, and if applicable, what is the course of</td>
<td></td>
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</tr>
</tbody>
</table>
3.8 The anticipated costs incurred for the participant, if any.

3.9 Description of the anticipated proportional payment, in this occurrence, made to the participant.

### 4. Confidential data and new information

<table>
<thead>
<tr>
<th>No</th>
<th>Verified Items</th>
<th>Yes</th>
<th>No</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td>Records identifying the participant will be kept confidential, to the extent permitted by the applicable laws and regulations. These records will not be made public. If the results of the study are published, the participant’s identity will remain confidential.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.2</td>
<td>Explanation on the representatives of the sponsor/sponsor-investigator, the REC and the regulatory authorities will be granted access to the participant’s medical records for verification of the clinical procedures or clinical data, without violating his/her confidentiality, and that by signing the informed consent form, the participant is authorizing access.</td>
<td></td>
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</tr>
<tr>
<td>4.3</td>
<td>The participant’s personal physician will be kept informed of the participant’s condition during the study, if and only if the participant gives his/her specific consent to do so.</td>
<td></td>
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</tr>
<tr>
<td>4.4</td>
<td>The name, address and telephone number of the person to contact for further information or in the case of a study-related injury.</td>
<td></td>
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</tr>
<tr>
<td>4.5</td>
<td>Identifying the study sponsor.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4.6</td>
<td>Purpose of the clinical study.</td>
<td></td>
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</tr>
<tr>
<td>4.7</td>
<td>Description of the categories of individuals or research organizations under contract or regulatory authorities to whom will be granted access to study-related records.</td>
<td></td>
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</tr>
<tr>
<td>4.8</td>
<td>Explanation on other individuals have access to personal records, appropriate measures will be taken to protect the confidentiality of said data.</td>
<td></td>
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</tr>
<tr>
<td>4.9</td>
<td>Explanation on confidentiality requirements concerning the personnel directly or indirectly involved in data management permitting the identification of the participant.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Verified Items</td>
<td>Yes</td>
<td>No</td>
<td>*NA</td>
</tr>
<tr>
<td>----</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td></td>
<td>Respect of the confidentiality records: Study conducted only in Quebec: Reference, Quebec Charter of Human Rights and Liberties, L.R.Q., cC-12, A5 and A9 Reference, Health and Social Services Act (L.R.Q.), A19 Reference, Laws Protecting Access to Public Sector Documents and Protection of Personal Data, L.R.Q., C.A-2.1 Reference, Laws Protecting Personal Data in the Private Sector, L.R.Q.c.P-39.1 Study conducted in Canada: PIPEDA, except for Quebec Studies conducted in the USA: HIPAA.</td>
<td></td>
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</tr>
</tbody>
</table>

5. Formal Aspects

<table>
<thead>
<tr>
<th>No</th>
<th>Verified Items</th>
<th>Yes</th>
<th>No</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1</td>
<td>Identification of the participant: i.e., complete name and initials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.2</td>
<td>A space for signatures of the participant or the participant’s legal representative, the person who led the discussion on the ICF and, when applicable, the investigator or a witness. Each person signing the ICF should also personally date it.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.3</td>
<td>Site identification</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6. Vulnerable Participants

<table>
<thead>
<tr>
<th>No</th>
<th>Verified Items</th>
<th>Yes</th>
<th>No</th>
<th>*NA</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.1</td>
<td>Confirm that when minors (&lt;18 years of age) are involved in a study, that their parents’ consent is required.</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>6.2</td>
<td>Confirm that when minors are involved in a study, that the ICF is written in terms understood by the participant. A space should be set aside for the participant’s signature.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
7. Miscellaneous – to be added if applicable

<table>
<thead>
<tr>
<th>No</th>
<th>Verified Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1</td>
<td>The language used in this consent form should be non-technical and easily understood by the participant.</td>
</tr>
<tr>
<td>7.2</td>
<td>Ensure that the ICF provided to the participant or to the his/her legal representative contains the information that the ICF was approved by the REC.</td>
</tr>
<tr>
<td>7.3</td>
<td>The ICF should contain the names and addresses of the people to contact for information concerning participation in the study (ombudsman, participant’s representative).</td>
</tr>
</tbody>
</table>
SOP 08 - Appendix 2
Confirmation of the ICF Verification List

<table>
<thead>
<tr>
<th>STUDY NAME, PROJECT OR NUMBER OF THE DRUG:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICF VERSION:</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>AUTHOR OF THE ICF:</td>
</tr>
</tbody>
</table>

DATE OF THIS REVISION: _________________
{dd / mmm / yyyy}

REVIEWED BY: ______________________  ______________________  ______________________
Name in block letters Signature Title

Appendix 1 – ICF Verification list, attached □ or comments:

___________________________________________________________________________________________
___________________________________________________________________________________________
___________________________________________________________________________________________

ICF approved □ Amendments required □

* Please identify the attached comments by referring to the study number, the number and date of the ICF version

ICF for submission

<table>
<thead>
<tr>
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SECTION II - Ethics Review Process

SOP 09 – Rights and Protection of Research Participants

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1. Policies
   Within the framework of the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH), in compliance with the Tri-Council Policy Statement; Ethics for Research Involving Human Subjects, the Civil Code of Québec, the Act Respecting Access to Documents Held by Public Bodies and the Protection of Personal Information of Québec as well as the Guide d’éthique de la recherche et d’intégrité scientifique of the Fonds de la recherche en santé du Québec, this standard operating procedure (SOP) describes procedures and states policies regarding the rights and protection of participants in a clinical study.

   This SOP concerns all institutional personnel working in clinical research and should be followed by all those working on clinical studies involving human participants.

2. Objective
   The objective of this operating procedure is to describe the process which ensures the rights protection and well being of research participants.

3. Procedures
3.1 Generalities
   The rights, safety and well-being of the study participants are the most important considerations and should prevail over interests of science and society (ICH 2.3).

   Medical care given to and medical decisions made on behalf of participants should always be the responsibility of qualified physician.

   The Confidentiality of records that could identify participants should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements (ICH 2.11).
The Institution:

The person exercising the highest authority in the public body should, by a directive, determine the terms and conditions according to which the information may be released by the personnel of the body. The personnel is required to comply with the directive (Act Respecting Access to Documents Held by Public Bodies and the Protection of Personal Information 2001, a. 59.1. c. 78, a. 1);

Responsibility for respect for the rules of protection for human participants, managing biological data or other information collected from a study participant, the confidentiality of information stored in hospital and research files as well as the complementarities between both hospital and research files rests with the person with the highest authority within the public body.

The Research Ethics Committee:

The REC should protect the rights, safety and well-being of all research participants. Particular consideration should be paid to clinical studies which include vulnerable populations, like children or persons unable to determine for themselves the impact of their participation in a clinical study.

Sponsor-Investigator and/or Investigator:

The sponsor-investigator and procedures should address the costs of treatment of study participants in the event of study-related injuries in accordance with the applicable regulatory requirements (ICH 5.8.2);

The institution must be informed of all research activities of the sponsor-investigator or investigator being conducted on its premises and by its staff (not on premise). Each clinical study is subject to mandatory declaration and should be approved and followed by the Research Ethics Committee;

The rights, safety and well-being of the study participants are the most important considerations and should prevail over interests of science and society (ICH 2.3).

The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist (ICH 2.7);

The Confidentiality of records that could identify participants should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements (ICH 2.11).

3.2 Access to Documents

An Act Respecting Access to Documents Held by Public Bodies and the Protection of Personal Information, L.R.Q., 1982, C. 30:

3.2.1 This Act applies to documents kept by a public body in the exercise of its duties, whether it keeps them itself or through the agency of a third party (a. 1. 1982, c. 30, a. 1);
3.2.2 The act applies whether the documents are: recorded in writing or print, on sound tape or film, in computerized form or otherwise (a. 1. 1982, c. 30, a. 1).

Right to Access:

3.2.3 Every person has a right of access, on request, to the documents held by a public body (a. 9. 1982, c. 30, a);

3.2.4 The right of access to a document may be exercised by examining it on the premises during regular working hours or by remote access (a. 10. 1982, c. 30, a. 10; 1990, c. 57, a. 4; 2001, c. 32, a. 82);

3.2.5 The exercise of the right of access to a document is subject to the rights respecting intellectual property (a. 12. 1982, c. 30, a. 12).

Act Respecting Health Services and Social Services, R.S.Q., Chapter S-4.2, Section I, Chapter II, 1991

3.2.6 The record of a user is confidential and no person may have access to it except with the consent of the user or the person qualified to give consent on his behalf, on the order of a court or a coroner in the exercise of his functions, where this Act provides that an institution may be required to release information contained in the record or where information is communicated for the purposes of the Public Health Act (chapter S-2.2) (a. 19. 1992, c. 21, a. 2; 1999, c. 45, a. 1; 2001, c. 60, a. 161).

Access for Research:

3.2.7 Consent to a request for access to a user's record for study, teaching or research purposes should be in writing; in addition, it should be free and enlightened and given for specific purposes. Otherwise, it is without effect (a. 19.1. 1999, c. 45, a. 2).

Period of Authorization:

3.2.8 The consent is valid only for the time required for the attainment of the purposes for which it was granted or, in the case of a research project approved by a Research Ethics Committee, for the period determined, where that is the case, by the Research Ethics Committee (a. 19.1.1999, c. 45, a.2).

3.2.9 Notwithstanding section 19, the director of professional services of an institution or, if there is no such director, the executive director may authorize a professional to examine the record of a user for study, teaching or research purposes without the user's consent (a 19.2. 1999, c. 45, a. 2).

Note: If information collected allows link back to a participant, then the approval has to be signed by the DPS and the REC

Prerequisite Requirements:

Before granting such authorization, the director should, however, ascertain that the criteria determined under section 125 of the Act respecting Access to
documents held by public bodies and the Protection of personal information (chapter A-2.1) are satisfied. If the director is of the opinion that the professional's project is not in compliance with generally accepted standards of ethics or scientific integrity, the director should refuse to grant the authorization.

**Period of Authorization:**

The authorization should be granted for a limited period and may be subject to conditions. It may be revoked at any time if the director has reason to believe that the authorized professional is violating the confidentiality of the information obtained or is not complying with the conditions imposed or with generally accepted standards of ethics and scientific integrity (a. 19.2. 1999, c. 45, a. 2).

### 3.3 Protection of Information and Respect for Participants’ Rights

**Act Respecting Access to Documents Held by Public Bodies and the Protection of Personal Information, L.R.Q., 1982, C. 30.**

3.3.1 Nominative information is confidential (a. 53. 1982, c. 30, a. 53; 1985, c. 30, a. 3; 1989, c.54, a. 150; 1990, c. 57, a. 11).

3.3.2 In any document, information concerning a natural person which allows the person to be identified is nominative information (a. 54. 1982, c. 30, a. 54).

3.3.3 Every person has the right to be informed of the existence of a nominative concerning him in a personal information file (a. 83. 1982, c. 30, a. 83; 1987, c. 68, a. 6; 1990, c. 57, a. 21; 1992, c. 21, a. 74).

**Civil Code of Québec, L.Q. 1991, C. 64:**

3.3.4 Every person is the holder of personality rights, such as the right to life, the right to the inviolability and integrity of his person, and the right to the respect of his name, reputation and privacy (a. 3. 1991, c. 64);

3.3.5 Every person is inviolable and is entitled to the integrity of his person. Except in cases provided for by law, no one may interfere with his person without his free and enlightened consent (a. 10. 1991, c. 64);

3.3.6 A person of full age who is capable of giving his consent may submit to an experiment provided that the risk incurred is not disproportionate to the benefit that can reasonably be anticipated (a. 20, 1991, c. 64);

3.3.7 Full age or the age of majority is 18 years, (A. 153);

3.3.8 A minor or a person of full age who is incapable of giving consent may not be submitted to an experiment if the experiment involves serious risk to his health or, where he understands the nature and consequences of the experiment, if he objects (A. 21, paragraph 1, 1998, c. 32, a. 1);

Moreover, a minor or a person of full age who is incapable of giving consent may be submitted to an experiment only if, where the person is the only participant of the experiment, it has the potential to produce benefit to the person's health or only if, in the case of an experiment on a group, it has the potential to produce
results capable of conferring benefit to other persons in the same age category or having the same disease or handicap. Such an experiment should be part of a research project approved and monitored by a Research Ethics Committee;

Consent to experimentation may be given, in the case of a minor, by the person having parental authority or the tutor and, in the case of a person of full age incapable of giving consent, by the mandatory, tutor or curator. Where a person of full age suddenly becomes incapable of consent and the experiment, insofar as it should be undertaken promptly after the appearance of the condition giving rise to it, does not permit, for lack of time, the designation of a legal representative, consent may be given by the person authorized to consent to any care the person requires; it is incumbent upon the competent Research Ethics Committee to determine, when examining the research project, whether the experiment meets that condition;

Care considered by the Research Ethics Committee to be innovative care required by the state of health of the person concerned does not constitute an experiment (a. 21. 1998, c. 32, a. 1).

3.3.9 A part of the body, whether an organ, tissue or other substance, removed from a person as part of the care he receives may, with his consent or that of the person qualified to give consent for him, be used for purposes of research (a. 22. 1991, c. 64).

3.4 Protection of Research Participants

The protection of human participants requires ensuring the same rights as users benefiting from health care and social services.

Indemnification to participants:

3.4.1 It is in compliance with the law and ethics that the study participant is compensated for his participation in an experiment. However the indemnification to be legally valid should be limited to the losses and constraints sustained. An experiment may not give rise to any financial reward other than the payment of an indemnity as compensation for the loss and inconvenience suffered (Civil Code of Québec, 1991, C. 64, a. 25); Note: compensation can be for lunch (cafeteria), parking …

3.4.2 Thus, the compensation payment should comply with two essential conditions to free participation: absence of unjust allowance and compensation based on his pro rata participation (FRSQ, Part 2, Section 13, ICH 4.8.10 k and 3.1.8);

3.4.3 Each research team member is held to professional confidentiality. Each human participant has the right to professional confidentiality, should he be under age or of legal age. (Translated from FRSQ, Part 2, Section 14).
4. References

Health Canada, Guidance for Industry, Good Clinical Practice: Consolidated guideline, ICH Topic E6, 1997

Health Canada, Food and Drug Act– Part C, Division 5, Drugs for clinical trials involving human subjects, August 31 2004


Québec, Civil Code of Québec, L.Q. 1991, C64

Fonds de la recherche en santé du Québec (FRSQ), Guide d’éthique de la recherche et d’intégrité scientifique, Standards en éthique de la recherche et en intégrité scientifique du FRSQ (2e édition), août 2003

Quebec, An act respecting health services and social services (R.S.Q., c. S-4.2)

Quebec, An act respecting access to documents held by public bodies and the protection of personal information (R.S.Q., A-2.1)

SOP 08, Consent Process and the Informed Consent Document
SECTION II - Research Ethics Review Process

SOP 10 - Conflict of Interest

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1. Policies
Within the framework of principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH), in respect of the Tri-Council Policy Statement (TCPS): and following the FRSQ, this standard operating procedure (SOP) describes procedures and policy statements related to conflicts of interest.

This SOP concerns all institutional personnel working in clinical research and should be followed by all those working on clinical studies involving human participants.

2. Objective
All parties involved in clinical research should be independent, objective and loyal in their relations with research participants, sponsors, research establishments and professional corporations.

Conflicts of interest can affect various parties in a clinical study. The sponsor-investigator, investigator, REC, institution and even a research participant can be in a situation of conflict of interest. The objective of this standard operating procedure is to define the process of managing conflict of interest within an institution.

3. Procedures
3.1 Generalities
Investigators hold trust relationships with research participants, research sponsors, institutions, their professional bodies and society. These trust relationships can be put at risk by conflicts of interest that may compromise independence, objectivity or ethical duties of loyalty (TCPS, Section 4).
During clinical studies, all parties are responsible for disclosing any conflict of interest. In accordance with the TCPS (a.4.1), investigators and members of RECs shall disclose actual, perceived or potential conflicts of interest to the REC.

At the JGH, each member of the REC signs a declaration to divulge and fully disclose actual, perceived or potential conflicts of interest to the Chair. When a conflict is present, the member is asked to leave the room during the REC deliberations and decision-making process.

With regard to the investigator, they are asked a series of questions in the application form regarding conflicts of interest. They are also under the obligation to provide the REC with full disclosure where there is actual, perceived or potential conflicts of interest.

### 3.2 Investigator

3.2.1 During the evaluation of a protocol by the REC, the investigator may provide information on any aspect of a study, but should not participate in the deliberations or in the vote/opinion of the REC (ICH 3.2.5).

3.2.2 The financial aspects of the clinical study should be documented in a written agreement between the sponsor-investigator, the investigator and the institution (ICH 5.9).

3.2.3 The investigator is obliged to disclose all details of his research activities including details about his clinical studies such as budget agreement, commercial interests, relations with consultants and all other pertinent information to the REC (TCPS, rule 4.1A).

3.2.4 The investigator should disclose to research participants all details concerning possible conflicts of interest, real or apparent (adapted from TCPS, article 4.1, par. 3). If such details should be known by the research participants, it is recommended that they be documented in the research participant’s source document.

3.2.5 An investigator must inform the REC of any bonus, for example, fees or any other benefit agreed upon in return for recruiting research participants (translated and adapted from FRSQ, Part 2 section 12). No bonus or fee can be offered to members of a research team for recruiting participants (translated and adapted from FRSQ, Part 2, section 11).

3.2.6 The investigator always remains responsible for the actions of team members who act in his name.

3.2.7 When the participation of an investigator in a clinical study is subject to U.S. regulations, a “Financial Disclosure Form” or the FDA form number 3455 describing financial interests should be completed for each investigator and returned to the sponsor/sponsor-investigator. A copy of this document should be kept with the essential study documentation. In conformity with the Financial
Disclosure Regulation, the spouse of a principle or secondary investigator and any dependant children should complete the “Financial Disclosure Form”(http://www.FDA.gov.)

3.3 **Members of Research Ethics Committee**

3.3.1 If an REC is reviewing research in which a member of the REC has a personal interest in the research under review (e.g. investigator or sponsor-investigator), conflict of interest principles require that the member not be present when the REC is deliberating or making its decision. The REC member may disclose and explain the conflict of interest and offer evidence to the REC provided the conflict is fully explained to the REC, and the person in question has the right to hear the evidence and to offer a rebuttal (TCPS, a. 1.12). It is recommended that the withdrawal of the sponsor-investigator or investigator from the discussion and decision process be documented in the REC minutes of the meeting.

3.3.2 The REC should review both the amount and method of payment to research participants to assure that it neither presents problems of coercion nor undue influence on the study participants. The remuneration should be established on a pro rata basis and should not be conditional to completing the study but rather, for example, allocated per visit (ICH 3.1.8).

3.3.3 The REC should ensure that information regarding payment to participants, including the methods, amounts, and schedule of payments, is set forth in the written informed consent form and any other written information to be provided to research participants. The manner in which a payment will be prorated should be specified (ICH 3.1.9).

3.3.4 No member of a REC can accept an undue or excessive honorarium for their participation on a REC.

3.4 **Institution/Institute**

3.4.1 REC’s should act without constraints and maintain an independent relationship with the institution with which they are affiliated.

3.4.2 Institutions should adopt specific policies for the prevention and management of conflict of interest. Conflict of interest, whether real or perceived, is detrimental to the smooth operation of public research and is likely to undermine the protection of human research participants (translated from FRSQ, part I, section 1).

3.5 **Research Participants**

3.5.1 That a participant in a research project may receive indemnification for loss and restriction suffered, complies with both ethics and the law, on condition that:

   I. the indemnification does not constitute an undue inducement
II. The indemnification is paid on a pro rata basis for their participation in the study

3.5.2 Indemnification should not have the effect of exerting excessive influence on the research participant.

3.5.3 The informed consent form (ICF) should mention and specify that a research participant who withdraws from the research study will be compensated for his participation on a pro rata basis.

4. References

Health Canada, Guidance for Industry, Good Clinical Practice: Consolidated guideline, ICH Topic E6, 1997

Health Canada, Food and Drug Act– Part C, Division 5, Drugs for clinical trials involving human subjects, August 31 2004

Food and Drug Administration (FDA), Code of Federal Regulations, 21 CFR part 312

Québec, Civil Code of Québec, L.Q. 1991, C64

Fonds de la recherche en santé du Québec (FRSQ), Guide d’éthique de la recherche et d’intégrité scientifique, Standards en éthique de la recherche et en intégrité scientifique du FRSQ (2e édition), août 2003


SOP 08, Consent Process and the Informed Consent Document
SECTION II - Research Ethics Review Process

SOP 11 – Recruitment of Research Participants

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1. Policies
Within the framework of the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH), this standard operating procedure (SOP) describes the process of recruitment of research participants for a clinical study. It applies to all clinical studies involving human subjects which take place in the institution.

This SOP concerns all institutional personnel working in clinical research and should be followed by all those involved in clinical studies involving human participants.

2. Objective
The objective of this operating procedure is to describe the principles that govern the process of recruitment research participants in a clinical study.

3. Procedures
3.1 Generalities
3.1.1 The investigator should ensure that all persons assisting with the study are adequately informed about the protocol, objectives, profile of the population to be recruited, investigational products(s), biological product(s), medical device(s), radiopharmaceutical(s) and their study-related tasks and functions (ICH 4.2.4).

The training of the Research Team held at the beginning of the clinical study should be documented. This documentation should be kept with the documents essential to the study.
3.1.2 With the goal of assuring compliance with GCP (ICH 4.2.4) and this SOP, it is necessary for the investigator to discuss with members of the research team, their responsibilities with respect to the process of recruitment. It is recommended that delegation of responsibilities regarding recruitment of research participants to designated members of the research team be documented in the Task Delegation Form (appendix 1, SOP 2). This document should be kept with documents essential to the study.

3.1.3 Reference to the Civil Code of Quebec (L.Q., 1991, c 64):

A person of full age who is capable of giving his consent may submit to an experiment provided that the risk incurred is not disproportionate to the benefit that can reasonably be anticipated (a. 20. 1991, c. 64, a. 20).

A minor or a person of full age who is incapable of giving consent may not be submitted to an experiment if the experiment involves serious risk to his health or, where he understands the nature and consequences of the experiment, if he objects.

Moreover, a minor or a person of full age who is incapable of giving consent may be submitted to an experiment only if, where the person is the only subject of the experiment, it has the potential to produce benefit to the person’s health or only if, in the case of an experiment on a group, it has the potential to produce results capable of conferring benefit to other persons in the same age category or having the same disease or handicap. Such an experiment should be part of a research project approved and monitored by a Research Ethics Committee. The competent Ethics Committees are formed by the Minister of Health and Social Services or designated by that Minister among existing research ethics boards; the composition and operating conditions of these Committees are determined by the Minister and published in the Gazette Officielle du Québec.

Consent to experimentation may be given, in the case of a minor, by the person having parental authority or the tutor and, in the case of a person of full age incapable of giving consent, by the mandatory, tutor or curator. Where a person of full age suddenly becomes incapable of consent and the experiment, insofar as it should be undertaken promptly after the appearance of the condition giving rise to it, does not permit, for lack of time, the designation of a legal representative, consent may be given by the person authorized to consent to any care the person requires; it is incumbent upon the competent Ethics Committee to determine, when examining the research project, whether the experiment meets that condition.

Care considered by the Research Ethics Committee to be innovative care required by the state of health of the person concerned does not constitute an experiment (a. 21. 1991, c. 64, a. 21; 1998, c. 32, a. 1).
3.1.4 An Act respecting health services and social services, R.S.Q. S-4.2, part I, Title II, Chapter II, 1991:

The record of a user is confidential and no person may have access to it except with the consent of the user or the person qualified to give consent on his behalf, on the order of a court or a coroner in the exercise of his functions, where this Act provides that an institution may be required to release information contained in the record or where information is communicated for the purposes of the Public Health Act (a. 19. 1991, c. 42, a. 19; 1992, c. 21, a. 2; 1999, c. 45, a. 1; 2001, c. 60, a. 161).

Notwithstanding section 19, the director of professional services of an institution or, if there is no such director, the executive director may authorize a professional to examine the record of a user for study, teaching or research purposes without the user's consent.

Note: If information collected allows link back to a participant, then the approval has to be signed by the DPS and the REC)

Criteria
Before granting such authorization, the director should, however, ascertain that the criteria determined under section 125 of the Act respecting Access to documents held by public bodies and the Protection of personal information (chapter A-2.1) are satisfied. If the director is of the opinion that the professional's project is not in compliance with generally accepted standards of ethics or scientific integrity, the director should refuse to grant the authorization.

Granting and revocation of authorization
The authorization should be granted for a limited period and may be subject to conditions. It may be revoked at any time if the director has reason to believe that the authorized professional is violating the confidentiality of the information obtained or is not complying with the conditions imposed or with generally accepted standards of ethics and scientific integrity (a. 19.2. 1999, c. 45, a. 2).

3.2 Recruitment Methods

3.2.1 Before initiating a study, the investigator should inform and submit for approval to the Research Ethics Committee the recruitment methods that he intends to use, the same applies for research participants’ remuneration and compensation (ICH 4.4.1 and 4.8.10).

3.2.2 The investigator should be able to demonstrate (based on retrospective data) a potential for recruiting the required number of suitable research participants within the agreed recruitment period, outlined in the protocol (ICH 4.2.1).
Proof of this may be required by the sponsor, sponsor-investigator, Research Ethics Committee, Institution, as well as during monitoring or audit of the study by regulatory authorities.

3.2.3 The investigator should define recruitment strategies in relation to the population to be studied. The methods should be appropriate and non-coercive; they should have been approved by the Research Ethics Committee and may include:

I. Letters;

II. Telephone calls;

III. Advertisements via television, radio, newspaper, etc…

3.2.4 During the recruitment process, the investigator should be particularly vigilant concerning factors that could interfere with the study:

I. Difficulties in following-up research participants (i.e. residing far from the study site);

II. Inability of certain research participants to follow the protocol constraints (i.e. linguistic problems);

III. Possible conflicts (i.e. attending physician, research participants taking part in other research protocols).

3.2.5 The investigator should define strategies to motivate potential participants (such as closer follow-up and teaching), taking into account that he/she cannot force or unduly influence a research participants to take part or continue to take part in the study.

3.2.6 The investigator should not permit research participants unless they are eligible, according to criteria defined by the protocol.

3.3 Recruitment

Normally, for a clinical study requiring regular (i.e. non-urgent) care, recruitment should include the following steps:

3.3.1 Plan, when the protocol permits, a meeting with the research participant and inform the investigator of the date of the encounter. It is important to add that no research activity in anticipation of a clinical study can be conducted before the research participant has signed the informed consent form. Moreover, it should not be asked of the patient to follow instructions such as providing a urine sample, refraining from taking usual medication, fasting, etc., before he has signed the informed consent form.

In conformity with section 4.8.7 of the ICH, before informed consent form can be obtained, the investigator or the person designated by him must provide enough time to the research participant or his/her legal representative to be informed of the details of the study and decide whether or not to participate. All questions regarding the study should be answered to the satisfaction of the
research participant or his/her legal representative. In Quebec, consent to care not required by a person's state of health, to the alienation of a part of a person's body, or to an experiment shall be given in writing. It may be withdrawn at any time, even verbally (Civil Code of Quebec. a. 24. C.64, a.24).

3.3.2 Verify eligibility criteria.

3.3.3 In conformity with section 4.5 of SOP 08, Consent Process, it should be ensured that the participant properly understands the nature of the clinical study that he/she agrees to participate in the study and that he has signed the informed consent form. It should be underlined that in conformity with article 24 of the Civil Code of Quebec, consent to an experiment can be verbally withdrawn at any time by the research participant.

The FRSQ requires researchers to conform to the following standards:

- The primary physician of a person does not take part in the process of solicitation with this person, unless the REC approved of this process based on the need for this process;
- When this need was recognized by the REC, the primary physician must explicitly warn the solicited patients of his double role.
- When the potential research participants are identified by a consultation of the user files or a patients list, the first contact must be carried out by a person of the establishment rather than by the researcher.

3.4 Recruitment Reports

3.4.1 In conformity with section 8 of the ICH/GCP, the following information related to the recruitment of participants forms part of the essential study documents:

I. **Screening Log:** this document identifies participants figuring in the pre-study screening (ICH 8.3.20);

II. **Subject Enrolment Log:** this document lists enrolled research participants chronologically by study number (ICH 8.3.22);

III. **Subject identification codes list:** this document permits the identification of all research participants who have taken part in the study, in case follow-up of a participant is necessary. This list is confidential. Under no circumstances can it be provided to the sponsor (ICH 8.3.21).

Forms can be created for this information.

3.4.2 All of the following information should be kept by the Investigator with the essential study documentation:

I. Advertisements used to recruit research participants, if applicable;
II. Dated approval from the Research Ethics Committee regarding advertisements for the recruitment of research participants, as the case may be;

III. The screening log identifying participants screened as well as those who were included, or not, in the study;

IV. The confidential list of identification codes of all research participants who were given a study number;

V. The participant enrolment log that lists enrolled research participants chronologically by study number.

4. References

Quebec, Civil Code of Quebec, L.Q. 1991, C64


Health Canada, Guidance for Industry, Good Clinical Practice: Consolidated guideline, ICH Topic E6, 1997

Health Canada, Guidance for Industry, Essential documents for the conduct of a clinical trial, ICH Topic E6, Section 8


Quebec, An act respecting health services and social services (R.S.Q., c. S-4.2)

SOP 01, Organizing A Site for Clinical Research

SOP 02, Research Team: Role Definitions, Responsibilities and Task Delegation

SOP 08, Consent Process and the Informed Consent Document

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SOP 12 – Follow-up of Research Participants

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1. Policies
Within the framework of the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH), this standard operating procedure (SOP) describes the process of follow-up of research participants recruited for a clinical study.

This SOP concerns all institutional personnel working in clinical research and should be followed by all those working on clinical studies involving human participants.

2. Objective
In order to ensure the proper course of the clinical study and to be in conformity with ethics, the investigator should make sure that all measures are in place for the best possible follow-up of research participants. Protection of human participants requires ensuring that those taking part in a study retain the same rights as users of healthcare or social services. The objective of this operating procedure is to ensure that the rights, the dignity and well-being of research participants are protected by proper follow-up.

3. Procedures
3.1 Generalities
3.1.1 As mentioned in GCP of the ICH 5.8.2, the investigator should ensure that procedures or policies of the sponsor/sponsor-investigator address the costs of treatment of study participants in the event of study-related injuries. In order to ensure protection of research participants he should ascertain that this information is found in the participant informed consent form (SOP 08).
3.1.2 The investigator should ensure follow-up for research participants no longer using the investigational product or who were withdrawn from the study (ICH 6.5.3.d).

3.1.3 The investigator should inform the REC when the recruitment and follow-up of participants is finished or when the study is prematurely terminated (ICH 4.1.12). The process should be documented and records kept with the essential documentation of the study (SOP 1).

3.1.4 In order to conform to the directives of ICH 4.2.3, 4.2.4, 5.18 and 5.20, and to ensure the well-being of research participants, it is important that the research team be properly trained in the protocol, objectives, profile of the population to be recruited, eligibility criteria, research products, as well as in all aspects of the study covered by the protocol (SOP 03 and 04). If they are not mentioned in the protocol, alternative treatments should be discussed (instructed) with the research team.

3.1.5 With the goal of ensuring better comprehension and greater compliance with this SOP, it is necessary that the investigator discusses with the members of the research team the responsibilities that each one holds in running the study and in the follow-up of research participants.

3.2 Follow-up of research participants during the recruitment process

3.2.1 The sponsor-investigator or investigator should ensure that research participants have received all necessary and pertinent information concerning the clinical study during the recruitment process (SOP 08 and 11).

3.2.2 In conformity with principle 4.8.7 of the ICH and as defined in SOP 08, the research participant should have had enough time, before giving consent, to review and discuss the details related to the study and to decide whether to take part in the study or not.

3.3 Follow-up of the research participant during the clinical study

3.3.1 The investigator or his delegate should ensure that the research participant adheres to all aspects of the protocol (medication taken, examinations done, questionnaires filled out...). This should be documented in the source documents (SOP 22).

3.3.2 In conformity with principle 4.12 of the ICH, if the study is abandoned or terminated prematurely for an unspecified reason, the investigator/institution should inform the research participant promptly and ensure that suitable treatment and follow-up are provided.
3.3.3 In the event that the research participant moves, the investigator or his delegate should obtain the new contact information so as to ensure follow-up of the participant. All contacts with the research participant in order to obtain this information (telephone, email, letter or other) should be documented in essential documentation (SOP 22).

3.3.4 If the research participant no longer wants to participate in the study, the investigator or his delegate should include this information in the source documents. If the reason(s) for this withdrawal are available (“no reason”), they should be noted in the source documents. In this case, the research participant should be informed of other possible treatments and where they can be obtained. In this case, follow-up should be in accordance to the requirements of the protocol.

3.3.5 The investigator should also inform the REC of any withdrawals. This information can be presented at the time of the submission of the annual report.

3.3.6 In the case of an adverse event, the research participant should be followed until resolution of the event or according to the protocol. This follow-up should be documented in the source documents.

3.3.7 In conformity with principle 4.8.2 of the ICH, the research participant or his/her legal representative should be promptly informed of all additional information that could influence his willingness to continue participating in the study.

3.4 Follow-up of research participants after the end of the clinical study

3.4.1 The sponsor or the sponsor-investigator can define in the protocol a period of follow-up of research participants after the end of the study.

3.4.2 Following the end of the study, it is necessary to document follow-up of the research participant in the case of:
   I   an adverse event unresolved at the end of the study;
   II  worsening of the disease treated;
   III withdrawal from the study for a reason other than an adverse event.

4. References

Health Canada, Guidance for Industry, Good Clinical Practice: Consolidated guideline, ICH Topic E6, 1997
SOP 01, Organization a Site for Clinical Research.
SOP 03, Site Research Team: Competence, Knowledge and Training
SOP 04, Preparing the Team for a Study
SOP 08, Consent Process and the Informed Consent Document
SOP 11, Recruitment of Research Participants
SOP 22, Source Data and Document Management
SECTION II - Research Ethics Review Process

SOP 13 – Dealing with Scientific Misconduct and Protocol Deviations

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1. Policy
Within the framework of the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH) issued by Health Canada, this standard operating procedure (SOP) describes the management, documentation and submission of protocol deviations and incidents of scientific misconduct.

This SOP concerns all institutional personnel working in clinical research and should be followed by all those working on clinical studies involving human participants.

2. Objective
To ensure integrity of the data and validity of the final results of the clinical study, the investigator or those he/she delegates should observe the protocol requirements meticulously.

The objective of this operating procedure is to describe procedures for documenting scientific misconduct or protocol deviations and their submission to the appropriate bodies.

3. Procedures

3.1 Generalities
To ensure adherence to ICH principle 4.5.1, the investigator/institution should conduct the study in compliance with the protocol approved by the sponsor/sponsor-investigator and, if applicable, regulatory authorities and to which the REC has given its approval/favourable opinion. The investigator/institution and sponsor/sponsor-investigator should sign the protocol or other contract to confirm the agreement.
As indicated in ICH 4.5.2, the investigator should not implement any deviation from, or changes to the protocol without agreement by the sponsor/sponsor-investigator and approval/favourable opinion from the Research Ethics Committee after evaluation of the proposed modification. This rule may not apply if the proposed modification is required to eliminate an immediate risk to research participants or if it is related only to a logistical or clerical aspect (change of monitor, telephone number, etc.) of the study.

To ensure conformity with ICH principle 4.5.3, the investigator or a person he/she has designated, should document in writing and explain any deviations from the approved protocol.

3.1.1 The investigator should comply with applicable regulatory requirements related to the obligation to inform the Research Ethics Committee of all instances of non-compliance including protocol variations or modifications to eliminate any immediate risk to research participants (ICH 3.3.8.a). Such communications with the Research Ethics Committee should be documented and filed with the study-related essential documentation (SOP 01).

3.1.2 The investigator should accurately and regularly document all incidents of scientific misconduct or deviation from the protocol in the source documents and case report forms (CRFs) or any other documents stipulated in the protocol.

3.1.3 To comply with the requirements of GCP of the ICH 4.24, 5.18 and 5.20, and to ensure the well-being of research participants, it is important to provide the research team with training in protocol objectives, target population profile, eligibility criteria investigational products, biological products, medical devices and radiopharmaceuticals as well as all aspects of the study mentioned in the protocol.

3.2 Scientific Misconduct

Falsification of generated or documented research data and the intentional omission of data during the course of a clinical study constitute scientific misconduct.

3.2.1 Any scientific misconduct by the investigator or a member of the research team should be reported to the investigator, the sponsor or sponsor-investigator and the Research Ethics Committee/institution. Each institution is responsible for defining the procedures for dealing with cases of scientific misconduct. The statement of scientific misconduct and the method of dealing with the misconduct should be documented.

Scientific misconduct can undermine the integrity of both the investigator and the institution. It can also put in question the validity of submitted or published clinical study data as well as compromise the research objective.

3.3 Protocol Deviation

The protocol should provide a means to minimize the number of irregularities in the conduct of the study that could adversely affect the quality of the analysis (i.e. protocol non-compliance, withdrawals, missing values).
3.3.1 Research participants should be informed of the importance of complying with the protocol as explained.

3.3.2 The sponsor or sponsor-investigator should be informed immediately of any protocol deviation and receive relevant explanation. The deviations, as well as actions taken as a result of these deviations should be documented in the source documents.

The degree of validity of the final results and conclusions of the study depend upon the quality and integrity of the data.

If eligibility criteria are regularly overridden, the protocol will have to be reviewed and if necessary, amended. Amendments should take into account the statistical consequences of protocol deviations as well as blinding methodology (if required).

The Statistical Analysis Section should be prepared at the beginning of the clinical study and should indicate how protocol deviations will be analyzed.

The final study report should state the frequency and type of protocol deviations and explain their effect on the results.

3.4 Submission of Protocol Deviations to the Research Ethics Committee

3.4.1 The investigator should inform the Research Ethics Committee of all protocol deviations. If the deviation results in a protocol modification, approval by the Research Ethics Committee will be required before it can be applied (ICH 4.5.2 and SOP 07), except if:

I. The change is purely administrative (i.e. telephone number, change of monitor, etc).

II. The modification must be implemented immediately for the well-being of research participants.

All documentation related to non-compliance with the protocol should be available for inspection by Health Canada, FDA, or an independent inspector designated by the sponsor.

4. References


Health Canada, Guidance for Industry, Good Clinical Practice: Consolidated guideline, ICH Topic E6, 1997


Québec, An act respecting health services and social services (R.S.Q., c. S-4.2).

Fonds de la recherche en santé du Québec (FRSQ), Guide d’éthique de la recherche et d’intégrité scientifique, Standards en éthique de la recherche et en intégrité scientifique du FRSQ (2e édition), août 2003
SOP 01, Organizing a Site for Clinical Research
SOP 07, Protocol and Protocol Amendment, Submission for Review by the Research Ethics Committee
SECTION III – Data Management, Security and Confidentiality

SOP 17 – Managing Investigational Products, Biological Products, Medical Devices and Radiopharmaceuticals Under Study

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4. References

1. Policy

Within the framework of the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH), this standard operating procedure (SOP) describes policies which deal with the management of investigational products, biological products, medical devices and radiopharmaceuticals. Management of these products includes receipt, labeling, storage, prescription and distribution of, accounting for, and the return or authorized destruction of the investigational products, biological products, medical devices and radiopharmaceuticals under study.

This SOP procedure concerns all institutional personnel working in clinical research and should be adhered to by all those working on clinical studies involving human participants.

2. Objectives

The objectives of this standard operating procedure are:
• To define standard operating procedures which describe how investigational products, biological products, medical devices and radiopharmaceuticals are managed within the establishment;

• To provide basic standards in order to ensure compliance with applicable regulatory requirements.

• To ensure that procedures for management of research products specific to a sponsor/sponsor-investigator, are followed.

3. Procedures

3.1 Generalities

In order to ensure the safety of research participants, integrity of the data and conformity with regulatory requirements, it is important to recall that responsibility for investigational products, biological products, medical devices and radiopharmaceuticals accountability at the study site rests with the investigator/institution (ICH 4.6.1).

In general, the type of investigational product, biological products, medical devices and radiopharmaceuticals under study, as well as the site where the clinical study is carried out, dictate the procedures to be employed. These specific instructions should be outlined in the protocol and applied by the research team within the institution.

As documented in the Plan d’action ministériel en éthique de la recherche et en intégrité scientifique – MSSS of Québec – mesure 16, […] the investigational medications should be subject to the same controls as medications available by prescription, in conformity with a. 116 and 117 (appendix 1) of an Act respecting health services and social services.

As documented in “An Act respecting health services and social services, Organization and Management of Institutions Regulation”, subject to the control of the director of professional services of the hospital centre, the head of the pharmacy department or the pharmacist shall: lay down and enforce policies for preparing, distributing and controlling the use of medications, drugs and poisons in the hospital centre (a. 77).

3.1.1 The pharmacist is in charge and is responsible for the investigational products (drugs). According to the structure of the institution, the pharmacy assumes functions related to the investigational product in order to standardize management and documentation. The investigator can delegate functions relating to biological products, medical devices and radiopharmaceuticals to a qualified person within the institution. It is important to document this delegation of tasks, as described in SOP 02 and to retain this documentation with the essential study documents, as described in SOP 01.

The Prescribing guidelines from the Jewish General Hospital, department of pharmacy read as follows:

In order to comply with the article 77, alinea 2 du règlement sur l’organisation et l’administration des établissements, créé en vertu de la Loi sur les services de santé et
les services sociaux where it is stated that “the chief Pharmacist is responsible of controlling the use of all the medications in the hospital”; the hereby measures must be followed:

- All medications, including study medications, must be delivered to the Pharmacy Department and stored in the Pharmacy Department.

- All medications, including study medications, must be dispensed by the pharmacy Department in agreement with the enactments of the articles 116 and 117 of the Loi sur les services de santé et les services sociaux.

The Quebec Order of Pharmacists states that study drug dispensing by Principal Investigators or by study coordinators or nurses directly contravenes the Pharmacy Bill (L.R.Q., chap. P-10) et de la Loi sur les services de santé et les services sociaux (L.R.Q., chap. M-5).

3.2 Receipt and Inventory of Investigational Products, Biological Products, Medical Devices and Radiopharmaceuticals

The investigator/qualified investigator, or the person designated by the investigator, or the pharmacist in the case of an investigational product should:

3.2.1 At the time of delivery of the investigational products, biological products, medical devices and radiopharmaceuticals, review the shipping instructions and ensure that they were followed. All documentation related to transportation and receipt of the investigational products, biological products, medical devices and radiopharmaceuticals should be retained with the essential study documents (SOP 01);

3.2.2 Within a short time, make an inventory of products received in order to ensure that the information on the shipment invoice corresponds to the products sent and received, including the quantity and lot number, if applicable. The result of the inventory should be documented and retained with the essential study documentation, as described in SOP 01.

3.2.3 List any product defects: packaging, labeling, quantity, etc. and follow-up with the sponsor or sponsor/investigator as soon as possible; report any inconsistency or divergence found during the inventory of investigational products, biological products, medical devices and radiopharmaceuticals received. This inspection should be documented and retained with the essential study documentation (SOP 01).

3.3 Labeling and Coding of Investigational Products, Biological Products, Medical Devices and Radiopharmaceuticals.

3.3.1 As documented in Health Canada’s Food and Drug Regulations, C.05.011: The sponsor/sponsor-investigator shall ensure that the drug bears a label on which appears the following information in both official languages.
I. A statement indicating that the drug is an investigational drug to be used only by a qualified investigator;

II. name, number or identifying mark of the drug;

III. expiration date of the drug;

IV. recommended storage conditions for the drug;

V. lot number of the drug;

VI. name and address of the sponsor/sponsor-investigator;

VII. code or protocol identification;

VIII. information required by subparagraph C.03.202(1)(b)(vi), if the drug is a radiopharmaceutical as defined in section C.03.201.

3.3.2 As described in paragraph 86 of Health Canada’s Medical Devices Regulations, no person shall import or sell a medical device for investigational testing unless the device has a label that indicates:

I. The name of the manufacturer;

II. The name of the instrument;

III. The statements “Instrument de recherche” and “Investigational Device”, or any other statement in English and French, that conveys that meaning;

IV. The statements “To be used by qualified investigators only (or qualified researchers)” and “Réservé uniquement à l’usage de chercheurs qualifiés (ou de chercheurs compétents)” or any other statement, in English and French, that conveys that meaning;

V. In the case of an in vitro diagnostic device, the statements « The performance specifications of this device have not been established » and « Les spécifications de rendement de l’instrument n’ont pas été établies » or any other statement, in English and French, that conveys that meaning.

3.3.3 The label on investigational products, biological products, medical devices and radiopharmaceuticals should not under any circumstances be completely hidden, withdrawn or modified without the authorization of the sponsor/sponsor-investigator. If, because of the requirements of the institution, an additional label (name of subject, name of institution, etc) is added, it should not completely cover the original label of the investigational product, biological products, medical devices and radiopharmaceuticals. In order to respect the confidentiality of research participant’s information, when containers which hold medication are returned to the sponsor, no information which could identify a research participant (nominative data) must appear on the label.

3.4 Storage of Investigational Products, Biological Products, Medical Devices, and Radiopharmaceuticals
• Investigational products must be stored in the pharmacy.
• Biological products, medical devices and radiopharmaceuticals should be stored in a secure environment as defined in SOP 01 and ICH 5.13.

The investigator, or the person designated by the investigator, or the pharmacist in the case of an investigational product should:

3.4.1 Establish and maintain controlled access for authorized personnel;
3.4.2 Develop procedures to control physical access to the storage site;
3.4.3 Store investigational products in a locked room;
3.4.4 Store investigational products in a location with appropriate and controlled temperature/humidity, as stated in the protocol, and should record, if applicable, the temperature/humidity as indicated in the protocol or in another study document;
3.4.5 Store investigational products, biological products, medical devices and radiopharmaceuticals as specified by the sponsor and in accordance with applicable regulatory requirements (ICH 4.6.1 and 4.6.4).

3.5 Distribution of Investigational Products, Biological Products, Medical Devices and Radiopharmaceuticals

The investigator, or the person designated by the investigator, or the pharmacist in the case of an investigational product should:

3.5.1 Inform each study participant about the correct use of the investigational product(s), biological products, medical devices and radiopharmaceuticals and should check, at intervals appropriate for the study, that the instructions are being followed properly by all participating study (ICH 4.6.6);
3.5.2 The investigator should ensure that investigational products, biological products, medical devices and radiopharmaceuticals are used only in accordance with the approved protocol (ICH 4.6.5).

In the case of a clinical study utilizing a drug (ICH 5.14):

3.5.3 Document and identify the person who is authorized to prescribe the drug;
3.5.4 Document and sign in the source document and, if necessary, in the Case Report Forms (CRFs) or in forms provided for by the protocol, assignment of the drug to the research participant;
3.5.5 Document in the source document and, if necessary, in the case report forms, or in the forms provided for by the protocol, any modification to, or deviation from, the drug dosage required by the protocol, as well as the reason for this modification or deviation;
3.5.6 Inform the research participant of his responsibility to return all unused medication as well as all medication packaging (bottle, container, syringe, etc.) even if empty, as specified in the protocol;

3.5.7 Document any delegation of tasks, as defined in SOP 02. Documentation of delegation should be retained with the essential study documentation, as described in SOP 01.

3.5.8 Submit to the REC all significant deviations from the drug dose/schedule that could have an impact on the health of the research participant. The submitted documents should be kept with the documentation essential to the study, as described in SOP 01.

**In the case of a clinical study using an investigational device:**

3.5.9 Document and specify the person who is authorized to prescribe the investigational device;

3.5.10 Submit and sign in the source documents and, if applicable, in the case report forms (CRFs) or in the forms provided for by the protocol, assignment of the investigational device to the research participant;

3.5.11 Document any delegations of tasks, as defined in SOP 02. Documentation of delegation should be retained with the essential study documents, as described in SOP 01.

3.6 Accounting for Investigational Products, Biological Products, Medical Devices and Radiopharmaceuticals

**The investigator or the person designated by the investigator the pharmacist in the case of an investigational product should:**

3.6.1 Document the quantity of drug used and returned for each research participant;

3.6.2 Compare, the amount of drug returned/used versus the allotted drug, for each research participant, if applicable;

3.6.3 Account for and document any inconsistency;

3.6.4 For the safety of the research participant, perform a study participant or pharmacy follow-up in the event of inconsistency in accounting, and document this inconsistency;

3.6.5 Under no circumstances, assign to another study participant, to a person outside the study, or at another site, drug assigned to a study participant and not used;

3.6.6 Retain this documentation with the study documentation, as defined in SOP 01.

**In the case of a clinical study utilizing an investigational device:**

3.6.7 Document and sign, if applicable, return of the device by the participant;

3.6.8 Under no circumstances, assign to another person or to another site, a device assigned to a participant and not used;
3.6.9 Maintain this documentation with the essential study documents, as described in SOP 01.

3.7 Return/Destruction of Investigational Products, Biological Products, Medical Devices and Radiopharmaceuticals

The investigator, or the person designated by the investigator, or the pharmacist in the case of an investigational product should:

3.7.1 Ensure that all documentation on the management of investigational products is complete and exact and is maintained for 25 years in accordance with Canadian regulations. This documentation should be kept with the essential study documentation as defined in SOP 01;

3.7.2 Return to the sponsor/sponsor-investigator any investigational products, biological products, medical devices and radiopharmaceuticals received within the framework of a clinical study or follow the instructions in the protocol or another study document relating to this subject;

3.7.3 Ensure in the case of destruction within the institution, that the institution or the pharmacy has appropriate procedures for the destruction of investigational products;

3.7.4 Ensure that the destruction was performed in accordance with procedures and that documentation relating to the process of destruction was, completed, signed and placed with the essential study documentation;

3.7.5 Ensure that the same process of destruction is used and documented in the case of defective or outdated products.

4. References


Health Canada, Regulations amending the food and drug regulations (1024 - clinical trials), (SOR/2001-203).

Health Canada, Medical Devices Regulations – Appendix no 1101 - (SOR/98-282).


Health Canada, Medical Devices Regulations, (SOR/98-282), May 7 1998.

Québec, An act respecting health services and social services (R.S.Q., c. S-4.2).

Québec, An Act respecting health services and social services, Organization and Management of Institutions Regulation, c. S-5, r.3.01.

Fonds de la recherche en santé du Québec (FRSQ), Guide d’éthique de la recherche et d’intégrité scientifique, Standards en éthique de la recherche et en intégrité scientifique du FRSQ (2e édition), août 2003.
Ministère de la santé et des services sociaux (MSSS), Plan d’action ministériel en éthique de la recherche et en intégrité scientifique – A6, Les médicaments d’expérimentation, Québec, 1998.

SOP 01, Organizing a Site for Clinical Research.
SOP 02, Research Team: Role Definitions, Responsibilities and Task Delegation
SOP 18 - Management of Biological Specimens: Collection and Storage

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4. References

1. Policy

Within the framework of the principles inherent of the Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH), this standard operating procedure (SOP) describes the policies surrounding management of biological specimens, such as blood and its components, cells, tissues and organs, from subjects participating in clinical studies. The management of biological specimens starts with their collection and ends with their destruction.

This SOP concerns all institutional personnel working in clinical research and should be adhered to by all those working on clinical studies involving human participants.

2. Objective

The objective of this operating procedure is to describe the management of biological specimens, from their collection to their destruction, within the institution.

3. Procedures

3.1 Generalities

In order to ensure the safety of participants, the integrity of data and adhesion to regulatory requirements, it is important to recall that responsibility for the collection of biological specimens from research participants lies with the investigator/institution.

According to the type of biological specimens collected, it is important to follow specific instructions for collection and management of specimens, as defined in the protocol. These specific operational procedures, including the maintenance and calibration of the equipment which will be used during the clinical study, should also be
defined (external laboratories, pathologists, or others). Data on maintenance and calibration should be registered and kept with the research team to insure accurate procedures.

3.1.1 The investigator can delegate responsibility for functions related to biological specimens to another qualified person. It is important to document this delegation as described in SOP 02 and to conserve this documentation with the essential study documentation, as described in SOP 01.

3.2 Collection of Biological Specimens

3.2.1 Before any specimen collection, the research participants should be well informed regarding the purpose of this procedure and should have understood and signed the informed consent form, as described in SOP 08.

3.2.2 The investigator or his/her delegate should ensure that the equipment meets the requirements of the protocol and that a process of maintenance and calibration is established (ICH 8.3.7).

3.2.3 Any documentation connected with maintenance of the equipment should be preserved with the essential study documentation (SOP 01).

3.2.4 The investigator or his/her delegate should ensure the safety and well-being of research participants during the collection of specimens.

3.2.5 In order to avoid any error, it is recommended that each specimen be identified as precisely as possible. The number of the protocol, the number of the research participant, as well as the date when the collection was made should be included, according to the specifications in the protocol.

3.2.6 All specimens collected for the clinical study should be listed. This documentation should be kept with the essential study documentation (SOP 01).

3.3 Storage of Biological Specimens

The investigator or his/her delegate should:

3.3.1 Ensure that storage of biological specimens takes place in a secure and suitable environment, as defined in SOP 01;

3.3.2 Establish and maintain controlled access for authorized personnel, in order to guarantee research participant’s confidentiality;

3.3.3 Develop procedures to control physical access to the storage site;

3.3.4 Specify the storage time for biological specimens as defined in the protocol;

3.3.5 Store biological specimens in a location which conforms to the requirements of the protocol. Storage conditions should be checked regularly. The checking process should be documented and the documentation retained with the essential study documentation;

3.3.6 Make preparation for a backup system in the event of a power or equipment failure;
3.3.7 Ensure the viability of the specimens by using shipping materials as specified by the protocol (example: dry ice) if the specimens are sent outside the institution or country for analysis. Whenever specimens are moved from the storage site, documentation concerning authorization from the person responsible for storage should be retained with the essential documentation of the study;

3.3.8 Ensure, if the specimens are shipped, that applicable laws and standards of transport are respected. The operation should be documented and the documentation kept with the essential documentation of the study.

3.4 Analysis of Biological Specimens

3.4.1 According to the requirements of the protocol concerning analysis of the specimens, they can be analyzed at the time of collection or at the end of the clinical study.

3.4.2 The investigator should know, within a reasonable time, the results of the analysis related to the follow-up of a research participant, with reference to the protocol.

3.4.3 The investigator should be in a position to know all the results of the analysis by the end of the study or as specified in the protocol and in the participant informed consent form.

3.4.4 Research personnel should be informed of any modification in laboratory norms or changes in the calibration of material used for analysis of the specimens.

3.5 Destruction of Biological Specimens

According to the requirements of the protocol and of the institution, specimens can be destroyed, if applicable.

3.5.1 The investigator should ensure that documentation related to the destruction was completed, signed and retained with the essential documentation.

4. References

Health Canada, Guidance for Industry, Good Clinical Practice: Consolidated guideline, ICH Topic E6, 1997

WHO 2001, Standard Operating Procedures for Clinical Investigators, TDR
SOP 01 Organizing a Site for Clinical Research
SOP 02 Research Team: Role Definitions, Responsibilities and Task Delegation
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SECTION III – Data Management, Security and Confidentiality

SOP 22 – Source Data and Document Management

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4. References

1. Policy

Within the framework of the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH), this standard operating procedure (SOP) aims to ensure that valid clinical data are collected from observations or actions of study subjects and reported in source documents. Equally, it aims to ensure that the process used for data collection is complete, accurate and verifiable.

As described in the law and in Health Canada’s Food and Drugs Regulations, this SOP defines what are considered data and source documents, as well as defining the duration of storage of said data or source documents.

2. Objective

The objective of this operating procedure is to describe the process of collection and storage of data and source documents, and to ensure that management of the process complies with the principles of GCP of the ICH. To achieve this goal, it is imperative that the case report form (CRF) represents the participant’s data precisely and that the said data are complete, accurate, precise and up-to-date.

3. Procedures

3.1 Confidentiality and Direct Access to Data and Source Documents
All pertinent documents should be identified, dated and signed. Electronic signatures are acceptable.

3.1.1 In the interest of accuracy of the source documents, which include pharmacy and laboratory documents, radiology films, if applicable, the sponsor-investigator or the investigator should have a written document or computerized system for research participant documentation which will make it possible to compare the source data/documents and the CRF.

3.1.2 Research participants authorize access to their data in the belief that all verified and collected information will be kept confidential by the sponsor/sponsor-investigator, representatives authorized by sponsor/sponsor-investigator, auditors and inspectors of the regulatory authorities (SOP 08).

3.1.3 Any person with direct access to the source data should respect the Declaration of Helsinki, GCP of the ICH and applicable regulatory requirements for the maintenance of confidentiality of the identity of study participants and of the proprietary information of the sponsor/sponsor-investigator.

3.2 Signature Sheet

A signature sheet identifying those who have access and those who can enter or correct source data should be kept in the investigator’s file as an essential study document, as described in item 8.3.24 of the table of section 8, Management of Essential Documentation of the Trial of the ICH and SOP 01.

3.3 Designation of Source Documents

Source documents can be defined in the protocol in order to allow their verification during the study. Moreover, the protocol should identify the parameters that should be entered directly into the CRF; in this case, these data will be considered as source data. The designation of source documents includes, but is not limited to:

a) Documentation of the process of obtaining informed consent (ICF);

b) The ICF signed and dated by the research participant and the person who obtained the consent;

c) The medical file including medical history, diagnoses and medical follow-up;

d) Any communication between the various parties, i.e. sponsor/investigator investigator/participant. Examples of communication: email, telephone messages, etc.;

e) Demographic data: participant’s name, date of birth and sex;

f) Concomitant medications, current and previous, as the case may be, according to the protocol;

g) Inclusion or exclusion and randomization criteria;
h) Dates of study visits, including the beginning and end of the study, start and stop dates for medication, dates of laboratory tests and other diagnostic procedures;

i) Results of objective tests (X-rays, laboratory results, electrocardiograms, etc.) reviewed, signed and dated by the investigator or his authorized representative and interpretation of the result: "clinically relevant" or not;

j) Details of adverse events (AEs) or serious adverse events (SAEs), including beginning and end dates, etiology, relevant tests, treatment received and the consequences, as well as all available information on this topic in the source data;

k) Primary and secondary variables of effectiveness;

l) The participant number, the randomization number and the allotted CRF number, if relevant.

Any document in which clinical study data is recorded for the first time, is considered to be a source document (note, appointment book, subject’s medical file, etc.). All these source documents should be signed, handled and filed according to the applicable regulations.

3.4 Paper or Electronic Clinical Data

The sponsor-investigator or the investigator/qualified investigator is responsible for:

3.4.1 Reporting case report form (CRF) data precisely as required by the protocol. These data should correspond to the data and the source documents on all points, and for all research participants.

3.4.2 Re-examination of the clinical study data in agreement with the principles of the ICH.

3.4.3 Storage of data and source documents in agreement with SOP 01 and SOP 23.

3.4.4 The maintenance and accuracy of the data and the source documents for all research participants.

3.4.5 In the case of an electronic source data document, ensuring that the document is printed, dated and signed by himself or his delegate, to confirm its content. This document should be preserved and filed with the other study source documents (SOP 01).

3.4.6 In the case of an electronic source data document with electronic signature, making track changes available, for the period of storage of the documents, according to the regulations in force. The person using the electronic signature should not be able to modify the tracking system.

3.4.7 In the case of source data entered directly into the electronic CRFs, as stated in the protocol, using a track change system, for the duration of storage of the documents according to the regulations in force. The management of electronic data is described in SOP 23.
3.4.8 Preserving a certified copy or the original for electronic data tracking.

3.5 Documentation of Source Data

3.5.1 All source data collected should be kept in the source document from the time of collection or observation in a secure place.

3.5.2 For documentation, the following standard practices should be observed:
   a) Data should be entered in a sequential manner, without leaving any empty spaces;
   b) Data should be dated and signed by the authorized person;
   c) The date when the data were collected as well as the date of data entry, should appear for data obtained after a visit (late data);
   d) Late data cannot be inserted between existing lines or written in the margin, it should be inscribed following other entries with the notation of late entry;
   e) Data written by hand should be legible and written with permanent ink;
   f) Data entered by several team members: each entry should be signed and dated by the authorized person who made the entry;
   g) Use of liquid corrector or correcting material is prohibited;
   h) Work sheets or work forms can be created by the site to collect information necessary to the protocol. Data collected on these documents are an integral part of the source documents;
   i) Missing elements (i.e. visit or tests not conducted) should be clearly reported in the source document;
   j) Entries entered directly into the CRF are defined as source data;
   h) Data to be entered directly into the CRF should be mentioned in the protocol.
   i) Source document should always contain the name of the patient and the hospital or unit number, if applicable

3.6 Correction of Source Data

3.6.1 Corrections made to source data should follow the same procedure as corrections to CRFs:
   a) A single line through the data to be corrected (it should be possible to read the original data);
   b) The initials of the person who corrected the data and the date of correction, according to the format described in the protocol;
   c) Corrections should be made, preferably, by the person who made the entry or by others authorized to do so (see item 3.2, signature sheet);
d) The use of liquid corrector or correcting material is prohibited.

3.7 Storage of Source Documents

The sponsor-investigator or the investigator should:

3.7.1 Ensure that, in the case of a clinical study using a drug or medical device, the source documents are retained for a given period of time as described in Canadian regulation (C.05.012 (4)) being 25 years.

3.7.2 Ensure, in the case of source data registered on thermal paper (i.e. electrocardiogram, respiratory function test, etc.), that a dated and signed photocopy of the original document has been made and is attached to the original document.

3.7.3 Clearly identify source documents (including the medical files of research participants) and the investigator’s file for archiving (ICH 1.51 and 1.52).

3.7.4 Record in logs, manage and store clinical study information in a manner which will permit the preparation of complete and accurate reports as well as permit their interpretation and verification.

3.7.5 Ensure, in the case of a clinical study with a drug or medical device, that the records department is aware that a file is related to a clinical study, that it cannot be purged and that it should be stored for 25 years, as described in Health Canada regulations.

3.7.6 Ensure that, in the case of a clinical study without a drug or medical device, the duration of storage of documents should be in conformity with the document entitled « calendrier de conservation des documents » submitted by the institution to provincial authorities. (Quebec Archives Act, chap. A-21.1 a. 8, 9 and 35) (Recueil de règles de conservation des documents des établissements de santé et services sociaux, section 4, dossier X1-0350, dossier de l’usager).

3.7.7 Ensure that the same period of storage for documents applies to the identification of documents for filing, recording of the information, and guarantee that the records department is informed that a medical file is attached to a clinical study.

4. References

Health Canada, Guidance for Industry, Good Clinical Practice: Consolidated guideline, ICH Topic E6, 1997

Declaration of Helsinki, 2002


Quebec, Civil Code of Quebec, L.Q. 1991, C64

Quebec, Archives Act (R.S.Q., A-21.1 a. 8, 9 and 35)
Québec, An act respecting access to documents held by public bodies and the protection of personal information (R.S.Q., A-2.1)

Association des hôpitaux du Québec, Recueil de règles de conservation des documents des établissements de santé et services sociaux, section 4, X1-0350, dossier de l’usager, édition 2004

SOP 01, Organizing a Site for Clinical Research

SOP 08, Consent Process and Informed Consent Document
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1. Policy

Within the framework of the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH) and those adhered to by Health Canada, as well as regulations of the FDA, this standard operating procedure (SOP) describes the management of clinical study data in terms of collection and entry into case report forms (CRFs), whether paper or electronic format.

This SOP concerns all institutional personnel working in clinical research and should be adhered to by all personnel working on clinical studies involving human participants.

2. Objectives

One of the objectives of this operating procedure is to define the different stages of management of clinical data entered onto the CRFs, whether on paper or electronically. This SOP describes the stages of collection, capture and storage of data, as well as quality control and corrections to clinical data collected during the study.

The other objective is to ensure that the collection, follow-up, control and confidentiality of all clinical data entered in a CRF, paper or electronic, conform to the principles of the ICH and the laws and regulations in force. In order to achieve this goal, it is imperative that the system used for applicable capture and processing of data is validated, and that the databases in which clinical data are stored accurately represent the participant’s data.

3. Procedures

3.1 Generalities
The sponsor-investigator, who is responsible for the management of clinical data for the study, should:

3.1.1 In accordance with the ICH, employ appropriately qualified individuals to supervise the overall conduct of the study, to handle and verify data, to conduct statistical analyses, and to prepare the study reports (ICH 5.5.1).

3.1.2 In the case where management of clinical data is performed directly by a service within the institution, develop instructions according to the recommendations made by the Society for Clinical Data Management (SCDM) and The Good Clinical Data Management Practices.

3.1.3 Manage authorizations for access to clinical data within the clinical research unit, whether physical or electronic access to the clinical study data.

3.1.4 Ensure the protection and security of clinical study data.

3.1.5 Ensure adherence to applicable regulatory requirements regarding confidentiality of the identity of research participants and their data by using unambiguous identification codes that allows identification of all data reported for each participant (ICH 5.5.5).

3.1.6 Precisely enter the data from the case report forms as required by the protocol. This data should correspond at every point with the data and source documents for all research participants.

3.1.7 Ensure that the electronic system used for clinical data management is valid and complies with regulatory requirements (ICH 5.5.3a), FDA and MSSS.

3.1.8 Retain the original or a certified copy of the certified data backup as well as an audit trail (ICH 5.5.3.F and 5.5.4).

3.1.9 Ensure that clinical study reports are prepared and provided to regulatory agency(ies) as required by the applicable regulatory requirement(s) (ICH 5.22).

3.1.10 Ensure that a summary of the study results is provided to the REC (ICH 4.13).

3.1.11 Safeguard the blinding, if any (during data capture and processing) (ICH 5.5.3g).

3.2 Confidentiality and Direct Access to Clinical Data

3.2.1 A document identifying persons authorized to access, enter or correct clinical data in the CRFs, should be retained with the essential study documentation, as described in ICH-GCP, section 8.3 Essential Documents for the Conduct of a Clinical Trial point 8.3.24, and the document of the MSSS, Cadre global de gestion des actifs informationnels - Volet sécurité, a. 4.1.2, par. 3. Moreover, the MSSS document states that a control mechanism should be set up for tracking entry/exit of persons accessing the site.

3.2.2 This document should be updated according to the roles and responsibilities delegated by the sponsor-investigator or the investigator, as described in SOP 02.
3.3 Collection and Clinical Data Capture

3.3.1 All clinical study information should be recorded, processed, and stored in a way that allows its accurate reporting, interpretation and verification (ICH 2.10).

3.3.2 In order to ensure the integrity and tracking of all clinical data, a procedure for collecting, capturing, controlling, verifying, correcting and processing data should be established while respecting the fact that the study is blinded, if applicable (ICH 5.5.3g).

3.3.3 Two methods can be used for the data capture: single or double data entry, this is dependant on type of CRF used and the location where it is carried out (site, CRO, etc). The method of capture is defined by the investigator or the sponsor-investigator in the protocol or other document.

3.3.4 A system for tracking data entry and modification should be available for the period of document retention according to the regulations in force.

Paper CRFs:

3.3.5 Paper CRFs should be filled out according to SOP 24. Any modification made to the clinical data before capture should be justified and authorized by the investigator or his delegate. The process of modification should correspond to the procedure described in SOP 24. The CRF should be signed and dated by the investigator or his delegate, as described in the delegations/signatures document SOP 02 and in section 8.3 item 8.3.24 in ICH-GCP.

3.3.6 Data entry onto paper CRFs is carried out according to the method of double data entry by two people. Comparison of the two entries and correction of errors can be made by a third person.

3.3.7 If clinical data is captured directly by the research team, only those authorized by the investigator can then enter the CRF data into the database. This delegation of tasks will be documented, as described in SOP 02.

3.3.8 In the case where capture of clinical data is made by an external organization (CRO), as defined by the protocol, a copy of the CRF should retained by the investigator.

Electronic CRFs:

3.3.9 Installation of an electronic system should be validated within the infrastructure of the clinical research unit, in order to ensure its reliability and precision, as well as its expected performance (ICH 5.5.3. &FDA Guidance for Industry: Computerized System used in Clinical Trials).

3.3.10 Only persons authorized by the sponsor-investigator or the investigator and those who have an authenticated identification have access to the electronic data management system. Measures of protection, detection and correction should be in place (electronic signature or secure electronic signature).
3.3.11 In the case of online data entry, both methods of data entry are applicable.

3.3.12 The sponsor-investigator or the investigator should ensure that those using the clinical data processing system are trained in the use of the electronic system.

3.3.13 If, as stipulated in the protocol, clinical data are transferred to another system, the transfer should be validated and secure.

3.4 Quality Control and Modifications to Clinical Data

3.4.1 In order to ensure the integrity of the data, the sponsor-investigator should establish quality control systems so that studies are conducted in accordance with the protocol, with GCP and with the regulatory requirements.

3.4.2 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly (ICH 5.1.3).

3.4.3 In order to decrease errors during the data capture process (single or double), interactive quality controls can be established, whether it is for paper or electronic CRFs.

3.4.4 In order to ensure coherence of the data within the same CRF, other quality controls should be applied once data capture is completed.

3.4.5 Once the contents of a CRF are confirmed, all modifications made to the data by authorized persons should be justified and documented.

3.4.6 These modifications can be requested and documented on paper or electronically using the Data Clarification Form (DCF), prepared by the research team or by the CRO in charge of data capture at the time the clinical study was initiated. These forms should be re-examined and signed by the investigator or his delegate. The original document should be retained by the sponsor/sponsor-investigator and a copy should be retained by the investigator (ICH 8.3.15).

3.4.7 A tracking system (paper or electronic) of all data modifications should be retained for 25 years in the case of clinical studies using an investigational product or according to the regulations in force for clinical studies without investigation products. This system should be accessible in the event of an audit and inspection.

3.5 Clinical Data Processing

Processing of clinical data should be described in the protocol or in the statistical analysis plan.

If the sponsor/sponsor-investigator uses electronic data processing systems at the site or at a remote site, he should ensure that the data processing is performed in accordance with study methodology such as blinding, if applicable (ICH 5.5.3 g).

3.5.1 The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical study, including safety
data and the critical efficacy endpoints at certain intervals, and to recommend to the sponsor whether to continue, modify, or stop a study (ICH 5.5.2).

3.5.2 The IDMC should have written operating procedures and maintain written records of the minutes of all their meetings (ICH 5.5.2).

3.5.3 The sponsor-investigator can perform interim statistical analyses, while the study is being conducted, if so stipulated in the protocol.

3.6 Storage of Clinical Data

3.6.1 For any clinical study, the investigator should ensure that the clinical data (paper or electronic) are protected against the effects of time and against all accidental destruction.

3.6.2 In the case of a clinical study using a drug or medical device, paper or electronic CRFs, like all other source documents, should be retained for the necessary storage period required by Canadian regulations, Health Canada (C.05.012 (4)) of 25 years.

3.6.3 In the case of a clinical study without a drug or medical device, the period of retention should comply with the schedule of storage of documents submitted by the institution to the provincial authorities. (Loi sur les archives. L.R.Q., chap. A-21.1 art. 8, 9 and 35) (Recueil de règles de conservation des documents des établissements de santé et services sociaux, section 4, dossier X1-0350, dossier de l’usager).

3.6.4 The same period of document retention applies to the identification of the documents for archiving to, the recording of the information and to the assurance that the archiving department has been informed that a medical file is related to a clinical study and that this file cannot be purged.

4. References

Health Canada, Guidance for Industry, Good Clinical Practice: Consolidated guideline, ICH Topic E6, 1997


Food and Drug Administration (FDA), Guidance for Industry: Computerized systems used in clinical trials, April 1999

Québec, Archives Act (R.S.Q., A-21.1 a. 8, 9 and 35)

Québec, An act respecting access to documents held by public bodies and the protection of personal information (R.S.Q., A-2.1)

Ministère de la santé et des services sociaux (MSSS), Cadre Global de Gestion des Actifs Informationnels appartenant aux organismes du réseau de la santé et des services sociaux : Volet Sécurité, septembre 2002
SOP 01, Organizing a Site for Clinical Research.
SOP 02, Research Team: Role Definitions, Responsibilities and Task Delegation
SOP 24, How to Fill In a Case Report Form and Modify Data
SOP 25, Security and Confidentiality of Data
SOP 24 – How to Fill In a Case Report Form and Modify Data

1. **Policy**

   Within the framework of the principles inherent to Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH) and published by Health Canada, this standard operating procedure (SOP) describes how a case report form (CRF) should be completed and how corrections or modifications should be made to the CRF, whether paper or electronic.

   This **SOP concerns all institutional personnel working in clinical research** on studies involving human participants and **should be adhered to by all those authorized to complete and sign CRFs and to correct or modify data entered onto CRFs**.

2. **Objectives**

   One of the objectives of this operating procedure is to define the process of collection of clinical data required by the protocol in order to ensure the integrity of said data recorded on a CRF, paper or electronic. Data recorded on a CRF can be generated from source data or documents, or can be directly collected in the CRF in accordance with the protocol.

   The other objective of this SOP is to ensure the legibility, authenticity and accuracy of all recorded clinical data collected in a paper or electronic CRF, in accordance with the principles of the ICH.

3. **Procedures**

   3.1 **Generalities**

   The sponsor-investigator or the investigator should make sure that all clinical study data recorded on a paper or electronic CRF, are accurate, complete and legible.
All the clinical study information should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification (ICH 2.10).

3.2 **Recording Data on Case Report Forms**

3.2.1 Data recorded in the CRF, which are drawn from source data or documents, should correspond to the data appearing in these documents. All variations should be explained, documented and approved by the sponsor-investigator or the investigator or his delegate.

3.2.2 CRFs should be completed only by authorized persons. This authorization should be documented, as defined in SOP 02.

3.2.3 The sponsor-investigator or the investigator or his delegate should only allow individuals with the required qualifications or training in CRFs completion and data verification to take part in this task. Confirmation of this qualification or training should be completed, as described in SOP 03.

3.2.4 For reasons of security and confidentiality of research participants and their data, only non-ambiguous research identification codes should be used for identification of all data reported in the CRF for each research participant (ICH 5.5.5, SOP 25).

3.2.5 The CRF should be completed as soon as the data are available or during the study participant’s evaluation or follow-up visit.

3.2.6 In the case of a paper CRF, use of a black ball-point pen is recommended, especially if the CRF is made up of several copies with carbon paper.

3.2.7 If, for any reason, information required in the CRF cannot be provided, it is recommended that specific codes be defined for the missing data. These codes should be defined at the time the CRFs are designed.

3.2.8 Data referred to in the protocol, which are directly recorded on paper or electronic CRFs, should be signed and dated by the investigator or his delegate.

3.3 **Modifying Case Report Forms**

3.3.1 If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data (ICH 5.5.4).

3.3.2 In order to respect this principle, a tracking mechanism for all modifications of the data should be established. This process of control, verification and correction should allow for comparison with the source data, and should make it possible to determine by whom, when and why the modification was made.

**Paper Case Report Forms**

3.3.3 If errors are noted and modifications made to the CRF before being sent to entry and data processing personnel, the incorrect data should be crossed out with a single line, so as to remain legible, and the new data written next to the incorrect data. The person who makes the correction should initial and date the change. If applicable, the reason for correction may also be indicated.
3.3.4 **The use of corrector fluid or other correction material is not authorized.**

3.3.5 Any modifications made to paper CRFs should be justified, reviewed, authorized and approved by the investigator. To confirm this approval, it is recommended that the investigator signs and dates the CRF only when the correction process is finished and the CRF is ready to be transmitted to personnel responsible for capture and processing of the data, designated by the sponsor/sponsor-investigator.

3.3.6 In the case where correction to the data is made after the CRF is retrieved from the site, any necessary data modification requires completion of the data clarification form (DCF), as described in SOP 23. The original DCF is retained by the sponsor/sponsor-investigator and one copy given to the investigator (ICH 8.3.15).

**Electronic Case Report Forms**

3.3.7 Any modification or addition to the information should be made by those delegated by the sponsor-investigator or investigator and trained in recording and correction of data on electronic CRFs.

3.3.8 Any modification or addition to the information should be confirmed and signed by the sponsor-investigator or investigator using an electronic signature.

3.3.9 The sponsor-investigator should ensure that the electronic system guarantees tracking and stores all successive modifications in memory (ICH 5.5.4 and FDA Guidance for the Industry Part 11, Electronic Records; Electronic Signatures – Scope and Application).

3.3.10 The sponsor-investigator or the investigator should maintain a copy of the certified data backup (ICH 5.5.3.f).

3.3.11 If it is stipulated in the protocol that the clinical data are transferred to another system, the transfer should be validated and secure as mentioned in the protocol. This transfer should be documented in the protocol.

3.4 **Confirming and Signing Case Report Forms**

3.4.1 Once the CRF is completed, the sponsor-investigator or the investigator should ensure the integrity and coherence of the collected information.

3.4.2 The CRF should be signed and dated by the sponsor-investigator or the investigator, as defined by the delegation/signature form (SOP 02). This delegation should be retained with the essential study documents (SOP 01).

4. **References**

Health Canada, Guidance for Industry, Good Clinical Practice: Consolidated guideline, ICH Topic E6, 1997

Food and Drug Administration (FDA), Guidance for Industry: Computerized systems used in clinical trials, April 1999

Ministère de la santé et des services sociaux (MSSS), Cadre Global de Gestion des Actifs Informationnels appartenant aux organismes du réseau de la santé et des services sociaux : Volet Sécurité, septembre 2002

SOP 01, Organizing a Site for Clinical Research
SOP 02, Research Team: Role Definitions, Responsibilities and Task Delegation
SOP 03, Site Research Team: Competence, Knowledge and Training
SOP 23, Clinical Data Management, Paper or Electronic Format
SOP 25, Security and Confidentiality of Data
SOP 25 –Security and Confidentiality of Data

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1. Policy

This standardized operating procedure (SOP) describes procedures to be followed to ensure the security and confidentiality of data in a clinical study. These procedures respect the principles in Good Clinical Practice (GCP) of the International Conference on Harmonization (GCP), regulations of the Ministère de la santé et des services sociaux (MSSS) concerning security issues, as well as US Regulations of the FDA (21 CFR, part 11) concerning electronic data.

This SOP concerns all institutional personnel working in clinical research and should be followed by all those working on clinical studies involving human participants.

2. Objectives

The first objective of this operating procedure is to describe the process that ensures the quality, integrity and confidentiality of clinical data collected within the framework of a clinical study.

The other objective is to describe procedures for the protection of data from any risk of accidental or involuntary destruction.

3. Procedures

3.1 Generalities

3.1.1 The sponsor-investigator or the investigator is responsible for authorizing access to the clinical data. This authorization should be documented in the protocol and on the form for delegation of tasks, as defined in SOP 02.

3.1.2 Every person with direct access to clinical data should comply with the Declaration of Helsinki, the directives of the ICH-GCP and regulatory requirements for the maintenance of confidentiality, research participants’
identity and respect for the proprietary information of the sponsor or the sponsor-investigator.

Authentication of the person who has access to the data constitutes the most important aspect of security. It determines the overall level of protection and is linked to key elements of data security.

3.2 Data Security

3.2.1 A mechanism for control of access to secure premises should be established and documented; (reference SOP 02 and the MSSS cadre global de gestion des actifs informationnels – Volet Sécurité) It is recommended that the control mechanism use magnetic cards or a biometric recognition system that allows tracking of movement in and out of the premises, if applicable.

3.2.2 A tracking document with the signatures and initials of all persons authorized to register data or to make corrections to the CRFs, should be retained with the essential study documentation (ICH 8.2 and 8.3.24).

3.2.3 Physical security concerns the premises where study files, containing essential documents and clinical data, as well as computer equipment used for data management, such as telecommunication servers, database servers and computers are located. These rooms should:

a) Be located in an area protected from possible disasters (ex: water or fire damage, etc.);

b) Be protected by a secure access control system.

3.2.4 Logical security mainly concerns management of access to data which includes identification, authentication and authorization. In order to ensure logical security, the following measurements should be applied:

a) Authorization for access is limited to members of the research team and those identified by the protocol, the consent form and the delegation of tasks form as mentioned in SOP 02;

b) Privileges for physical or electronic access to data are granted to personnel and updated according to the roles and responsibilities defined by the sponsor-investigator or the investigator (SOP 02);

c) Designated by sponsor/sponsor-investigator, the person in charge of system management, called a system administrator, can suspend the access authorization of a user after a given number of errors. Other users should be informed of this suspension. The delegation of tasks form should show this suspension (SOP 02).

d) If a member of the research team leaves (resigns, illness, preventive leave, other reason), his access authorization should be cancelled. The delegation of tasks form should reflect this cancellation (SOP 02);
e) A different identification code should be given to each user of the data management system. The password, confidential and specific for each user, that gives access to the system should be changed regularly according to the period defined by the system administrator;

f) The system administrator should ensure the confidentiality of the authentication of system users. He should also document the tracking of access;

g) A plan for saving and recovering data should be established, in the event of loss or disaster;

h) Standardized procedures for logical security should be developed, enforced and respected.

3.3 **Data confidentiality**

As mentioned in SOP 22 and according to the Act respecting access to documents held by public bodies and the protection of personal information:

a) A public body may not release nominative information without the consent of the person concerned. Notwithstanding the foregoing, a public body may release nominative information without the consent of the person concerned in the following cases and strictly on the following conditions:

- to a person who is authorized by the Commission of access to information, in accordance with article 125, to use the information for the purpose of study, research or statistics (a. 59, 1982, C. 30, has.59; 1983, C. 38, A.55; 1984, C. 27, A.1; 1985, C. 30, A. 5; 1987, C. 68, A. 5; 1990, C. 57, A. 13);

b) Nominative information is confidential, except for some cases (a. 53, 1982, c. 30, s. 53; 1985, c. 30, s. 5; 1989, c. 54, s. 150; 1990, c. 57, s. 11);

c) In any document, information concerning a natural person which allows the person to be identified is nominative information (a. 54, 1982, c. 30, s. 54);

d) Every person has the right to be informed of the existence of nominative information concerning him in a personal information file (a.83, 1982, c 30, s. 83, 1987, c.68, s.6; 1990, c.57, a.21; 1992, c.21, a. 74);

3.3.1 In conformity with the requirements of the applicable regulations concerning protection of personal information, confidentiality of files in which research participants may be identified must be protected (ICH 2.11 & the MSSS).

3.3.2 A research participant who authorizes access to data relating to him/her should be reasonably assured that the sponsor/sponsor-investigator, the investigator, representatives authorized by the sponsor/sponsor-investigator, the REC and auditors and inspectors of the regulatory authorities have all taken precautions so that verified and collected data remain confidential (ICH 5.15.1 & SOP 08).
3.3.3 Confidentiality of data should be maintained and respected in the course of and after the clinical study (SOP 09)

4. References

Health Canada, Guidance for Industry, Good Clinical Practice: Consolidated guideline, ICH Topic E6, 1997

Health Canada, Food and Drug Act– Part C, Division 5, Drugs for clinical trials involving human subjects, August 31 2004

Declaration of Helsinki, 2002

Quebec, An act respecting access to documents held by public bodies and the protection of personal information (R.S.Q., A-2.1)

Ministère de la santé et des services sociaux (MSSS), Cadre Global de Gestion des Actifs Informationnels appartenant aux organismes du réseau de la santé et des services sociaux : Volet Sécurité, septembre 2002

Fonds de la recherche en santé du Québec (FRSQ), Guide d’éthique de la recherche et d’intégrité scientifique, Standards en éthique de la recherche et en intégrité scientifique du FRSQ (2e édition), août 2003


SOP 01, Organizing a Site for Clinical Research

SOP 02, Research Team: Role Definitions, Responsibilities and Task Delegation

SOP 08, Consent Process and the Informed Consent Document

SOP 22, Source Data and Document Management
SECTION IV - Ongoing Communication and Study Closure

SOP 14 – Research Ethics Committee (REC): Ongoing Communications

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   Appendix 1 – Example of Letter of Submission to the Ethics Committee

1. Policy

Within the framework of the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH), the Tri-Council Policy Statement (TCPS), as well as the from the Fonds de la recherche en santé du Québec (FRSQ), this standard operating procedure (SOP) outlines policies regarding Research Ethics Committees (REC) and describes procedures for the management of communications between the investigator and the Ethics Committee.

All research involving living human participants, cadavers, human remains, tissues, body fluids, embryos or foetuses, will be assessed and approved by the REC according to the TCPS (rule 1.1), prior to being initiated. Moreover, it is stated in the FRSQ (page 20) that research conducted on gametes or based on personal information contained in medical files should also be submitted to a REC.

This SOP concerns all institutional personnel working in clinical research and should be followed by all those working on clinical studies involving human subjects.

2. Objective

To ensure respect for the rights, protection, safety and well-being of research participants, the institutional Research Ethics Committee is responsible for reviewing and periodically monitoring biomedical research projects involving human participants. For all clinical studies, communications between investigator and the REC starts with
the preparation of documents for submission, and continues during the study until submission of the final report. The objective of this standard operating procedure is to describe the communications process (submission, follow-up, etc.) between the investigator and the REC, during the course of clinical studies.

3. Procedures

The Board of Directors of the institution is ultimately responsible for both the quality of the research and research ethics. The Board appoints the Research Ethics Committee for this purpose. The institution defines the responsibilities of the REC by specifying its mandate, membership, length of term for each member and accountability to the Board of Directors (translated from FRSQ, part 1, section 1).

The REC should safeguard the rights, safety and well-being of all research participants. Special attention should be paid to studies that may include vulnerable populations (ICH 3.1.1).

3.1 Documents to be Submitted to the Research Ethics Committee

The investigator is responsible for submitting the following documents to the REC:

3.1.1 No objection letter (NOL) in the case of a CTA (Clinical Trial Application) submission or CTAM (Clinical Trial Application Modification) to Health Canada;

3.1.2 Study protocol and protocol modification. The complete protocol should be submitted and reviewed by the REC;

3.1.3 Participant informed consent forms (ICF) and ICF modifications including all translations that will be used;

3.1.4 Research participant recruitment methods (ads, posters, etc.);

3.1.5 Written documentation to be provided to potential or actual research participants;

3.1.6 Investigator’s Brochure (for studies with drugs) or product monograph, if applicable;

3.1.7 Other available information on the safety of the study investigational products, biological products, medical devices and radiopharmaceuticals, if applicable;

3.1.8 Information on participants’ compensation (this information is usually included in the ICF);

3.1.9 Upon request, Curriculum Vitae of investigator or update if applicable, and other documents pertaining to his/her competence;

3.1.10 Any other documents required by the REC such as letters of approval from Director of Department and/or Director of Nursing, budget, investigator’s summary, if applicable.

3.1.11 The investigator should keep a copy of these documents in the file of study-related essential documents.
3.2 Preparation of Documents and Submission to the Research Ethics Committee

The investigator is responsible for submitting pertinent documents to the REC. Tasks required for the submission may be delegated, but the responsibility rests with the investigator.

3.2.1 The investigator is responsible for the reading and signing of the submission for the different committees even if it has been prepared by a member of the study team;

3.2.2 The investigator, to prevent any delays in the implementation of a clinical study, should be aware of the frequency and schedule of meetings of the REC, as well as periods when the Committee does not convene.

3.2.3 The investigator, to prevent any delays in the implementation of a clinical study, should be aware of the frequency and schedule of meetings of the institutional scientific review committee (if applicable) which will assess the scientific value of a clinical study, or of other committees if any, as well as periods when they do not convene. At the JGH the scientific and ethical aspects of the study are assessed jointly by the REC.

3.2.4 The investigator should be aware of the cut-off date (deposition of documents to be approved) for submission to different committees as well as of the number of copies of each document to be submitted (At the JGH, 15 copies).

3.2.5 The investigator should affirm his adherence to good clinical practice to the REC. Documents related to this adherence should be available for consultation and kept with the file of study-related essential documents.

3.2.6 The investigator should complete an application form available on the hospital website: www.jgh.ca/rec. The investigator should know if other specific forms are to be used to complete the submission.

3.2.7 The investigator should know if there are any review fees for the Research Ethics Review Process. This information is available on the REC website: www.jgh.ca/rec.

3.2.8 The investigator should keep a copy of all submission documents together with any related correspondence, with the file of study-related essential documents.

3.2.9 The investigator should ensure that all documents mentioned in item 4.1 of the present document are submitted to the REC and listed in a cover letter. In this letter, each document referred to should be identified by a version number and date if applicable; see example in Appendix 1, Example of Letter of Submission to the Research Ethics Committee.

3.2.10 The investigator should keep a copy of this submission letter with the study related essential documentation file.
3.2.11 If the Institution’s REC has documented its policies and standard operating procedures, the investigator should ensure that these are available for audits or inspections.

3.2.12 The investigator should ensure compliance with the policies and procedures of the institution’s REC.

### 3.3 Response of the Research Ethics Committee

3.3.1 The investigator should ensure that the letter of response from the REC includes the following information:

- I. Clinical study identification, protocol number and title;
- II. Name and version date of all documents reviewed by the REC;
- III. Date of review by the REC;
- IV. Decision/opinion/approval of the clinical study, including required modifications, if applicable;
- V. Procedures for appealing the decision/opinion of the REC;
- VI. Any other information, if applicable;
- VII. Date of renewal of approval;
- VIII. Signature of the Chair of the REC and date of the response.

3.3.2 In compliance with the ICH (3.2.1 et 3.2.2) and according to the FRSQ (page 40), a list of the members of the REC and their qualifications, as well as the procedures of the said committee should be available.

3.3.3 The investigator should keep a copy of the REC’s letter of response with the study related essential documentation file.

3.3.4 In Phase I, II and III clinical drug studies submitted to Health Canada, the investigator should ensure that the Research Ethics Board Attestation form (REBA) is completed, signed and kept with the study related essential documentation file. This form should be submitted only upon request by Health Canada.

3.3.5 If any form other than the one provided by Health Canada is used to document approval of the study by the REC (approval letter) and its compliance with GCP of the ICH, this documentation should be kept with the study related essential documentation file and be available for submission to Health Canada, if required.

### 3.4 Communication with the REC during the Study

To ensure study follow-up, the following communications with the REC should be documented:

3.4.1 Modifications to the study protocol or participant informed consent form during the course of a clinical study may be submitted one by one to the REC.
3.4.2 The investigator **should report promptly** the following information to the REC:

I. Any significant protocol change or deviation;

II. Any serious adverse event involving a research participant enrolled at the institutional site;

III. For multi-centre studies, any serious, unexpected, adverse event involving a research participant at any site. (this information is to be forwarded by the sponsor/sponsor-investigator);

IV. Any new information that may have an impact on the safety or conduct of the study, safety of the research participant or his/her willingness to continue participating in the study.

3.4.3 The following information **should be reported regularly, minimally annually**, to the REC by the investigator.

I. Updates to the Investigator’s Brochure or product monograph, if required;

II. Subsequent to the date of approval, at least annually and early enough to obtain a new approval before the previous one expires, prepare and submit a study follow-up report. The following items should be listed in this report:

   a) Institutional identification of the clinical study if applicable, protocol number and title;

   b) Previous approval date;

   c) Update of number of participants recruited (enrolled, treated, terminated), withdrawals and reasons for withdrawal.

   d) All changes of personnel on the clinical research team;

   e) All insignificant changes, even administrative, to the protocol;

   f) All deviations/violations of the protocol;

   g) All serious adverse events during the review period;

   h) Any information recently reported or obtained particularly regarding risks associated with the research;

   i) Any other information required by the institution, if applicable. A continuing review form is available on the REC website: www.jgh.ca/rec.

If the frequency of the REC’s review process is more than once a year, this information should be reported.

3.5 **Communication with the REC at the End of the Study**

3.5.1 When the clinical study is finished (at the least when each participant has completed the study) according to ICH 4.13, the investigator should submit a
final study report to the REC. The following items should be included in this report:

I. Total number of participants: recruited, who completed the study, who have been withdrawn and reasons for withdrawal;

II. Study results if known;

III. Any other information required by the institution. A completion form is available on the hospital website: www.jgh.ca/rec.

3.5.2 The investigator should keep a copy of those documents with the study related essential documentation file.

4. References

Health Canada, Guidance for Industry, Good Clinical Practice: Consolidated guideline, ICH Topic E6, 1997

Health Canada, Food and Drug Act– Part C, Division 5, Drugs for clinical trials involving human subjects, August 31 2004


Fonds de la recherche en santé du Québec (FRSQ), Guide d’éthique de la recherche et d’intégrité scientifique, Standards en éthique de la recherche et en intégrité scientifique du FRSQ (2e édition), août 2003
SOP 14 - Appendix 1

Example of a Letter of Submission to the Research Ethics Committee

Date of Submission

(Name of REC)
(Address of REC)

Re: Request for Approval

Protocol: (Protocol number) (Version number and Date of protocol)
(Protocol title)

To the Chair and Members of the Ethics Committee:

In conformity with GCP of the ICH, enclosed please find the following documents related to the above-mentioned protocol, for review by the REC.

List of submitted documents
(If required)
Please find attached Health Canada form*, Research Ethics Board Attestation which is to be completed and signed.
*If the REC does not complete this document, request the documents provided by the institution.

Thank you for the attention that you and the Committee will give to this project.

____________________________
(Name of investigator/qualified investigator)

Attached documents:
1. Health Canada Form, Research Ethics Board Attestation;
2. Protocol (Version 0, December 2004);
3. Protocol Amendment (Version 1, January 2005);
4. (Study with drugs) Investigator’s Brochure (7th edition, November 2004);
5. Product Monograph (if applicable);
6. Participant Informed Consent Form – English Version, No 1 – December 10th 2004);
7. Participant Informed Consent Form – Spanish Version, No 1 – December 10th 2004);
8. Advertisement, 11X14 Poster, English and Spanish Versions (December 15th 2004);
9. If applicable, other documents required by the REC.
SECTION IV - Ongoing Communication and Study Closure

SOP 15 – Management of Communication During a Study

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1. Policy

Within the framework of the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH), this standard operating procedure (SOP) describes communication procedures within the research team and with parties such as the sponsor (if applicable), REC and regulatory authorities.

This SOP concerns all institutional personnel working in clinical research and should be followed by all those working on clinical studies involving human participants.

2. Objective

The objective of this operating procedure is to define channels of communication and exchange of information among the investigator, the research team and research participants. It also defines principles of communication between the investigator and the sponsor and, according to applicable regulatory requirements, communications with the sponsor-investigator, investigator, REC and regulatory authorities.

3. Procedures

To ensure the safety of research participants as well as success of the study, it is important to remember that it is the responsibility of the investigator and/or sponsor-investigator to convey the necessary information to the research team, the research participants, the REC, sponsor and regulatory authorities, where applicable.

During the study implementation process, it is essential to define channels of communication as well as to clarify the function of each, within the team.
3.1 Communications Within the Research Team

3.1.1 While organizing the clinical study, the investigator should provide the research team with all information or data relevant to the safety of research participants and to the smooth conduct of the study, as described in SOP 04.

3.1.2 During the course of the study, means of communication (meetings or other) should be organized with all parties involved in the study (if applicable, laboratories, pharmacy, radiology,…) for follow-up on:

I. Recruitment of Research Participants;
II. Research participants;
III. Adverse events;
IV. Administrative matters;
V. Other study-related matters.

3.1.3 It is recommended that all communications, including the names of participants, meeting date, summary of discussions and resolutions adopted, be documented.

3.1.4 It is recommended that the date of dispatch or receipt of all documents sent or received, be recorded. In the case of a fax, the time of transmittal, date and name of person responsible are good examples of useful information to document.

3.2 Communications with Research Participants

3.2.1 As described in SOP 08, research participants should be provided with all relevant information, directly or through a representative/witness, prior to their consent, during the study and after, if applicable.

3.2.2 Research participants or their legal representatives, and witness (when applicable) should receive satisfactory answers to study questions, at all times.

3.2.3 Verbal communications with research participants or their representative/witness should be accurate, clear and understandable by all parties. This communication should be recorded in the source documents with date, reason for discussion, measures taken if necessary and signature of team member involved.

3.3 Communications with the Research Ethics Committee

3.3.1 As described in SOP 14, communication with the REC starts with preparing documents for submission, continues during the study and goes on until submission of the final study report.

3.3.2 All communications with the REC should be documented and kept with the source documents.

3.4 Communications with the Sponsor or Regulatory Authorities
3.4.1 As described in SOP 16, the investigator should inform the sponsor and regulatory authorities, if applicable, of any adverse and serious adverse events that occur at his site. Communication of information should be continuous.

3.4.2 As described in SOP 13, information regarding protocol deviations should be forwarded to the sponsor.

4. References


SOP 04, Preparing the Team for a Study
SOP 08, Consent Process and the Informed Consent Document
SOP 13, Dealing with Scientific Misconduct and Protocol Deviations
SOP 14, Research Ethics Committee (REC): Ongoing Communications
SOP 16, Management of Adverse Events – Serious Adverse Events and Adverse Reactions – Serious Adverse Reactions
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SOP 16 – Management of Adverse Events - Serious Adverse Events and Adverse Reactions - Serious Adverse Reactions

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3. References

1. Policy

Within the framework of the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH) issued by Health Canada, this standard operating procedure (SOP) describes the management of adverse events (AE), or serious adverse events (SAE), adverse reactions (AR) or serious adverse reactions (SAR) and procedures for reporting to the REC and regulatory authorities, if applicable.

This SOP concerns all institutional personnel working in clinical research and should be followed by all those working on clinical studies involving human participants.

2. Objectives

To ensure the safety of participants, the investigator and research personnel are required to follow each participant in a clinical study with the utmost care. This operating procedure describes methods of collection, documentation, investigation and assessment, as well as submission and follow-up, of AE/SAEs or AR/SARs which occur in the course of a clinical study with, or without, drugs or medical devices.

This SOP also defines AE/SAEs or AR/SARs, the responsibilities of the sponsor-investigator and investigator, as well as deadlines for reporting these AE/SAEs or AR/SARs.

3. Procedures

3.1 Generalities
3.1.1 Adverse Drug Reaction (ADR)
- Any noxious and unintended response to a drug that is caused by the administration of any dose of the drug

3.1.2 Serious Adverse Drug Reaction (SADR)
- An adverse drug reaction that requires in-patient hospitalization or prolongation of existing hospitalization, that causes congenital malformation, that results in persistent or significant disability or incapacity, that is life threatening or that result in death

3.1.3 Adverse Event
- Any adverse occurrence in the health of a clinical trial subject who is administered a drug, that may or may not be caused by the administration of the drug, and INCLUDED an adverse drug reaction

3.1.4 With respect to any adverse event, the investigator/institution should ensure that appropriate medical treatment is provided to a participant during and after his participating in the study (ICH 4.3.2);

3.1.5 The investigator/institution should inform the participant when medical care is needed regarding intercurrent illnesses (ICH 4.3.2);

3.1.6 The investigator should promptly report to the REC any adverse reaction that is serious and unexpected, as well as any new information that could adversely affect participants’ safety or the conduct of the study (ICH 3.3.8);

3.1.7 The investigator should also comply with the applicable regulatory requirements related to the reporting of unexpected serious adverse drug reactions (SADR) to the regulatory authorities and the REC (ICH 4.11.1);

3.1.8 In the case of a death, the investigator must provide the sponsor/sponsor-investigator and REC with all additional requested information (autopsy reports, medical reports, etc.) (ICH 4.11.3);

3.1.9 The investigator should, according to the protocol, report to the sponsor/sponsor-investigator all AEs or laboratory abnormalities identified in the protocol as critical to safety assessment (ICH 4.11.2);

3.1.10 The investigator should immediately report to the sponsor or sponsor-investigator all SAEs, except those that do not need expedited reporting according to the protocol or other document (Investigator’s Brochure, etc.). These expedited reports should be promptly followed up with detailed written reports (ICH 4.11.1);

3.1.11 The investigator should accurately and regularly document all adverse events in the source documents and case report forms (CRFs).

3.1.12 To comply with ICH directives, 2.3 and 2.7, of information related to AEs/SAEs or AR/SARs, it is important to harmonize the collection, assessment and communication.
I. The rights, safety and well-being of the study participants are the most important considerations and should supersede the interests of science and society (ICH 2.3).

II. Medical care given to, and medical decisions made on behalf of research participants, should always be the responsibility of a qualified physician (ICH 2.7).

To make the text more easily understood, ICH definitions for clinical studies using investigational products will be used. These definitions are found in the SOP addendum, *List of Acronyms and Terminology*.

3.2 **Management of AEs and SAEs in Studies with No Investigational Products**

GCP, international standards of science and ethical quality apply to the design and conduct of studies involving human participants as well as to the recording and reporting of data related to these studies. Compliance with these standards guarantees that the rights, safety and well-being of research participants are protected according to the principles of the Declaration of Helsinki, and that clinical study data are reliable. The principles established by the ICH should be applied to all clinical studies likely to have an impact on the safety and well-being of human participants (Introduction of the ICH).

In the case of clinical studies without an investigational product, it is recommended that the sponsor-investigator and investigator follow the same procedures for collecting clinical data related to adverse events and serious adverse events, assessing and reporting to their REC and regulatory authorities, if applicable.

3.3 **Collection of Clinical Data Related to AE/SAEs or AR/SARs**

3.3.1 Research participants should be informed of their responsibility to report all physical changes which occur during the clinical study or afterwards. It is recommended that this information be documented in the source documents.

3.3.2 In the case of research participant who is not competent, or a minor, the investigator or clinical study personnel should collect all data related to the AE or AR from the legal representative.

3.3.3 Whatever the AE or AR reported by the participant, research personnel involved in the clinical study should discuss it with the investigator who is responsible for determining the causality of the AE or AR.

3.3.4 To ensure the participant’s well-being and a better assessment of the AE or AR, all data (laboratory results, concomitant medications, etc.) should be collected by the research team responsible for the research participant.

3.3.5 Each clinical event or worsening or deterioration of a clinical condition after inclusion of the research participant in a clinical study should be reported to the investigator and documented in the source documents and case report forms, unless otherwise specified in the protocol.
3.3.6 All laboratory abnormalities should be reported to the investigator for assessment. Laboratory abnormalities deemed clinically significant should be documented as described in the protocol.

3.4 Assessment of AE/SAE or AR/SAR

According to the information gathered, the investigator/qualified investigator will clinically assess the event and provide the subject with appropriate medical care. The assessment includes:

3.4.1 **Intensity**: the intensity of an event can be classified as *mild*, *moderate* or severe according to criteria most often specified in the protocol, for example: mild, moderate or severe hepatitis. However, the medical importance of the event itself, for example, a severe headache, may be inconsequential and not require an immediate report to the sponsor/sponsor-investigator and appropriate regulatory authorities if applicable. The terms, serious and severe, are not synonymous.

3.4.2 **Severity**: events are classified as *serious* if associated with effects threatening the life or physiological functions of a research participant. The severity of an event determines if it should be reported. Definition of a serious event is found in the SOP addendum, List of Acronyms and Terminology.

3.4.3 **Incidence**: adverse event is classified as *unforeseen* or *unexpected* if, by nature or intensity, it is not reported in the Investigator’s Brochure (for investigational products that are not approved) or Information Brochure/Summary (for an approved product). The *serious* and *unexpected* nature of an event determines the type of report to present to regulatory authorities and REC. The sponsor/sponsor-investigator is responsible for establishing if the reported adverse event is unforeseen or unexpected.

3.4.4 **Causality**: in the case of clinical studies with an investigational product, the investigator determines, according to his clinical judgement, if there is a reasonable doubt as to causal relationship. Attribution may be *certain*, *likely*, *possible* or *unlikely*. Other expressions may be used to describe the degree of causality; no international classification exists for this subject.

3.5 Report and Follow-up of AE/SAEs and AR/SARs

The investigator is responsible for:

3.5.1 Reporting AEs/SAEs or AR/SARs, according to his assessment and the directives of the ICH, in the source documents, case report forms and other specific report forms, if applicable;

3.5.2 Submitting the SAE/SARs to the sponsor/sponsor-investigator when they are brought to his attention and within the time required by the protocol. It is critical that any relationship between a serious event and the investigational product is indicated in the submission even if the information is incomplete. This
assessment by the investigator will allow the sponsor/sponsor-investigator to fulfill regulatory obligations regarding prompt reports;

3.5.3 Submitting immediately, to the REC, all initial and follow-up reports on SAE/SARs requiring prompt reporting, sent by the sponsor/sponsor-investigator, that is to say, those assessed as unforeseen/unexpected and for which a causal relationship between investigational product and SAE cannot be ruled out. SAE/SARs reports other than those requiring prompt reporting occurring at other sites should also be submitted to the REC, if applicable;

3.5.4 Submitting to the REC all SAE/SARs which occur at his site, at least annually for continuing review. Usually AE/ARs are not reported to the REC. To that effect, each site should comply with the rules of its REC;

3.5.5 Following up all AE/SAEs or AR/SARs that occur in the course of the study. Follow-up on SAE/SARs should be sent to the sponsor/sponsor-investigator according to the protocol and submitted as well to the REC according to their requirements;

3.5.6 Notifying, according to protocol procedures, the sponsor/sponsor-investigator of all unforeseen/unexpected SAE/SARs that occur following termination of the study and which have a reasonable causal relationship with the investigational product.

In the case of clinical studies, the sponsor/sponsor-investigator must comply with the regulatory requirements of Health Canada regarding prompt reporting of unexpected SAE/SARs and for which a causal relationship with the investigational product cannot be ruled out.

3.5.7 Fatal and life-threatening SAE/SARs:

a. In the case of a study involving medication, within 7 days following awareness of the event;

b. The sponsor/sponsor-investigator should provide Health Canada with a detailed report of the SAE/SAR within 8 days of the first communication;

c. In the case of a study involving a medical device, within 10 days following awareness of an event that has occurred in Canada and caused a fatal outcome or serious deterioration in the health of a subject, user or another person, adapted from Rules on medical devices regulations, a. 60 (i). The obligation to report promptly to Health Canada, an event which occurred abroad, applies only if the manufacturer has notified regulatory authorities in the country at issue, of his intention to adopt remedial actions or if these regulatory authorities have asked him to do so. Rules on Medical Devices, regulations a. 59. (2) and a. 60 (1b).

3.5.8 Non-fatal SAE/SARs:

a. In the case of a study involving medication, within 15 days following awareness of the event;
b. In the case of a study involving a medical device, within 30 days following awareness of an event that has occurred in Canada and did not cause death or serious deterioration to the health of a subject, user or another person, but may do so if it reoccurs, adapted from Rules on medical devices regulations, a. 60 (ii).

The obligation to promptly report to Health Canada, an event which occurred abroad, applies only if the manufacturer has notified regulatory authorities in the country at issue of his intention to adopt remedial actions or if these regulatory authorities have asked him to do so, adapted from Rules on medical devices regulations, a. 59 (2) and a. 60 (1b).

If a protocol is subject to foreign regulations, these should be scrupulously observed. However, regarding investigational products, the United States, Japan and the European Union all subscribe to the regulatory principles and GCP described in this SOP.

4. References


Health Canada, Medical Devices Regulations, (SOR/98-282), May 7 1998.


Ministère de la santé et des services sociaux (MSSS), Comité central d’éthique du MSSS.
SECTION IV - Ongoing Communication and Study Closure

SOP 21 – Study Closure

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1. Policy

This standard operating procedure (SOP) follows the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH).

This SOP concerns all institutional personnel working in clinical research and should be adhered to by all those working on clinical studies involving human participants.

2. Objective

The objective of this operating procedure is to guide the research team during the closing of a clinical study.

3. Procedures

3.1 Information

In this SOP, good practices relating to the closing of a study will be described, in a series of steps to be completed after the last research participant has completed his/her final visit.

It should be noted that in addition to the steps described, the budgets related to the clinical study should be verified and, if necessary, any further amounts owing to research participants should be paid. Payments for various contracts or agreements signed at the beginning of the study should also be completed.

If publication of the study results is considered, it should first be verified that all participating sites are closed and all the data analyzed; this option is usually foreseen in
the contract between the sponsor/sponsor-investigator, the investigator and the institution.

3.2 Monitoring

The sponsor or sponsor/investigator may have made provisions for a final monitoring visit once all research participants have completed all the visits required by the protocol. For the closing of any study, the following steps should be completed:

3.2.1 All adverse events/serious adverse events (AE/SAEs) and all adverse reactions/serious adverse reactions (AR/SARs) should be documented and reported to the sponsor or regulatory agencies. They also should be recorded in the source documents as well as in the CRFs, as described in SOP 16. Moreover, it is necessary to ensure that all SAE/SARs (including the unexpected SAEs submitted by the sponsor/sponsor-investigator to the investigator/qualified investigator) were submitted to the REC. Follow-up procedures for the AE/SAEs and the AR/SARs that are still ongoing at the time of the study closure should be in compliance with the protocol.

3.2.2 In compliance with the protocol and GCP, the investigator should inform the sponsor/sponsor-investigator, the REC and regulatory authorities, if applicable, of any unexpected SAE/SARs following the study closure that can be reasonably associated with the investigational product;

3.2.3 All case report forms should be completed in accordance with the data and source documents. All completed CRFs should be forwarded for study data management;

3.2.4 The process of request for data clarification should be completed and confirmed by the investigator;

3.2.5 All questions left outstanding from preceding monitoring, verification/audit or inspection visits should be resolved;

3.2.6 Updating of the essential study documents should be finished and, if applicable, preparation of documents to be returned to the sponsor or the sponsor-investigator should be undertaken (reference ICH section 8, Essential Documents for the Conduct of a Clinical Study);

3.2.7 Often the sponsor or sponsor-investigator will arrange a so-called closing visit to the site to ensure that all these procedures are completed;

3.2.8 Accounting for the investigational products, biological products, medical devices and radiopharmaceuticals should be completed and, if applicable, the investigational products, biological products, medical devices, radiopharmaceuticals, its codes and the study-related material should be returned to the sponsor/sponsor-investigator.
3.3 Study-Related Material

3.3.1 At the end of the study, accounting for all investigational products, biological products, medical devices, radiopharmaceuticals used and unused, should be recorded and this documentation retained with the essential documentation of the study, as described in SOP 17 and SOP 01.

3.3.2 When accounting/reconciliation is finished, and following the sponsor/sponsor-investigator’s specifications, the investigational products, biological products, medical devices and radiopharmaceuticals should be returned or destroyed if permitted by the sponsor/sponsor-investigator. This destruction of the investigational products by the local pharmacy should be done in accordance with the institution’s written procedures regarding the destruction of investigational products. The codes of the investigational products should also be returned to the sponsor/sponsor-investigator or handled according to the requirements of the protocol.

3.3.3 All unused CRFs and all used or unused study-related material should be returned to the sponsor or sponsor-investigator at the end of the study and in accordance with specifications, unless the sponsor or sponsor-investigator allows them to be destroyed on-site, in accordance with local procedures for destruction of confidential documents.

3.3.4 As described in the protocol, laboratory specimens (blood, tissues, etc.) should all be returned to the sponsor/sponsor-investigator for evaluation and storage. However, if the protocol indicates that the specimens should be stored on-site, the investigator should ensure that they are stored in compliance with the protocol (reference to SOP 18).

3.4 Research Ethics Committee (REC) and Regulatory Organizations

The REC, as well as the regulatory authorities, should be informed that the clinical study has ended, in agreement with section 4.13 of the ICH, which stipulates that the investigator should inform the institution, if applicable, of the end of a study. The investigator/institution should also provide a summary of the study outcomes to the, REC as well as the reports required by regulatory organizations.

If the sponsor/sponsor-investigator submitted a clinical study application to Health Canada, they should also be informed that the study has ended.

3.5 Clinical Study Report

As indicated in the guidelines of ICH (E3), a study report is required for any study carried out on human participants. The report is written once all the data are corrected and analyzed and the study is finished. Sometimes this report is written long after the end of the study. If the protocol mentions that interim analyses should be carried out, an interim report should be produced.

Certain elements should be listed in the report, such as: information on the referenced protocol; the name of the investigator; the end date inclusion of participants; the total
number of research participants included; the number of participants having completed the study; the number of participants withdrawn from the study, the number of serious adverse events or serious adverse reaction; etc. The structure of the report is defined in the ICH (E3).

3.6 Archiving

Storage of all study documents should be planned at the beginning of the study in order to meet regulatory requirements.

3.6.1 Storage should guarantee safety and confidentiality of the information.

3.6.2 Storage should be adequately identified to the investigator or sponsor-investigator.

3.6.3 In the case of a clinical study with medication or a medical device, the investigator should inform his institution’s archiving service of the storage period for clinical study documents which should be in compliance with Canadian regulations on filing, Health Canada, C.05.012 (4), being 25 years. He should also notify the persons in charge of archiving that these documents should not be purged.

3.6.4 In the case of a clinical study without drug or medical device, the investigator inform his institution’s archiving service of the period of storage for clinical study documents which should be in compliance with the “calendrier de conservation des documents” presented by the institution to provincial authorities (Archives Act, chap. A-21.1 art. 8, 9 et 35 and AHQ, Recueil de règles de conservation des documents des établissements de santé et services sociaux, section 4, dossier X1-0350, dossier de l’usager).

3.7 Verification/Audit and inspection

A verification/audit or an inspection is always possible even if the study is finished. An inspection can be required by the sponsor and conducted by its internal personnel, an external inspector or a regulatory organization (Canada Health, FDA or other). As soon as the sponsor/sponsor-investigator is notified, he should inform the investigator as well as the research team of this verification/audit or inspection. If the investigator is notified of a verification/audit or an inspection, he should immediately notify the sponsor/sponsor-investigator (SOP 20).

4. References

Health Canada, Food and Drug Act– Part C, Division 5, Drugs for clinical trials involving human subjects, August 31 2004


Health Canada, Guidance for Industry, Good Clinical Practice: Consolidated guideline, ICH Topic E6, 1997

Health Canada, Food and Drug Act– Part C, Division 5, Drugs for clinical trials involving human subjects, August 31 2004

Québec, Archives Act (R.S.Q., A-21.1 a. 8, 9 and 35)

Association des hôpitaux du Québec (AHQ), Recueil de règles de conservation des documents des établissements de santé et services sociaux, section 4, X1-0350, dossier de l’usager, édition 2004

SOP 01, Organizing a Site for Clinical Research

SOP 16, Management of Adverse Events - Serious Adverse Events and Adverse Reactions - Serious Adverse Reactions

SOP 17, Managing Investigational Products, Biological Products, Medical Devices and Radiopharmaceutical Under Study

SOP 18, Management of Biological Specimens: Collection and Storage

SOP 20, Preparation for an Audit or Inspection Visit

SOP 22, Source Data and Document Management

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SECTION V - Preparing for Monitoring/Audit/Inspection Visit

SOP 19 - Preparation for Monitoring Visits

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1. Policy

This standard operating procedure (SOP) follows the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH). It particularly targets the responsibilities of the sponsor-investigator regarding the obligation to monitor the quality of all aspects of the study, and the responsibilities of the investigator who must authorize this monitoring.

This SOP concerns all institutional personnel working in clinical research and should be adhered to by all those working on clinical studies involving human participants.

2. Objective

The objective of this operating procedure is to guide the research team in its preparation for a monitoring visit.

3. Procedures

3.1 Information

It is important to know that monitoring of the study is the responsibility of the sponsor/sponsor-investigator as well as the institution. The ICH obliges the sponsor/sponsor-investigator to implement and maintain quality assurance and quality control systems to ensure that studies are conducted and data generated, documented (recorded), and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s) (ICH 5.1.1).

The investigator must permit monitoring and auditing by the sponsor as well as the REC of the Institution, and inspection by the appropriate regulatory authority(ies).
The ICH (1.38) defines monitoring as the act of overseeing the progress of a clinical study, and of ensuring that it is conducted and reported in accordance with the protocol, Standard Operating Procedures (SOP), Good Clinical Practice (GCP), and applicable regulatory requirement(s).

As described in ICH (5.18.1), the purpose of study monitoring is to verify that:

a. The rights and well-being of human participants are protected;

b. Reported study data are accurate, complete, and verifiable from source documents;

c. The study is conducted in compliance with the currently approved protocol/amendment(s), GCP, and applicable regulatory requirement(s).

It should be recalled that no document (original or copy) which allows the identification of a research participant (nominative data) should leave the institution.

The elements described in this procedure are reference tools for the proper preparation for a monitoring visit.

3.2 Availability of the Investigator/Qualified Investigator

The investigator is entirely responsible for the study. Where there is delegation of tasks, it should be registered on the “tasks delegation” list, as required by the ICH, and this list should be retained with the essential study documentation, SOP 01, Study-related Essential Documents Management section.

3.2.1 During monitoring visits, it is important that team members be available for discussions, for study updates and to answer questions.

3.2.2 It is strongly recommended that the investigator be available at the time of visits, especially when issues concerning follow-up of research participants or the protocol are on the agenda.

3.2.3 The investigator should be informed in advance of a monitoring visit.

3.3 Preparation for a Monitoring Visit

3.3.1 Ensure that the sponsor/sponsor-investigator and the quality assurance officer (QAO) communicate in order to fix the time and content of the monitoring visit. This communication is often coordinated by the monitor. It is important to retain the written communication records with the essential documentation of the study.

3.3.2 Ensure the availability of all parties from different services, if applicable, at the time of the visit.

3.3.3 Ensure the identity of monitors upon arrival.
3.3.4 In order to respect confidentiality, ensure that monitors are accompanied by a team member during their visit to premises where confidential material is stored.

3.3.5 Verify that all the Case Report Forms required by the visit have been completed.

3.3.6 Verify that all patient files, data and source documents required by the monitoring visit are complete and available.

3.3.7 Verify that the essential documentation of the study is complete (i.e. recent correspondence, participant screening log, participant enrollment log, participant identification code lists, up-to-date medical/nursing licenses, updated Curriculum Vitae and documents related to the management of investigational products, biological products, medical devices and radiopharmaceuticals if applicable).

3.3.8 Ensure that the monitor will have access to all premises where the study takes place, including sites where study material or investigational products, biological products, medical devices and radiopharmaceuticals are stored, if applicable.

3.3.9 Ensure that any questions or items that remained outstanding from the last monitoring visit, have been resolved.

3.3.10 Ensure, where a CRF or an electronic source document is used, that during the visit, the monitor has the necessary access.

3.3.11 Have, where possible, a tracking document containing the names, signatures, initials, dates of beginning and end of the functions of individuals who will have access to study documents, delegated by the sponsor/sponsor-investigator. This document can be retained with the essential documentation of the study and could be used at the time of monitoring or audit visits.

3.3.12 Have a suitable location equipped, if applicable, with the tools required for monitoring (telephone line, internet access, etc.).

3.4 Documents Required for the visit

3.4.1 Case Report Forms and all related documents (i.e. laboratory reports, patient diaries, etc.);

3.4.2 Informed Consent Form for each research participant;

3.4.3 Participants’ medical or record files, as well as investigator’s clinic chart, if applicable;

3.4.4 Documentation related to the management of Investigational products, biological products, medical devices and radiopharmaceuticals as well as decoding documentation;

3.4.5 Essential Study Documentation;

3.4.6 Documentation relative to biological specimens, if necessary;
3.4.7 All updates or new documentation that should be conveyed to the sponsor or sponsor-investigator;

3.4.8 All documentation related to the declaration of SAE/SARs submitted by or to the sponsor/sponsor-investigator or investigator.

4. References

Health Canada, Food and Drug Act– Part C, Division 5, Drugs for clinical trials involving human subjects, August 31 2004

Health Canada, Guidance for Industry, Good Clinical Practice: Consolidated guideline, ICH Topic E6, 1997

SOP 02, Research Team: Role Definitions, Responsibilities and Task Delegation
SECTION V - Preparing for Monitoring/Audit/Inspection Visit

SOP 20 - Preparation for an Audit or Inspection Visit

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4. References

1. Policy
This standard operating procedure (SOP) follows the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonization (ICH) concerning verification/audit and inspection of all aspects of a clinical study.

This SOP concerns all institutional personnel working in clinical research and should be adhered to by all those working on clinical studies involving human participants.

2. Objective
The objective of this operating procedure is to guide the research team in its preparation for an audit or inspection visit.

3. Procedures

3.1 Information
The elements described in this procedure are reference tools to properly prepare for a verification/audit or inspection visit.

The ICH (1.6 ) describes verification/audit as a systematic and independent examination of study-related activities and documents to determine whether these activities were conducted in compliance with the protocol, sponsor or sponsor-investigator's standard operating procedures (SOPs), with Good Clinical Practice (GCP), and applicable regulatory requirement(s) and also to verify that the data were recorded, analyzed and accurately reported according to these same directives.
The ICH 1.29 describes **the inspection** as an official examination by regulatory authorities of documents, facilities, records, and any other resources that are deemed by the authorities to be related to the clinical study and that may be located at the site of the study, at the sponsor or the sponsor-investigator's contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authorities.

The ICH 4.14 describe the **investigator/institution** must authorize the verification/audit and allow the appropriate regulatory organizations to carry out inspections.

### 3.2 Scenario for a Verification/Audit or Inspection

A verification/audit carried out by the sponsor or sponsor-investigator is done to ensure that the study complies with applicable standards and that data are accurate and of good quality. If carried out at the beginning of the study, a verification/audit can serve to correct errors before the study is completed; however, it can be carried out any time, in the course of the study or at the end. CROs and investigators can be audited by the sponsor or the sponsor-investigator.

No particular reason is needed to conduct a verification/audit or an inspection directed towards the sponsor/sponsor-investigator or the investigator’s site. The criterion most commonly cited for the selection of a site is the high number of research participants, who contribute to its results.

A verification/audit or an inspection directed towards the investigator is carried out when there is reason to believe that there are problems with the site’s data. Some of the problems can become apparent because of weak compliance of the site with the protocol, an overly low or high rate of adverse reaction or adverse events compared to other sites, a high rate of recruitment compared to other sites, etc. However, a verification/audit or an inspection can be carried out at a site for no particular reason.

### 3.3 Preparation for a Verification/Audit or Inspection Visit

3.3.1 The investigator should always be informed in advance and in writing, of a planned visit for audit or inspection purposes. For inspections by the FDA, the site should receive FDA form number 482 entitled *"Notice of Inspection"*. With this request, both parties will agree on a date that leaves a sufficient period for the research team to prepare for the visit. However, in the case of suspicion of fraud, FDA inspectors can arrive without notice.

3.3.2 When there is a request for inspection, the investigator should immediately inform the sponsor or the sponsor-investigator.

3.3.3 Communications concerning the request for verification/audit or inspection should be kept with the essential study documents. Usually, the sponsor or sponsor-investigator assists the research team in preparation for the verification/audit or inspection.
3.3.4 In order to prepare for a verification/audit or inspection visit, the research team should:

Verify that the original documents are available:

a) Essential documentation of the study as described in section 8, Essential Documents for the Conduct of a Clinical Trial, of the ICH or SOP 01;

b) Case Report Forms (CRFs);

c) Informed Consent Forms for all research participants

d) Medical files and other source documents;

e) Pharmacy Files (management of investigational products), if applicable, and any other document related to the study.

Check that the information contained in all these documents is complete, up-to-date and in agreement with the data or source documents.

3.3.5 If there were retrospective entries or corrections, they should have been dated and signed by the person who made the entry or the correction.

3.3.6 The research team should prepare the logistic aspects of this visit, for example:

a) Reserve office space for the visit;

b) Ensure that a photocopier and a telephone are available;

c) Ensure, in case photocopies of study documents are made, that tracking documentation will be employed and that this documentation will be retained with the essential documentation of the study;

d) Ensure that all the documents will be available promptly, in response to any possible request during the visit;

e) Ensure that research team personnel, including the investigator, will be available to provide explanations or to answer questions for at least a part of the visit.

f) If applicable, ensure that other departments involved in the study will be informed of this visit and that they will be available, if need be, for a visit, example: pharmacy, laboratory, etc;

g) If applicable, ensure that arrangements will be made to translate documents or to facilitate communication during the visit;

It should be recalled that no document (original or copy) identifying a research participant (nominative data) should leave the institution.

3.4 Conduct of a Verification/Audit or Inspection Visit

3.4.1 Verify the identity of the auditors or inspectors from the regulatory agency at the time of arrival.
3.4.2 For reasons of confidentiality, while they are in the institution, auditors or inspectors should be accompanied by a member of the research team.

Inspections by a regulatory agency, such as the FDA, Health Canada or another regulatory agency, can extend from a few days to a week or more if necessary.

Often this type of visit starts with an introductory meeting prepared by the auditors or inspectors.

This meeting is followed by an evaluation of the conduct of the study. The following questions could be asked: Who does what? Are delegations appropriate and recorded in writing? What equipment or material is being used? Who collects and enters the data? Is there active communication with the sponsor or the sponsor-investigator? Is the study adequately supervised? Do standard operating procedures exist? Are files which document training of the research team available?

Review of the study documentation is also carried out during this type of visit. Targeted documentation includes: regulatory documentation and that of the REC; compliance with the protocol; consent procedures; proof that every participant exists; eligibility of each research participant; comparison of the data and the source documents versus the case report forms (CRF); verification of the obligation of the investigator with respect to the regulatory requirements.

The auditors or the inspectors can ask to visit locations where study procedures are carried out; consequently, it is important to notify the affected departments before this visit.

At the end of the visit, the auditors or inspectors often hold a meeting with the research team and the investigator. This meeting allows for the clarification of elements or the correction of deficiencies noted during the visit.

The sponsor or the sponsor-investigator usually receives the report of the findings made during visit. He is also the one who brings the necessary help to the site with regards of the corrections of the observations made during the visit. It is important to quickly respond to all requests stemming from the observations made at the time of the visit. The report of observations remains open until all requests have been met.

3.4.3 Following inspection by a regulatory agency, a written report is submitted to the sponsor or to the investigator listing the observations or deviations noted during the inspection. All the deficiencies should be addressed with the proper corrective measures. These measures should be documented and transmitted in writing to the regulatory agency within the allotted time frame, normally 2 weeks following receipt of the final inspection report (FDA emits a report entitled "FDA Form 483").

3.4.4 The investigator should immediately contact the sponsor or the sponsor-investigator who will assist with the drafting of the required corrective measures, and their implementation.
If an auditor notes that serious or persistent cases of non-compliance are associated with a particular investigator/institution, the sponsor/sponsor-investigator will be asked to end the investigator/institution’s participation in the study. When participation of an investigator/institution in the study is cancelled for reasons of non-compliance, the sponsor/sponsor-investigator should, in the 15 days following termination, inform the regulatory organizations, Health Canada, rule C.05.015 of the regulation, ICH 5.20.2 and the REC that approved the trial (ICH 4.12).

4. References

Health Canada, Food and Drug Act– Part C, Division 5, Drugs for clinical trials involving human subjects, August 31 2004

Health Canada, Guidance for Industry, Good Clinical Practice: Consolidated guideline, ICH Topic E6, 1997

Health Canada, Guidance for Industry, Essential documents for the conduct of a clinical trial, ICH Topic E6, Section 8

SOP 01, Organizing a Site for Clinical Research