Fonds de la recherche en santé du Québec

Standard Operating Procedures (SOPs) to Ensure Good Clinical Practice at Clinical Research Sites

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FONDS DE LA RECHERCHE EN SANTÉ DU QUÉBEC (FRSQ)

Standard Operating Procedures (SOPs) to Ensure Good Clinical Practice at Clinical Research Sites

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Notice

The content of these Standard Operating Procedures (SOPs) has been registered to the Fonds de la recherche en santé du Québec (FRSQ) and is duly protected under the Copyright Act of Canada.

These SOPs were created specifically for use in publicly funded institutions in Quebec and are applicable to both academic research projects as well as pharmaceutical and device regulated clinical trials. They reflect the current best practices in clinical research in accordance with Provincial and Federal regulations and guidelines.

The FRSQ SOPs and available standardized training material on the SOPs can be adapted and customized for clinical research sites, research institutions or groups worldwide. Due recognition to FRSQ as the source of the material should be clearly stated in the adapted version of the materials.

The FRSQ assumes no responsibility for changes made to these SOPs without its prior written approval.

Letter from FRSQ's President and CEO

The Fonds de la recherche en santé du Québec (FRSQ) is very pleased to share these Standard Operating Procedures to Ensure Good Clinical Practice at Clinical Research Sites with clinical research organizations, centers and sites worldwide.

The FRSQ has identified Clinical Research as one of its main priorities in its current Strategic Development Plan. This initiative is part of the implementation process of this aspect of the Plan. Our goal is to promote, encourage and support quality clinical research practice at the local and international levels; while ensuring that Quebec becomes and remains an important player in the field of quality and ethical clinical research.

The Standard Operating Procedures (SOP) presented here are the result of a successful collaborative effort between the FRSQ, the Government of Quebec, four Quebec universities (McGill University, Université de Montréal, Université de Sherbrooke, Université Laval) as well as the 19 FRSQ-funded research centres. The goal of this collaboration was to create quality assurance material for clinical research activity that occurs in publicly funded institutions in Quebec (publicly funded as well as industry-sponsored). These SOPs are part of a larger quality assurance package that is currently being developed. This package includes training material on issues related to Good Clinical Research Practices.
The FRSQ SOPs were developed within the context of a publicly funded initiative (the GEREQ Project) that had the mandate to improve the Quality of Clinical Research in Quebec. One of the main objectives of this initiative was to help academic clinical researchers meet internationally recognized quality standards in their field-work activity and to make these standards available to researchers at a cost that they can afford.

Within this context, quality standards were developed and 3 activities were prioritized as being critical to assure the quality of clinical research field-work.

These are:
1) Training clinical research personnel in good clinical research practice (GCP)
2) Developing site specific standard operating procedures (SOP) for clinical site activity
3) Having a standard and validated information system dedicated to clinical research

The 26 FRSQ SOPs were developed by a provincial expert working group (including an observer from Health Canada's Inspectorate) and are not templates. They are complete SOPs written in a generic fashion so that they can be applied to all clinical research centers in Quebec (they are applicable to both academic research projects as well as pharmaceutical and device regulated clinical trials). They have been written as a comprehensive training resource tool for clinical research sites.

The FRSQ SOPs incorporate the following standards and regulations:

- International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices, 1996;
- Health Canada Therapeutic Products Directorate Food and Drug Regulations for Clinical Trials. Division 5. Canada Gazette Part II, Vol. 135, No. 13, June 7, 2001;
- USA Food and Drug Regulations, Code of Federal Regulations Chapter 21 Part 11;
  Tri-Council Policy Statement; Ethical Conduct for Research Involving Humans; Medical Research Council of Canada; Natural Sciences and Engineering Council of Canada; Social Sciences and Humanities Research Council of Canada, August 1998;
  Quebec and Canadian Laws, as applicable

The FRSQ SOPs are available in both English and French and can be adapted and customized for clinical research sites, research institutions or groups by the end-users themselves.

The available standardized training material on the SOPs assures the adequate training of clinical research staff once SOPs are implemented at the site.

Alain Beaudet
President and CEO
Fonds de la recherche en santé du Québec

Fonds de la recherche en santé Québec

ACRONYM & TERMINOLOGY LIST

Title	**Acronyms and terminology list**
Pages	12

History of validated version

Date dd/mmm/yyyy	Version	Pages	Description of change

Addendum approval

	Signature	Date *dd/mmm/yyyy*

Acronyms list

Acronymes français	Significations / Meaning	English Acronyms
BPC	Bonnes pratiques cliniques	
	Good Clinical Practices	*GCP*
C.c	Code civil du Québec	*C.c*
CEE	Comité d'examen de l'établissement	
	Institutional Review Board	*IRB*
CEI	Comité d'éthique indépendant	
	Independent Ethics Committee	*IEC*
CER	Comité d'éthique à la recherche	
	Research Ethics Board	*REB*
CICD	Comité indépendant de contrôle des données	
	Independent Data-Monitoring Committee	*IDMC*
CIH	Conférence internationale sur l'harmonisation	
	International Conference on Harmonisation	*ICH*
DGPSA	Direction générale des produits de santé et des aliments	
	Health Products & Food Branch	*HPFB*
	Food & Drug Administration	*FDA*
FCE	Formulaire de consentement éclairé	
	Informed Consent Form	*ICF*
FEC	Formulaire d'exposé de cas	
	Case Report Form	*CRF*
FRSQ	Fonds de la recherche en santé du Québec	*FRSQ*
IT	Incident thérapeutique	
	Adverse Event	*AE*
ITG	Incident thérapeutique grave	
	Serious Adverse Event	*SAE*
L.S.S.S.S.	Loi sur les services de santé et les services sociaux	*L.S.S.S.S.*
MON	Mode opératoire normalisé	
	Standard Operating Procedures	*SOPs*
ORC	Organisme de recherche sous contrat	
	Contract Research Organization	*CRO*
RIM	Réaction indésirable à un médicament	
	Adverse Drug Reaction	*ADR*
RIGM	Réaction indésirable grave à un médicament	
	Serious Adverse Drug Reaction	*Serious ADR*

Terminology

Adverse Drug Reaction (ADR), *(ICH/GCP 1.1)*
In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guidance for *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*).

Adverse Drug Reaction (ADR), *(Article C.05.001, Health Canada)*
Any noxious and unintended response to a drug that is caused by the administration of any dose of the drug.

Adverse Event (AE), *(article C.05.001, Health Canada)*
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 includes an adverse drug reaction.

Adverse Event (AE), *(ICH/GCP 1.2)*
Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guidance for *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*).

Applicable Regulatory Requirement(s), *(ICH/GCP 1.4)*
Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

Approval (in relation to Institutional Review Boards), *(ICH/GCP 1.5)*
The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

Audit, *(ICH/GCP 1.6)*
A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Biologic, *(Health Canada)*
A drug that is prepared using a biological starting or source material (e.g. derived from a microorganism, virus, animal, human, or plant), and using for example, either conventional manufacturing methods, recombinant DNA technology, and/or other novel approaches. Some examples of biologics include vaccines, blood and its derivatives, certain hormones, and enzymes, recombinant DNA products, gene therapies, and transgenics. Biologics make up one large category of drugs; the other major category of drugs is pharmaceuticals, or synthetic drugs made from chemicals.

Blinding/Masking, *(ICH/GCP 1.10)*
A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

Case Report Form (CRF), *(ICH/GCP 1.11)*
A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

Clinical Trial, *(Article C.05.001, Health Canada)*
An investigation in respect of a drug for use in humans that involves human subjects and that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug.

Clinical Trial/Study, *(ICH/GCP 1.12)*
Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Clinical Trial/Study Report, *(ICH/GCP 1.13)*
A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report.

Comparator (Product), *(ICH/GCP 1.14)*
An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

Compliance (in relation to trials), *(ICH/GCP 1.15)*
Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

Confidentiality, *(ICH/GCP 1.16)*
Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

Contract, *(ICH/GCP 1.17)*
A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

Contract Research Organization (CRO), *(ICH/GCP 1.20)*
A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

Documentation, *(ICH/GCP 1.22)*
All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

Drug, *(Article C.05.001, Health Canada)*
A drug for human use that is to be tested in a clinical trial.

Electronic signature, *(Statutes of Canada 2000, PIPEDA)*
A signature that consists of one or more letters, characters, numbers or other symbols in digital form incorporated in attached to or associated with an electronic document.

Essential Documents, *(ICH/GCP 1.23)*
Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see 8. Essential Documents for the Conduct of a Clinical Trial).

Flow chart
A table that illustrates and helps visualise a standard operating procedure process. The table is included in the procedure draft to facilitate understanding of the procedure.

Generic Standard Operating Procedure
A generic standard operating procedure is a SOP developed and validated by the FRSQ in which appendix 1, *Specific Instructions to the Site*, is left to be completed.

Good Clinical Practice (GCP), *(ICH/GCP 1.24)*
A Standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Good Clinical Practices, *(Article C.05.001, Health Canada)*
Good clinical practices means generally accepted clinical practices that are designed to ensure the protection of the rights, safety and well-being of clinical trail subjects and other persons, and the good clinical practices referred to.

ICH - International Conference on Harmonization,
(http://www.hc-sc.gc.ca/hpfb/inspectorate/ich_e.html)
ICH is a a joint initiative involving both regulators and industry as equal partners in the scientific and technical discussions of the testing procedures which are required to ensure and assess the safety, quality and efficacy of medicines.

Identifying Code, *(MSSS, cadre global de gestion des actifs informationnels)*
Identifying type, alphanumeric group, unique and normalised allowing identification of the user of an informational asset.

Impartial Witness, *(ICH/GCP 1.26)*
A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

Independent Data-Monitoring Committee (IDMC), *(ICH/GCP 1.25)*
An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

Independent Ethics Committee (IEC), *(ICH, GCP 1.27)*
An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.
The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guidance document.

Informed Consent, *(ICH/GCP 1.28)*
A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Inspection, *(ICH/GCP 1.29)*
The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

Institution (medical), *(ICH/GCP 1.30)*
Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

Instructions Specific to the Site
Specific instructions that outline in a detailed manner the activities related to the institution for a given standard operating procedure

Institutional Review Board (IRB), *(ICH, GCP 1.31)*
An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Interim Clinical Trial/Study Report, *(ICH/GCP 1.32)*
A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

Investigational Product, *(ICH/GCP 1.33)*
A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Investigator, *(ICH/GCP 1.34)*
A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Investigator's Brochure, *(ICH/GCP 1.36)*
A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

Investigator's Brochure, *(Article C.05.001, Health Canada)*
Investigator's brochure means, in respect of a drug, a document containing the preclinical and clinical data on the drug that are described in paragraph C.05.005

Investigator / Institution, *(ICH/GCP 1.35)*
An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

Legally Acceptable Representative, *(ICH/GCP 1.37)*
An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

Monitoring, *(ICH/GCP 1.38)*
The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Multicentre Trial, *(ICH/GCP 1.40)*
A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

Numeric or electronic signature, *(MSSS, Cadre global des actifs informationnels – volet sécurité)*
Data appended to an electronic document allowing the person receiving this document to know the source of the data, to attest its integrity, and to assure the transmitter adherence to the document content. We sometimes use the expression secured electronic signature.

Opinion (in relation to Independent Ethics Committee), *(ICH/GCP 1.42)*
The judgement and/or the advice provided by an Independent Ethics Committee (IEC).

Original Medical Record, *(ICH/GCP1.43)*
See Source Documents.

Password, *(MSSS, cadre global de gestion des actifs informationnels - volet sécurité)*
Authentifier in the format of an alphanumeric code is given to a user, allowing the user to obtain access to an on-line computer and to perform the needed operations.

Person responsible for SITE SOPs
A member of the institutional personnel involved in clinical research is designated by the institution to complete appendix 1, *Instructions Specific to the Site*. He/she may participate in the SOP revision process or in the SOP annual approval process. They may also participate in the training of institutional clinical research personnel for each standard operating procedure.

Protocol, *(Article C.05.001, Health Canada)*
A document that describes the objectives, design, methodology, statistical considerations and organization of a clinical trial.

Protocol, *(ICH/GCP 1.44)*
A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guidance the term protocol refers to protocol and protocol amendments.

Protocol Amendment, *(ICH/GCP 1.45)*
A written description of a change(s) to or formal clarification of a protocol.

Quality Assurance (QA), *(ICH/GCP 1.46)*
All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

Quality Control (QC), *(ICH/GCP 1.47)*
The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

Qualified Investigator, *(Article C.05.001, Health Canada)*
The person responsible to the sponsor for the conduct of the clinical trial at a clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located, and who is :

a) in the case of a clinical trial 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;
b) in any other case, a physician and a member in good standing of a professional medical association.

Radiopharmaceutical, (Health Canada)
Drugs, which are labelled with a radionuclide in tracer or therapeutic amounts, and which exhibit spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons. They can include drugs either of chemical or biological origin which are intentionally made radioactive, as well as, kits that are used for the preparation of radiopharmaceutical and radionuclide generators. Radiopharmaceuticals are used as diagnostic or therapeutic agents, and are always prepared and administered by health care professionals; they are never self-administered.

Randomization, *(ICH/GCP 1.48)*
The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.
méthodes, le déroulement ou les résultats d'un essai, les facteurs associés à un essai et les mesures prises.

Regulatory Authorities, *(ICH/GCP 1.49)*
Bodies having the power to regulate. In the ICH GCP guidance the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections (see 1.29). These bodies are sometimes referred to as competent authorities.

Research Ethics Board (REB), *(Article C.05.001, Health Canada)*
A body that is not affiliated with the sponsor, and

a) the principal mandate of which is to approve the initiation of, and conduct periodic reviews of, biomedical research involving human subjects in order to ensure the protection of their rights, safety and well-being; and
b) that has at least five members, that has a majority of members who are Canadian citizens or permanent residents under the *Immigration and Refugee Protection Act*, that is composed of both men and women and that includes at least
    i. two members whose primary experience and expertise are in a scientific discipline, who have broad experience in the methods and areas of research to be approved and one of whom is from a medical discipline or, if the clinical trial is in respect of a drug to be used for dental purposes only, is from a medical or dental discipline,
    ii. one member knowledgeable in ethics,
    iii. one member knowledgeable in Canadian laws relevant to the biomedical research to be approved,
    iv. one member whose primary experience and expertise are in a non-scientific discipline, and
    v. one member who is from the community or is a representative of an organization interested in the areas of research to be approved and who is not affiliated with the sponsor or the site where the clinical trial is to be conducted.

Secure electronic signature, *(Statutes of Canada 2000, PIPEDA)*
An electronic signature that results from the application of a technology or process prescribed by regulations made under subsection 48 (1).

Serious Adverse Drug Reaction (SADR), *(article C05.001, Health Canada)*
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 results in death.

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR), *(ICH/GCP 1.50)*
Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

(ICH/E2A, GUIDELINE FOR INDUSTRY)
Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Serious unexpected adverse drug reaction, *(Article C.05.001, Health Canada)*
A serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information set out in the investigator's brochure or on the label of the drug.

Site standard operating procedure (SOP)
A validated site standard operating procedure is a generic SOP for which appendix 1, *Instructions Specific to the Site* has been completed. This site standard operating procedure has been ratified by the director of the research center and/or by institution members according to internal procedures for the validation process. This SOP is in use in the institution.

Source Data, *(ICH/GCP1.51)*
All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents, *(ICH/GCP 1.52)*
Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Sponsor, *(Article C.05.001, Health Canada)*
An individual, corporate body, institution or organization that conducts a clinical trial.

Sponsor, *(ICH/GCP 1.53)*
An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Sponsor-Investigator, *(ICH/GCP 1.54)*
An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., 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.

Standard Operating Procedures (SOPs), *(ICH/GCP 1.55)*
Detailed, written instructions to achieve uniformity of the performance of a specific function.

Subinvestigator, *(ICH/GCP 1.56)*
Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows).

Subject Identification Code, *(ICH/GCP 1.58)*
A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

Subject/Trial Subject, *(ICH/GCP 1.57)*
An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

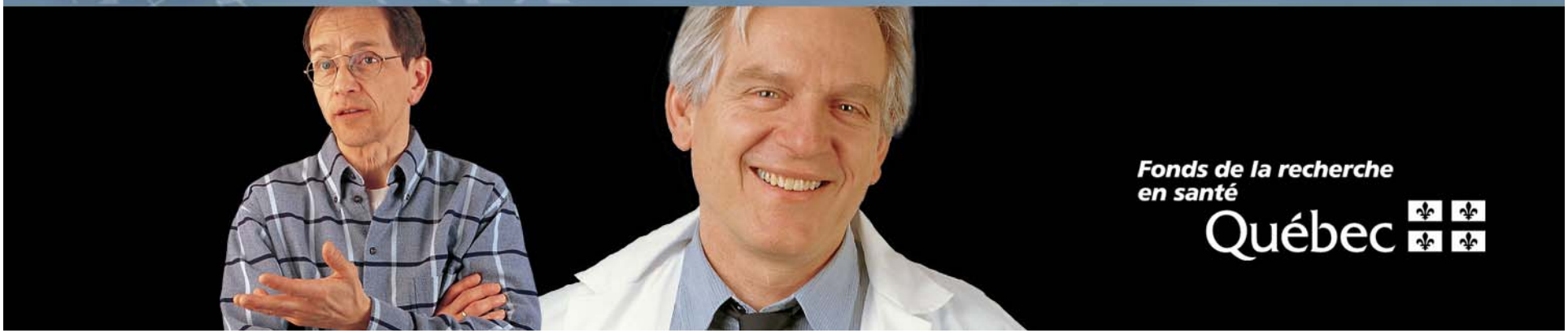
Trial Site, *(ICH/GCP 1.59)*
The location(s) where trial-related activities are actually conducted.

Unexpected Adverse Drug Reaction, *(ICH/GCP 1.60)*
An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the ICH Guidance for *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*).

Vulnerable Subjects, *(ICH/GCP 1.61)*
Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

Well-being (of the trial subjects), *(ICH/GCP 1.62)*
The physical and mental integrity of the subjects participating in a clinical trial.

Standard Operating Procedures (SOP)
General Training



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- SOPs are « detailed, written instructions to achieve uniformity of the performance of a specific function. » (ICH)

- SOPs apply to all research projects or clinical trials (sponsored or contractual) with human subject

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Objectives of Standard Operating Procedures

- Subjects are protected through standardized and well established work practices

- Compiled & published data are compliant with applicable regulations

HOW ?

By realizing all clinical trials in accordance with the good clinical practice (GCP) and to the applicable regulatory requirements

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Development of SOP

- Phase I
  - Professionals from the Health Care Institutions
  - An observer from Health Canada
  - Professional consultants
- Phase II
  - Site personnel
  - Support from a team of professional consultants

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Structure of Standard Operating Procedures

- Policy
- Objective(s)
- Site Responsibilities
- Procedures
- References
- Appendices

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Content of Site Standard Operating Procedures

- SOPs are adapted and personalized
  - According to each site's profile
  - In relation with the « cadre réglementaire » and other applicable documents of the site

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References used for Standard Operating Procedures

- International conference on harmonisation (ICH)
- Declaration of Helsinki
- Tricouncil Policy Statement ; Ethics for Research Involving Human Subjects
- FRSQ
- Act and regulation of Quebec
- MSSS
- Health Canada
- The « cadre réglementaire » and other regulatory documents of the site
- SCDM – Society for Clinical Data Management (US)
- FDA

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To whom Standard Operating Procedures are for ?

SOPs applies to all clinical research personnel involved in the research center

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Standard Operating Procedures

SOP

SOP01 Development, Approval and review of Standard Operating Procedures (SOPs)

Preparation

SOP02 Organizing a site for Clinical Research

SOP03 Research team: Role Definitions, Responsibilities and Task Delegation

SOP04 Site Research Team : Competence, Knowledge and Training

SOP05 Preparing the Team for a Study

SOP06 Study Feasibility Assessment

CTA

- SOP07 Conducting a Study in the Context of a Clinical Trial Application in Canada (CTA)

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Standard Operating Procedures

Ethics Committee

SOP08 Protocol and Protocol Amendment, Submission to Research Ethics Board

SOP09 Consent Process and Subject Informed Consent Form

SOP15 Research Ethics Board (REB): Ongoing communications

Subjects

SOP10 Rights and Protection of Study Subjects

SOP12 Subject Recruitment

SOP13 Subject Follow-up

Conflict et Misconduct

SOP11 Conflict of Interest

SOP14 Dealing with Misconduct And Protocol Deviations

Management and data

SOP16 Management of Communication During a Study

SOP17 Management of Adverse Events – Serious

Adverse Events and Adverse Reactions – Serious Adverse Reactions

SOP18 Managing of Investigational Products Under Study

SOP19 Management of Biological Specimens: Collection and Storage

SOP23 Management of Data and Source Documents

SOP24 Clinical Data Management, Paper or Electronic Format

SOP25 How to fill In a Case Report Form and Modify Data

SOP26 Security and confidentiality of Data

SOP20 Preparation for Monitoring Visits

SOP21 Preparation for an Audit or Inspection

SOP22 Study Closure

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Complement to Standard Operating Procedures

- Terminology and acronyms
  - An Acronyms and terminology list is available to facilitate the SOP reading

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Accessibility to the Standard Operating Procedures

- Through the Institutional Intranet network
- Through the research center secretariat

Questions ?

Title	**Development, Approval and Review of Standard Operating Procedures (SOPs)**
Code	SOP-01
No. of Pages	14

History of Validated Versions

Date dd/mmm/yyyy	Version	Pages	Description of change

History of SOP Implementation

Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy

Approval of Site SOP

	Signature	Date dd/mmm/yyyy

Table of contents

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 development, approval, implementation, management and change procedures of the SOPs and describes the operating policies of the SOPs in the institution.

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

The objective of this operating procedure is to define:

- The development of site SOPs;
- The SOP approval/validation process;
- The implementation of SOPs within the institution;
- The management and updating of SOPs.

3. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.1.4 Appointing the person responsible for site SOPs, within the institution;

3.1.5 Completing and updating appendix 3, "*Tasks delegation or Assignment of Responsibilities Form*", if any tasks or responsibilities are delegated.

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

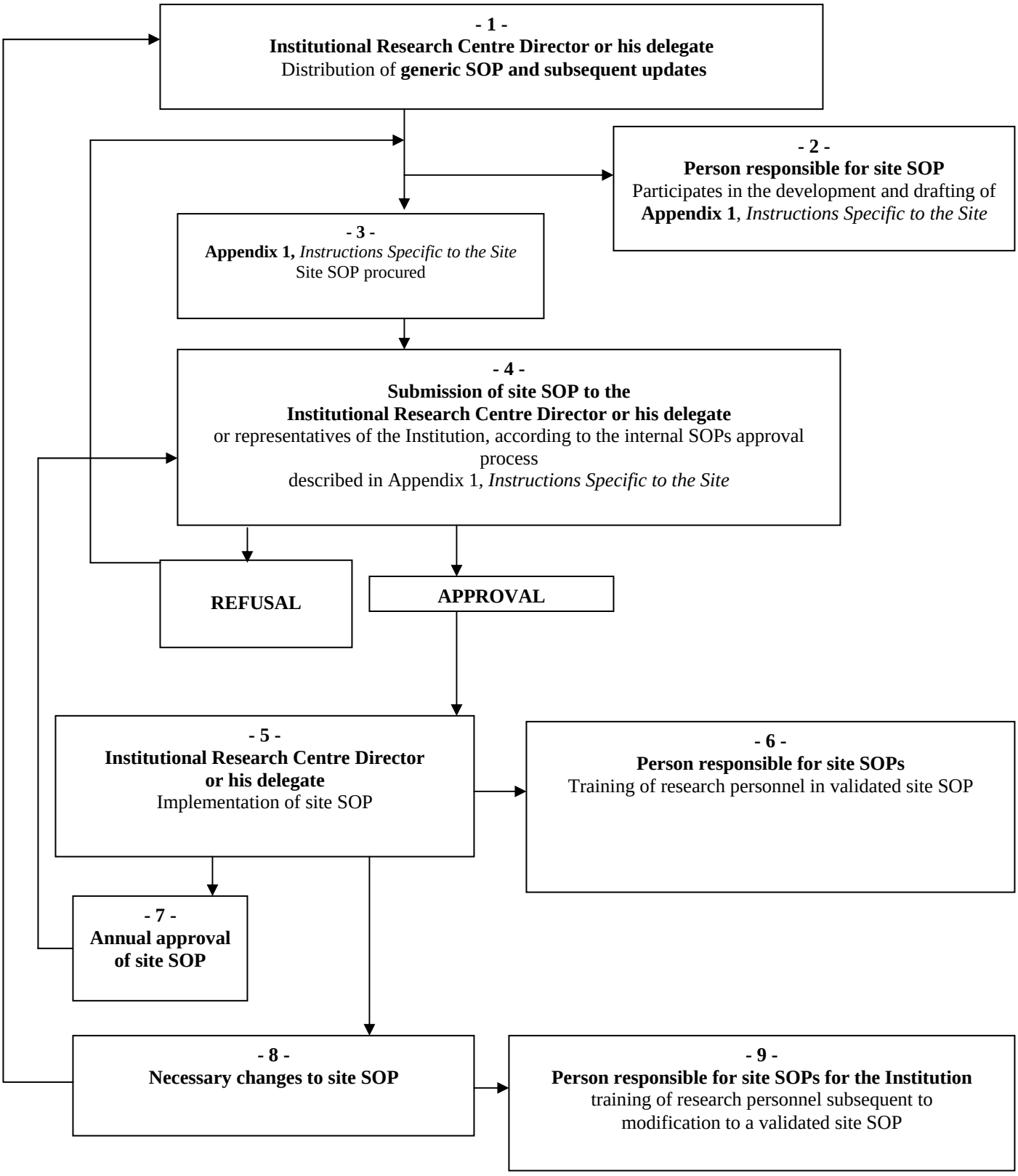
3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP, ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

Flow Chart



4.1 General Organization

4.1.1 Site SOP is produced in electronic format. The same format is used to update the site SOP.

4.1.2 The format used for the date is: day (dd), month in letters (mmm) and year (yyyy).

4.1.3 The approved and signed version is the only official version.

4.1.4 Site SOP in which the section, *Approval of Site SOP*, is not signed by those responsible is not valid.

4.1.5 Signed original SOPs and appendices are the property of the institution.

If an SOP dealing with the same subjects is in effect at the site:

a) A comparative review will be conducted by the person responsible for the site SOPs.

b) Following a written agreement between the Research Centre Director or his delegate and the person responsible for site SOPs, Appendix 2, *Request for Approval or change of Site SOP* will be used to give effect to the more stringent operating procedure according to points 4.2 to 4.5 of this document.

4.2 Development and Drafting of the SOP

All site SOPs should be written according to a standard format and divided into two defined parts as follows:

The first part describes procedures. The second is composed of appendices which consolidate forms or specific instructions within the institution where the SOP is being established.

4.2.1 Page Layout of SOP and appendices (page 1):

a) The **title** section will include:

I. The complete **title**, without any abbreviation, clearly describing the SOP;

II. The **code** contains the letters SOP for – standard operating procedure – and is followed by the corresponding SOP number**,** preceded by zero for the first nine SOPs;

III. **Page numbering** for an SOP will take into account the total number of pages including appendices and cover page.

b) The section, **History of Validated Versions** section, is completed from the first authorization and includes the following points:

I. The date of the validated version, day (dd), month in letters (mmm) and year (yyyy);

II. The number of the validated version, e.g. 01;

III. The total number of pages of the validated document including SOP and appendices;

IV. A description of any changes in the version referred to.

c) The section, **History of SOP Implementation,** is completed once clinical research personnel at the institution have been trained according to this validated SOP. It gives information on the date the SOP is put into practice within the institution. The version validated and its date of implementation should be indicated.

d) The section, **Approval of Site SOP**, includes the name and title of persons involved in the validation process for implementation of the SOP within the institution. Names should be written in block letters, and the document should be signed and dated.

4.2.2 Content of SOP and appendices:

a) Reference to the masculine gender shall mean either gender.

b) The writing style is in the active context and the present tense.

c) Titles and functions rather than names, are used.

d) Site identification should appear on the top left corner of every page.

e) All SOP and appendices pages should be numbered on the bottom right corner of each page, e.g. Page 1 of x.

f) The Table of Contents lists SOP items in sequence:

I. Item 1, **Policies**, refers to laws, rules or expectations regarding the mission, values, concept, vision, goals and the strategic objectives of a given field of activity. Moreover it designates those for whom this SOP is intended.

II. Item 2, **Objective(s),** describes the objective(s) foreseen for the institutional SOP.

III. Item 3, **Responsibilities**, indicates those within the institution responsible for each identified SOP activity.

IV. Item 4, **Procedures**, describes instructions for common procedures conducted within the scope of the SOP. The procedures show the various steps, describe a sequence of ordered activities, itemize critical processes and supply a framework for decision-making. They apply to the institution.

V. Item 5, **References,** outlines SOP policies that might interact with**,** or impact on**,** the described SOP.

VI. Item 6, **Appendices**, does not have a precise format. It is adapted to the specific needs of each standard operating procedure. Appendix 1 is reserved for site specific instructions.

4.2.3 Numbering of Site SOPs:

a) SOP identification for – standard operating procedures – followed by the corresponding SOP code number, starting with 01;

b) Followed by the letters EN for the English version;

c) Followed by the number of the validated version starting with 01.
e.g.: SOP01EN01 for the first validated version

4.2.4 Numbering change due to the amendment of a validated SOP:

a) SOP identification for – standard operating procedures – followed by the SOP code number starting with 01;

b) Followed by the letters EN for the English version;

c) Followed by the number of the next validated version, e.g. 02

e.g.: SOP01EN02 for a second validated *version.*

4.3 Approval and Implementation of Site SOPs

4.3.1 Each site SOP, together with appendices and references**,** should be submitted for approval to the Site Research Centre Director or his delegate by the person responsible for site SOP according to the institution's SOP approval process, as described in Appendix 1, *Instructions Specific to the Site*. Appendix 2, *Request for Approval or Change of Site SOP* should be used to complete this assignment.

4.3.2 Approval of an institution's SOP and appendices is confirmed by the dated signatures of members cited in the section of every SOP entitled *Approval of Site SOP* and corresponding appendices, the members are designated in Appendix 1 *Instructions Specific to the Site*.

4.3.3 Following approval, training of institutional personnel on standard operating procedures will be provided by the person within the institution responsible for the site SOPs. This training should be documented by the individuals trained, in the signed and dated form, Appendix 3 *Training Documentation,* a copy of which is included in this SOP.

4.3.4 Following a change or amendment to the institutional SOP, updated training should be provided by the person within the institution responsible for SOPs. This training should be documented by the individuals trained, using the signed and dated, Appendix 3, *Training Documentation,* a copy of which is included in this SOP.

4.4 Management of Site SOPs

4.4.1 The Research Centre Director or his delegate keeps the original signed (by all participants) version of the section, *Approval of Site SOP*, of each SOP in use in the institution.

4.4.2 These versions should be stored and filed such that they can easily be consulted. The filing system and its location should be noted in Appendix 1, *Instructions Specific to the Site*. All validated versions of the SOP, as well as all subsequent amendments or changes should be maintained in this file.

4.4.3 In the event that other filing systems are created within the institution (e.g. binders) for different sites or departments, a list of SOPs in circulation within the institution should be prepared and kept up to date by the Research Centre Director or his delegate. This list should be revised periodically at the time of annual review of site SOPs in use.

4.4.4 Within the institution, photocopies are allowed for internal use. See Appendix 1, *Instructions Specific to the Site*, for procedures for issuing photocopies. If a copy is needed for use outside the institution, authorization from the Research Centre Director or his delegate should be obtained. Guidelines for the management of the internal or external circulation of photocopies should be described in Appendix 1, *Instructions Specific to the Site*.

4.5 Annual Approval or Change of Site SOPs

4.5.1 Every site SOP should be reviewed and approved annually by the Research Centre Director or his delegate and, if necessary, by members of the institution involved in the SOP approval process as described in Appendix 1, *Instructions Specific to the Site*. Review can also take place as needed, if circumstances dictate. Appendix 2, *Request for Approval or Change of Site SOP*, should be used for this purpose.

4.5.2 Any revision or change to the site SOP requires a written request using Appendix 2, *Request for Approval or Change of Site SOP.* If alternate forms are used, they should be described in Appendix 1, *Instructions Specific to the Site*. The Centre Director or his delegate will then initiate the process for change as described in items 4.2, 4.3 and 4.4 of the present document.

4.5.3 The Research Centre Director or his delegate should participate in the revision process if a request is made to modify or amend Appendix 1, *Instructions Specific to the Site.* The request should be processed as described in the preceding paragraph.

4.5.4 In the case of request for revision/change to a site SOP by the person responsible for SOPs at the site, the Research Centre Director or his delegate should be notified by way of Appendix 2, *Request for Approval or Change to Site SOP.* If other forms are used for this purpose by the institution, they should be described in Appendix 1, *Instructions Specific to the Site*. The person responsible for site SOPs will then initiate the process for change as described in items 4.2, 4.3 and 4.4 of the present document.

5. 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-02 Organizing a site for Clinical Research

SOP-07 Conducting a Study in The Context of a Clinical Trial Application in Canada

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

4. **Specific Responsibilities of the Institution**

5. **Procedures**

6. **References**

7. **Appendices**

APPENDIX 2 REQUEST FOR APPROVAL OR CHANGE OF SITE SOP

SOP Code: _____

SOP Title: _____

Notice to the institution of a request for a modification by the person responsible for SOPs at the site: ☐

Notice to the person responsible for SOPs at the site of the institution's request for a modification: ☐

For approval: ☐ For change: ☐

APPLICANT :	**ADDRESSEE :**
_____	_____
Name in block letters	Name in block letters
_____	_____
Signature	Signature
_____	_____
Title	Title
_____	_____
Date issued dd/mmm/yyyy	**Date received** dd/mmm/yyyy

Please return this request duly completed along with the site SOP, to the Institutional Research Centre Director, within 10 working days from the receipt of this notice.

APPENDIX 2 REQUEST FOR APPROVAL OR CHANGE OF SITE SOP

SOP number:	Appendix number:
Date of SOP last validated version: dd/mmm/yyyy	Date of approval or change submission: dd/mmm/yyyy
Is there a French version?	Yes ☐ No ☐
Is there an updated French version?	Yes ☐ No ☐

Revision or Changes implemented

Approval of Site SOP

SOP approved by: (block letters)	Title:
Signature:	Date: dd/mmm/yyyy
SOP approved by: (block letters))	Title:
Signature:	Date: dd/mmm/yyyy
SOP approved by: (block letters)	Title:
Signature:	Date: dd/mmm/yyyy
SOP approved by: (block letters)	Title:
Signature:	Date: dd/mmm/yyyy

Refusal of Site SOP

Reason for refusal:

Document refused by: (block letters)	Title:
Signature :	Date: dd/mmm/yyyy

APPENDIX 3 TRAINING DOCUMENTATION

Date:	**Duration:**
Subject:	
Trainer: (block letters)	**Trainer's signature:**

Title and department	Employee's name (block letters)	Signature

Page ____ of _____

APPENDIX 4 TASK DELEGATION OR ASSIGNMENT OF RESPONSIBILITIES FORM

Type of tasks:

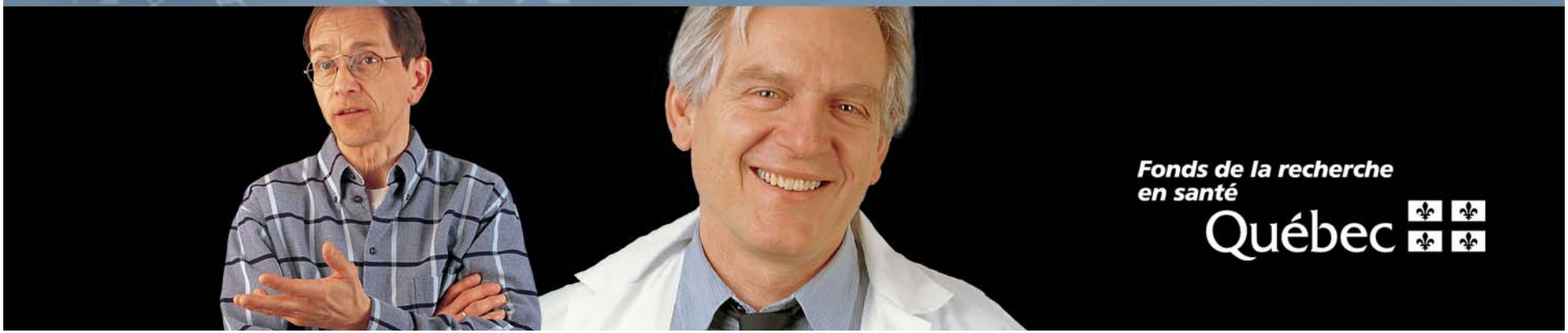
A) Signature for site SOPs approval
B) Review of site SOP for approval
C) Notice to the Ethics Committee of SOPs in application
D) Implementation and management of site SOPs
E) Training of clinical research personnel
F) Development of Appendix 1, *Instructions Specific to the Site*
G) Other _____
H) Other _____
I) Other _____

Name (block letters)	Title	Signature	Tasks	Start date	End date
Example: Mr. X	Research Center Director	Xxxxxxxxxxxxxxxxx	A, B, C, D	Jan 3rd, 2004	
Example: Mr. X	Assistant to the Director	Yyyyyyyyyyyyyyyyy	B, C, D	Jan 5th, 2004	

Name (block letters)	Title	Signature	Tasks	Start date	End date

Page ____ of _____

Standard Operating Procedures (SOP)
SOP-01
Development, Approval and Review of Standard Operating Procedures



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- **Objective**
  - Define:
    - The development of site standard operating procedures;
    - The SOP approval/validation process;
    - The implementation of SOPs within the institution;
    - The management and updating of SOPs.

- **Site responsibilities**
  - Research Center Director
  - Sponsor-Investigator or Investigator/Qualified Investigator
  - Person responsible for the Site SOPs

- **Management of Site SOPs**
  - Photocopies
- **Annual Approval or Change of Site SOPs**
  - Annually review and approval by the Research Center Director or his delegate
  - Revision/change to the site SOP44

Questions ?

Title	**Organizing A Site for Clinical Research**
Code	SOP-02
No. of Pages	14

History of Validated Versions

Date dd/mmm/yyyy	Version	Pages	Description of change

History of SOP Implementation

Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy

Approval of Site SOP

	Signature	Date dd/mmm/yyyy

Table of contents

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 subjects.

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. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP, ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. 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.

4.1 Creation of a Research Team

4.1.1 The sponsor-investigator or the investigator/qualified investigator should ensure that each clinical study is conducted according to GCP [-5] and should be qualified by education, training and expertise required to assume responsibility for the proper conduct of the study, ICH 4.1.1. Moreover, he should ensure that all persons assisting with the study are adequately informed about the protocol, investigational products and their study-related duties and functions, ICH 4.2.4, SOP 04.

4.1.2 In preparation for a clinical study, it is advisable that the sponsor-investigator or his delegate or the investigator/qualified investigator or his delegate:

I. Appoints, before submitting 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.

4.1.3 The sponsor-investigator or his delegate or the investigator/qualified investigator or his delegate should maintain a list of appropriate qualified persons to whom he has delegated significant study-related duties, ICH 4.1.5, SOP 03

4.2 Study Protocol Feasibility Assessment

4.2.1 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 require 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.

4.2.2 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 for the sponsor-investigator or investigator/qualified investigator, 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 06

4.2.3 The sponsor-investigator or investigator/qualified investigator should also make certain that systems and procedures are implemented to ensure the quality of all aspects of the clinical study.

4.2.4 Before beginning each clinical study, the investigator/qualified investigator should obtain approval from a research Ethics Committee, SOP 08 and 09.

4.3 Research Team Location and Needs

4.3.1 A sufficient number of facilities should be available to interview and examine study subjects and securely store study material, medication and instrumentation if necessary, SOP 18.

4.3.2 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 23, 24 and 26.

4.3.3 Procedures for the archiving of study-related documentation should be discussed and defined from the start; see Appendix 1, *Instructions Specific to the Site*.

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

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

4.3.6 In the case of clinical studies involving investigational products (drug), biological products, medical devices 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 investigational products, biological products, medical devices or radiopharmaceuticals should also be evaluated if this is to take place within the institution.

4.3.7 If applicable, secure space for local data management should be set up as described in SOP 24 and 26.

4.4 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

Many contractual documents have to be completed during clinical studies. For example:

4.4.1 Document confirming that the investigator/institution/qualified investigator will be conducting the clinical study according to the protocol approved by the sponsor or sponsor-investigator and to which the 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;

4.4.2 Document confirming the sponsor-investigator's or the investigator/qualified investigator's responsibility to respect the Declaration of Helsinki and the ICH GCP;

4.4.3 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 subject or visit;

III. Payment for subjects having completed the study;

IV. Payments schedule;

V. Reimbursement of expenses to participating subjects.

4.5 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 G*ood Clinical Practice* 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 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 2, *Clinical Study Related Essential Documentation,* ICH 8.2, 8.3 and 8.4.

5 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-03 Research Team: Role Definitions, Responsibilities and Task Delegation

SOP-04 Site Research Team: Competence, Knowledge and Training

SOP-06 Study Feasibility Assessment

SOP-08 Protocol and Protocol Amendment, Submission to Research Ethics Board

SOP-09 Consent Process and Subject Informed Consent Form

SOP-18 Managing Investigational Products, Biological Products, Medical Devices or Radiopharmaceuticals Under Study

SOP-24 Clinical Data Management, Paper or Electronic Format

SOP-26 Security and Confidentiality of Data

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

4. **Specific Responsibilities of the Institution**

5. **Procedures**

6. **References**

7. **Appendices**

APPENDIX 2 ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL STUDY

ICH Section 8

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.

Document Title		Purpose	Located in Files of	
			Investigator & Institution	**Sponsor & Sponsor - Investigator**
8.2.1	**Investigator's Brochure** (if applicable)	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	Signed protocol and modifications, if any, and sample case report form (CRF)	To document investigator and sponsor agreement to the protocol / modification (s) and CRF.	X	X
8.2.3	Information given to study subject			
	- I**nformed consent form** (including all applicable translations)	To document the informed consent	X	X
	Any other written information	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
	Advertisement for subject recruitment **(if used)**	To document that recruitment measures are appropriate and not coercive	X	**Sponsor - Investigator**
8.2.4	Financial aspects of the study	To document the financial agreement between the investigator /institution and the sponsor or sponsor-investigator for the study	X	X
8.2.5	**Insurance statement** (where required)	To document that compensation to subject(s) for study-related injury will be available	X	X
8.2.6	Signed agreement between involved parties, e.g.:	To document agreements		
	o Investigator /institution and sponsor or sponsor - investigator		X	X
	o Investigator/Institution and CRO		X	X (where required)
	o Sponsor or sponsor - investigator and CRO		X	X
	o Investigator/ Institution and authority(ies) (where required)		X	X

Document Title		Purpose	Located in Files of	
			Investigator & Institution	Sponsor & Sponsor - Investigator
8.2.7	Dated, documented approval/favourable opinion of institutional review board (IRB) /independent ethics Committee (IEC) of the following: o Protocol and any modifications o CRF (if applicable) o Informed consent form(s) o Any other written information to be provided to the subject(s)s o Advertisement for subject recruitment (if used) o Subject compensation (if any) o Any other documents given approval/ favourable opinion	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).	X	X
8.2.8	Institutional review board/ independent ethics Committee composition	To document that the IRB/IEC is constituted in agreement with GCP	X	X (where required)
8.2.9	Regulatory authority (ies) authorisation/ approval/ notification of protocol	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)	X (where required)	X (where required)
8.2.10	Curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and sub-investigator(s)	To document investigators qualifications and eligibility to conduct study and/or their competence to provide medical supervision of subjects	X	X
8.2.11	Normal value(s)/range(s) for medical/ laboratory/ technical procedure(s) and/or test(s) included in the protocol	To document normal values and/or ranges of the tests	X	X
8.2.12	Medical /laboratory/ technical procedures /test**s** o Certification or o Accreditation or o Established quality control and/or external quality assessment or o Other validation (where required)	To document that the Investigator/Institution have access to adequate facilities to perform required test(s), and support reliability of results	X (where required)	X

Document Title		Purpose	Located in Files of	
			Investigator & Institution	**Sponsor & Sponsor - Investigator**
8.2.13	Sample of label (s) attached to investigational product container(s) (where required)	To document compliance with applicable labelling regulations and appropriate instructions were provided to the subjects		X
8.2.14	Instructions for handling of investigational product (s) and study-related materials (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and study-related materials	X	X
8.2.15	Shipping records for investigational product(s) and study-related materials (where required)	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	X	X
8.2.16	Analysis certificate (s) of shipped investigational product(s) (where required)	To document identity, purity, and strength of investigational product(s) to be used in the study		X
8.2.17	Decoding procedures for blinded studies (where required)	To document how, in case of an emergency, identity of investigational product can be revealed without exposing the treatment to the remaining participating subjects.	X	X (third party if applicable)
8.2.18	Master randomisation list (where required)	To document method for randomisation of study population		X (third party if applicable)
8.2.19	Pre-study monitoring report	To document that the site is suitable for the study (may be combined with 8.2.20)		X
8.2.20	Study initiation monitoring report	To document that study procedures were reviewed with the investigator and the investigator's study staff (may be combined with 8.2.19)	X	X

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

Document Title		Purpose	Located in Files of	
			Investigator & Institution	**Sponsor & Sponsor - Investigator**
8.3.1	Investigator's brochure updates (if required)	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X
8.3.2	Any revision to: o Protocol/modifications(s) and CRF o Informed consent form o Any other written information provided to subjects o Advertisement for subject recruitment (if used)	To document revisions of these study related documents given effect during the study	X	X
8.3.3	Dated, documented approval/ favourable opinion of institutional review board (IRB)/ independent ethics Committee (IEC) of the following**:** o Protocol modification (s) o Revision (s) of: • Informed consent form • Any other written information to be provided to the subjects • Advertisement for subject recruitment (if used) o Any other documents given approval /favourable opinion o Continuing review of study (where required)	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).	X	X
8.3.4	Regulatory authority (ies) authorisations/ approvals/ notifications where required for: o Protocol modification (s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	X
8.3.5	Curriculum vitae for new investigator(s) and/or sub-investigator(s)	(See 8.2.10)	X	X

Document Title		Purpose	Located in Files of	
			Investigator & Institution	**Sponsor & Sponsor - Investigator**
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)	X	X
8.3.7	Updates of medical/laboratory/ technical procedures/tests o Certification or o Accreditation or o Established quality control and/or external quality assessment or o Other validation (where required)	To document that tests remain adequate throughout the study period (see 8.2.12)	X (where required)	X
8.3.8	Documentation of investigational product(s) and study-related materials shipment	(See 8.2.15)	X	X
8.3.9	Certificate (s) of analysis for new batches of investigational products	(See 8.2.16)		X
8.3.10	Monitoring visit reports	To document site visits by, and findings of, the monitor		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	X	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)	X	Sponsor-Investigator-
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	X	Sponsor-Investigator-

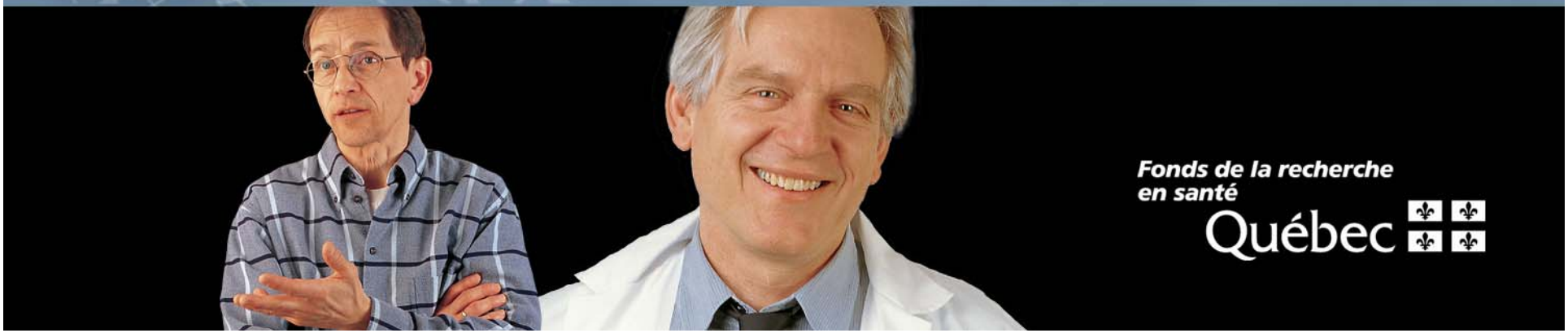
Document Title		Purpose	Located in Files of	
			Investigator & Institution	Sponsor & Sponsor - Investigator
8.3.14	Signed, dated and completed case report forms (CRF)	To document that the investigator or authorised member of the investigator's staff confirms the recorded observations.	X (Copy)	X (Original)
8.3.15	Documentation of CRF corrections	To document all changes/additions or corrections made to CRF after initial data recording.	X (Copy)	X (Original)
8.3.16	Notification by originating investigator to sponsor of serious adverse events and related reports	Notification by originating investigator to Sponsor/Sponsor-Investigator of serious adverse events and related reports in accordance with Item 4.11	X	X
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	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	X (where required)	X
8.3.18	Notification by sponsor/sponsor-investigator to investigators of safety information	Notification by sponsor/sponsor-investigator to investigators of safety information in accordance with 5.16.2	X	X
8.3.19	Interim or annual reports to IRB/IEC and authority (ies)	Provided interim or annual reports to IRB/IEC in accordance with 4.10 and to authority (ies) in accordance with 5.17.3	X	X (where required)
8.3.20	Subject screening log	To document identification of subjects who entered pre-study screening	X	X (where required)
8.3.21	Subject identification code list	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	X	Sponsor-Investigator
8.3.22	Subject enrolment log	To document chronological enrolment of subjects by study number	X	Sponsor-Investigator
8.3.23	Investigational products accountability at the site (if required)	To document that investigational product(s) have been used according to the protocol	X	X
8.3.24	Signature sheet	To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs	X	X
8.3.25	Record of retained body fluids/ tissue samples (if any)	To document location and identification of retained samples if tests need to be repeated	X	X

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:

Document Title		Purpose	Located in Files of	
			Investigator & Institution	**Sponsor & Sponsor - Investigator**
8.4.1	Investigational product (s) accountability at site (if required)	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.	X	X
8.4.2	Documentation of investigational product destruction (if required)	To document destruction of unused investigational products by sponsor/sponsor-investigator or at site	X (If discarded at site)	X
8.4.3	Complete subject identification code list	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	X	Sponsor - Investigator
8.4.4	Audit certificate (if available)	To document that an audit was performed		X
8.4.5	Study close-out final monitoring report	To document that the study close-out went according to prescribed requirements, and copies of essential documents are held in the appropriate files		X
8.4.6	Treatment allocation and decoding documentation (if required)	Document sponsor with any treatment decoding that may have occurred		X
8.4.7	Final report by investigator to IRB/IEC where required, and where applicable, to the regulatory authority (ies) (if required)	To document study completion	X	
8.4.8	Clinical study report	To document results and data study interpretation	X (If required)	X

Standard Operating Procedures (SOP)
SOP-02
Organizing A Site for Clinical Research



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- **Objective**
  - Describe procedures to be followed to ensure proper organization of the clinical study.

- **Creation of a Research Team**
  - The Sponsor-investigator or the investigator/qualified investigator should :
    - Conduct each clinical study according to *Good Clinical Practice*
    - Possess the knowledge, training and expertise required
    - Ensure that each person is adequately trained regarding protocol, investigational products and study related tasks

- **Creation of a Research Team**

  – The Sponsor-investigator or his delegate or the investigator/qualified investigator should :

    - Appoint members of the research team
    - Determine each team member's roles and the availability of relief personnel
    - Identify team members who need GCP training
    - Schedule training in protocol content and application
    - Maintain a list of appropriate qualified persons to whom he has delegated significant study-related duties

- **Study Protocol Feasibility Assessment**
- **Research Team Location and Needs**
  - Secure space with restricted access → confidentiality

- **Research Team Location and Needs**
  - Plan secure space for local data management if applicable
- **Budget and Financial Contract**
  - The health institution should :
    - Be aware of the financial implications
    - Receive direct and indirect costs

Questions ?

Title	**Research Team: Role Definitions, Responsibilities and Task Delegation**
Code	SOP-03
No. of Pages	10

History of Validated Versions

Date dd/mmm/yyyy	Version	Pages	Description of Change

History of SOP Implementation

Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy

Approval of Site SOP

	Signature	Date dd/mmm/yyyy

Table of contents

1. Policy

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 roles and responsibilities of every member of the research study 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 subjects.

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 record written procedures for the delegation of tasks and responsibilities.

3. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

4.1 **Roles Definition**

An investigator should be designated for each clinical study. This designated investigator is responsible for the well-being of research subjects, the conduct of the study, administration of the investigational product, if applicable, team and space requirements, conformity with the requirements of the Ethics Committee and GCP team training. Some of these tasks may be delegated to another team member.

4.1.1 **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 both initiates and conducts alone or with others a clinical study, and under whose immediate direction the investigational product is administered to the subject. 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.

4.1.2 **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 the clinical study 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 [-5]

4.1.3 **Roles Delegated in the Course of a Clinical Study:**

a) A **Subinvestigator** 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 Ethics Committee. Examples of the coordinator’s activities:

I. Ensures the well-being of subjects by providing them with all pertinent information regarding the clinical study ,

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

III. Prepares the protocol for submission to the Ethics Committee,

IV. Coordinates subject 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 can be prepared and distributed and can also be stored in the pharmacy according to the product description. Moreover, delivery, distribution to subjects, recording and, 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) to each subject and should check, at intervals appropriate for the study, that each subject is following the instructions properly, 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 Ethics Committee, may be carried out by office staff. At the request of the investigator/researcher, these parties should be added to the *Tasks Delegation or Assignment of responsibilities* form, Appendix 2 of the present document.

4.2 Responsibilities Description

4.2.1 The **Sponsor, Sponsor-Investigator** shall ensure that a clinical study is conducted in accordance with good clinical practices 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 of a 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 but 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.

4.2.2 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 Ethics Committee, and the regulatory authorities, ICH 4.1.1;

b) Be thoroughly familiar with the appropriate use of the investigational products 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) and their study-related tasks and roles, ICH 4.2.4 and SOP 02,

II. All study related medical decisions are taken, ICH 4.3.1,

III. Adequate medical care is provided to a subject in the case of any adverse event, ICH 4.3.2,

IV. A written and dated approval/favourable opinion from the Ethics Committee for the study protocol, written informed consent form, consent form updates,

subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects, ICH 4.4.1 and SOP 15,

V. The protocol approved by the sponsor/sponsor-investigator and Ethics Committee is abided by, ICH 4.5.1 and SOP 08,

VI. All accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor/sponsor-investigator in the CRFs and in all required reports, ICH 4.9.1 and SOPs 23, 24, 25 and 26,

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 and SOP 02,

VIII. Necessary measures are taken to prevent accidental or premature destruction of essential study documents for a clinical study, ICH 4.9.4 and SOPs 23, 24,

IX. All serious adverse events are immediately reported to the sponsor/sponsor-investigator and applicable authorities, ICH 4.11.1 and SOP 17.

The Investigator or a person designated by the investigator/institution should explain to each subject the appropriate way of using the biological product, medical device or radiopharmaceutical (if applicable) and should verify, at regular intervals, if all subjects are following instructions appropriately.

4.3 Tasks Delegation or Roles Assignment Description

4.3.1 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.

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

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

a) Names 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 2, *Tasks Delegation or Assignment of Responsibilities Form,* is an example that can be used to meet documentation requirements.

4.3.4 **Investigational Product, Biological Product, Medical Device or Radiopharmaceutical Specifications:**

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

The investigator should ensure that the investigational products, biological product, medical device or radiopharmaceutical are used only in accordance with the approved protocol, ICH 4.6.5;

Where allowed/required, the investigator/qualified investigator or institution, may/should assign some or all of the investigator's/institution's tasks for investigational product(s), biological product, medical device or radiopharmaceutical accountability at the study site to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/ institution, ICH 4.6.2;

In compliance with section A.6 – mesure 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.

5. 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.

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-02 Organizing a Site for Clinical Research.

SOP-08 Protocol and Protocol Amendment, Submission to Research Ethics Board

SOP-15 Research Ethics Board (REB): Ongoing Communication

SOP-17 Management of Adverse Events – Serious Adverse Events and Adverse Reactions Serious Adverse Reactions

SOP-23 Management of Data and Source Documents

SOP-24 Clinical Data Management, Paper or Electronic Format

SOP-25 How to Fill In a Case Report Form and Modify Data

SOP-26 Security and Confidentiality of Data

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

4. **Specific Responsibilities of the Institution**

5. **Procedures**

6. **References**

7. **Appendices**

APPENDIX 2 TASKS DELEGATION OR ASSIGNMENT OF RESPONSIBILITIES FORM

Clinical Study Name/Protocol :	Clinical Study Number/Protocol :

Type of tasks or responsibilities :

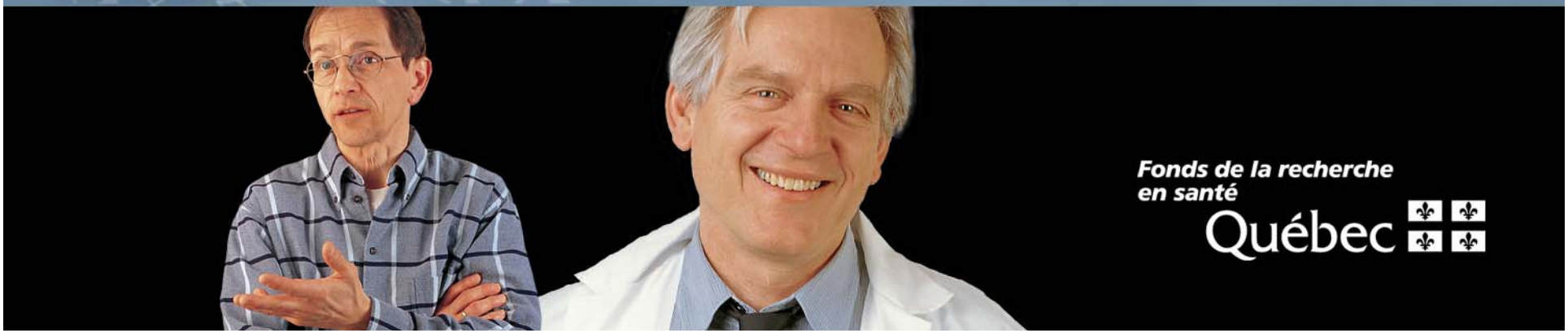
A) Case report form signature (CRF)
B) Physical exam
C) Subject recruiting
D) CRF entries and corrections
E) CRF process
F) Investigational product administration
G) Other _____
H) Other _____
I) Other _____

Name (Block letters)	Title	Signature	Initials	Tasks	Start date	End Date	Principal Investigator's Initials
Example : Pierre X	Principal Investigator		P.X.	A, B, C, D, E	Jan 3rd, 2004		
Example : Jean Y	Study Coordinator		J.V.	C, D, E, F	Jan 5th, 2004	Dec. 10, 2004	

Name (Block letters)	Title	Signature	Initials	Tasks	Start date	End Date	Principal Investigator's Initials
	Principal Investigator						

Page ____ of _____

Standard Operating Procedures (SOP)
SOP-03
Research Team: Role Definitions, Responsibilities and Task Delegation



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- **Objective**
  - Identify all members of the research team, to define their roles and responsibilities as well as to record written procedures for the delegation of tasks and responsibilities.

- **Roles Definition**
  - The investigator designated for each clinical study is responsible for the :
    - Well-being of research subjects
    - Conduct of the study
    - Administration of the investigational product
    - Team and space requirements
    - Conformity with the requirements of the Ethics Committee
    - GCP team training

- **Organisation and Management of a Clinical Study**
  - The Sponsor : an individual, a company, institution or organization which takes responsibilities for the initiation, management or financing of clinical study
  - The Sponsor-Investigator : an individual who both initiates and conducts a clinical study
- **Person responsible for the conduct of a clinical study**
  - The Investigator : a person responsible for the conduct of the study at a study site
  - The Qualified Investigator

- **Roles Delegated in the Course of a Clinical Study**
  - The Subinvestigator
  - The Study Coordinator
  - The pharmacist
  - Other parties

- **Responsibilities Description**
  - The Sponsor, Sponsor-Investigator
  - The Investigator/Principal Investigator

- **Tasks Delegation or Roles Assignment Description**
  - Describe on Tasks Delegation Form
  - Record signatures and initials of all persons
  - Maintain a list of appropriately qualified persons

- **Investigational Product Specifications**
  - Investigational product(s): the pharmacist
    - MSSS, Plan d'action ministériel en éthique de la recherche et en intégrité scientifique, mesure 16.
  - Experimental drugs should be submitted to the same type of control as prescription drugs
    - Deadline …..

Questions ?

Title	Site Research Team: Competence, Knowledge and Training
Code	SOP-04
No. of Pages	7

History of Validated Versions

Date dd/mmm/yyyy	Version	Pages	Description of Change

History of SOP Implementation

Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy

Approval of Site SOP

	Signature	Date dd/mmm/yyyy

Table of contents

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 Harmonisation (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 subjects.

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. Site Responsibilities

3.1 **The Director of the Research Centre, or delegate, is responsible for:**

3.1.1 Approving or updating the site SOP that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

4.1 **Competence and knowledge – Curriculum vitae**

Within the framework of clinical studies with drugs:

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 subjects 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 subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent, Declaration of Helsinki, B15, 2002.

Within the framework or clinical studies without drugs:

It is the duty of the researcher in medical research to protect the life, health, privacy and dignity of the human subject.

Medical research involving human subjects 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.

All medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent researcher. The responsibility for the human subject must always rest with a professionally qualified person and never rest on the subject of the research, even though the subject has given consent.

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 agreement 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 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.

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

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

4.1.3 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.

4.2 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 ensures that all persons assisting with the study are adequately informed about the protocol, investigational product(s), biological products, medical devices or radiopharmaceuticals, and study related tasks and functions, ICH 4.2.4:

4.2.1 The investigator/qualified investigator ensures that training of the study team in GCP of ICH is documented;

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

4.2.3 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;

4.2.4 Training documentation should include the title of the training, duration, participant name and training date, the person or organization who 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 a whole group training, an example of form is presented in Appendix 2.

5. 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-03 Research Team: Role Definitions, Responsibilities and Task Delegation

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

4. **Specific Responsibilities of the Institution**

5. **Procedures**

6. **References**

7. **Appendices**

APPENDIX 2 TRAINING DOCUMENTATION

Date :	**Duration :**
Training Subject:	
Trainer: (block letters)	**Trainer's Signature:**

Title and Department	Employee's Name (block letters)	Signature

Page ____ of _____

Standard Operating Procedures (SOP)
SOP-04
Site Research Team : Competence, Knowledge and Training

Fonds de la recherche en santé Québec

SOP-04
Site Research Team: Competence, Knowledge and Training

- **Objective**
  - 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.

- **Competence and Knowledge – Curriculum vitae**
  - Duty of the physician in medical research is to protect life, health, privacy and dignity of the human subject
  - Declaration of Helsinki : all medical research involving human should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person
  - Each individual involved in conducting a study should be qualified by education, training and experience

- **Competence and Knowledge – Curriculum vitae**
  - The investigator should be qualified by :
    - Education
    - Training
    - Experience
  - The investigator should maintain a list of appropriately qualified persons

- **Competence and Knowledge– Curriculum vitae**
  - List in form research team roles definition, responsibilities and tasks delegation:
    - investigator/qualified investigator
    - subinvestigators
    - Every other person to whom the investigator/qualified investigator has delegated related study tasks

- **Training**
  - The investigator/qualified investigator should :
    - Document all training related to qualifications of research team members and keep with the essential documents

Questions ?

Title	Preparing the team for a study
Code	SOP-05
No. of Pages	6

History of Validated Versions

Date dd/mmm/yyyy	Version	Pages	Description of Change

History of SOP Implementation

Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy

Approval of Site SOP

	Signature	Date dd/mmm/yyyy

Table of contents

1. Policies

Within the framework of the declaration of Helsinki and in accordance with the principles inherent with the Good Clinical Practice (GCP) of 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 subjects.

2. Objective

The objective of this operating procedure is to explain to the research team the clinical the processes for study setup.

3. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP, ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

4.1 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/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 require review of the confidentiality agreement by a legal advisor, before signing.

4.1.1 A copy of the signed and dated confidentiality agreement should be kept with the essential study documentation.

4.2 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 subject and society. A study should be initiated and continued only if the anticipated benefits justify the risks.

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.

4.2.1 The investigator/qualified 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;

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

4.2.3 According to ICH 5.6.3 principle, the investigator/qualified 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 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.

4.2.4 A copy of this agreement should be kept with the essential documentation related to the study.

4.3 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.

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

4.3.2 The investigator/qualified 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.

4.3.3 In the course of an initiation visit, familiarity with the protocol, objectives and procedures, subject inclusion and exclusion criteria, knowledge of the investigational product, biological products, medical devices or 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 product, biological products, medical devices or radiopharmaceuticals management, if applicable;

c) Monitoring and inspection activities;

d) Case report forms;

e) Management of study essential documents;

f) Subject informed consent form procedures;

g) Data management;

h) Management of biological samples;

i) Any other protocol-specific item.

4.3.4 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.

5. 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-02 Organizing a Site for Clinical Research, Study Related Essential Documentation Section

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

4. **Specific Responsibilities of the Institution**

5. **Procedures**

6. **References**

7. **Appendices**

Standard Operating Procedures (SOP)
SOP-05
Preparing the Team for a Study

Fonds de la recherche en santé Québec

- **Objective**
  - Explain to the research team the clinical processes for study setup.

- **Preparation – Confidentiality Agreement**
  - Commitment of the investigator/qualified investigator and the research team regarding the confidentiality of study information
  - In case of a study initiated by a sponsor or sponsor investigator, a confidentiality agreement should be signed and dated

- **Preparation – Protocol and Investigator's brochure**
  - Evaluate foreseeable risks and inconveniences in relation to the anticipated benefit for the subject and society
  - Initiate and continue a study only if the anticipated benefits justify the risks
  - Provide the investigator/institution with the protocol and an up-to-date Investigator's Brochure

- **Initiation Visit**
  - The investigator/qualified investigator should:
    - Ensure that all persons are adequately informed about the protocol, the investigational product and their study-related tasks and functions
  - The investigator/qualified investigator and all research team members should:
    - Be present during the initiation visit

Keep a written report describing involvement in the initiation visit and keep with the essential documentation

- **Initiation Visit**
  - Familiarity with the protocol
  - Objectives and procedures
  - Subject inclusion and exclusion criteria
  - Knowledge of the investigational product (if applicable), GCP and legal obligations of the research team
  - Management of AE/SAE, AR/SAR

- **Initiation Visit**
  - Monitoring and inspection activities
  - Case report forms
  - Subject informed consent form procedures
  - Data management
  - Management of biological samples

Questions ?

Title	Study Feasibility Assessment
Code	SOP-06
No of Pages	9

History of Validated Versions

Date dd/mmm/yyyy	Version	Pages	Description of Change

History of SOP Implementation

Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy

Approval of Site SOP

	Signature	Date dd/mmm/yyyy

Table of contents

1. Policy

There are no specific directives concerning the feasibility assessment of a clinical study. Common sense and experience should guide our understanding of 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 subjects.

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 subject population targeted for recruitment into the clinical study.

3. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

4.1 Clinical Study Assessment

Assessment of study feasibility can be based on a list of questions, the answers to which will allow the investigator/qualified investigator to make an informed decision regarding the feasibility of the study at his site. The questions, listed in Appendix 2, *Clinical Study Feasibility Check List*, are the following:

4.1.1 **Is this protocol scientifically, technically and ethically feasible?**

a) My field of 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) Subject eligibility criteria are realistic and well defined in the protocol.

d) If required, the comparative investigational product is available in my area.

e) This protocol is consistent with local ethical practices.

4.1.2 **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 subjects, within the established time limits, has been checked (subjects medical files consulted to confirm that there are enough subjects).

A user's file is confidential and its access is denied to everyone without the user's consent or that of a person enabled to act in his name, a court or a coroner's order in the performance of his tasks, in the case of these presents to allow the communication of information contained in the file if required from an institution or in the case of information transmitted for law application on public health. Health and Social Services Act, **a.19** .1991, c. 42, a. 19; 1992, c. 21, a. 2; 1999, c. 45, a. 1; 2001, c. 60, a. 161.

Notwithstanding Article 19, Professional Services Director of an institution or, in the absence of such a director, the General Director, can authorize a professional to look into a user's file for study, teaching or research purposes, without the user's consent. However, before giving such an authorization, the Director should make sure that the criteria prescribed by Article 125 under the Act respecting access to documents held by public bodies and the protection of personal information (Chapter A-2.1) are met. He should withhold his authorization if he is not convinced that the professional project complies with generally recognized ethical standards or scientific integrity. The authorization should be limited in time and may be submitted to certain conditions. It may be revoked at any time if the Director has reasons to believe that the professional does not respect the confidentiality nature of the acquired information or does not comply with the imposed conditions or generally recognized ethical standards or scientific integrity. Health and Social Services Act, **a. 19.2**. 1999, c. 45, a. 2.

d) According to the protocol, and if required, the number of potential subjects outside my site has been discussed (type of advertisement, etc.)

e) Protocol requirements which have an impact upon the consent of subjects to participate in the study 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.

4.1.3 **Do we have the time?**

a) The investigator/qualified investigator has sufficient time to personally see and treat subjects.

b) The investigator/qualified investigator has sufficient time to supervise the research team.

c) The investigator/qualified 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/qualified investigator have sufficient time to interact with the sponsor, sponsor-investigator and the research team.

e) The investigator/qualified investigator have sufficient time to properly 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/qualified investigator in the conduct and supervision of a clinical study for which he is ultimately responsible.

4.1.4 **Are there sufficient resources within the research team?**

a) The investigator/qualified investigator can delegate some of the medical aspects of the study to subinvestigators.

b) The investigator/qualified investigator can delegate a number of significant aspects of the study to coordinators.

c) The investigator/qualified 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.

4.1.5 **ICH principle 4.2.3 stipulates that the investigator/qualified 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 subject recruitment and follow-up has been verified.

c) The space to securely store subjects' study records and clinical study material has been evaluated.

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

e) Protocol required specific medical material as well as on-site, available medical material have been verified.

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

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 02.

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

5. References

Health Canada, Guidance for Industry, Good Clinical Practice: Consolidated guideline, ICHTopic **E6**, 1997.

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

SOP-02 Organizing a Site for Clinical Research

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

4. **Specific Responsibilities of the Institution**

5. **Procedures**

6. **References**

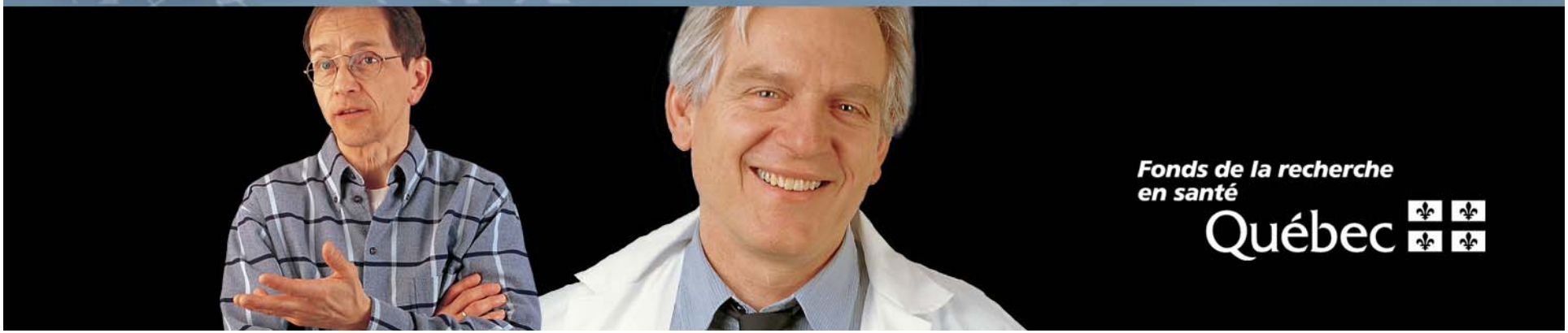
7. **Appendices**

APPENDIX 2 CLINICAL STUDY FEASIBILITY CHECK LIST

Protocol Title:				**Protocol Number:**
Questions	**Yes**	**No**	**N/A**	**Commentaries**
Part 1 – Science, technique and ethics				
The institution Scientific Committee will evaluate the protocol.				
The protocol is technically feasible.				
The protocol is compatible with the medical field, local authorities and site requirements.				
The protocol admissibility criteria are realistic and well defined in the protocol.				
The comparative product is available in my region.				
The protocol is compatible with the local ethical practices.				
Part 2 – Subjects				
The targeted population is present at my site				
Competitive studies at my site				
The number of available subjects to recruit within the time limits is confirmed (medical files, computerized listing)				
Subjects' availability outside my site (advertising)				
The evaluation of the subjects' participation agreement vs. the protocol requirements has been completed.				
Treatment or tests period acceptable				
Part 3 – Personnel Availability				
Investigator: available time to see and treat the patients.				
Investigator: available time to supervise his team				
Investigator: available time to generate, review and submit the study data.				
Investigator: available time to interact with the sponsor.				
Evaluation of the study required qualified personnel.				

Protocol Title:				Protocol Number:
Questions	**Yes**	**No**	**N/A**	**Commentaries**
Part 4 – Resources				
Evaluation of tasks delegations				
Evaluation of the available personnel vs. the study duration				
List of required technical and professional personnel				
Evaluation of the budget (team remuneration)				
Part 5 – Facilities and equipment				
Evaluation of the personnel working space				
Evaluation of the subjects' recruiting and follow-up space				
Evaluation of the space for (secure) storing of the subjects' study records				
Evaluation of the space for secure storing of the clinical study material				
Available material in line with the protocol requirements				
Available medical equipment in line with the protocol requirements				
Secure preserving space for the investigational product (pharmacy or other)				
Local laboratories compatibility				
Other services compatibility				
Written agreement confirmation with other site services				
Evaluation of the space for monitoring activities or others				
Part 6 – Others				

Standard Operating Procedures (SOP)
SOP-06
Study Feasibility Assessment



Fonds de la recherche en santé Québec

- **Objective**
  - Provide the research team with some tools with which to evaluate the feasibility of a clinical study

- **Clinical Study Feasibility Assessment**
  - Is the protocol scientifically, technically and ethically feasible ?
  - Do we have the population targeted by this protocol ?
  - Do we have the time ?

    The investigator/qualified investigator has sufficient time

The investigator/qualified investigator is ultimately responsible for the conduct of a clinical study

- **Clinical Study Feasibility Assessment**
  - *Are there sufficient resources within the research team ?*
  - *Do we have access to the necessary facilities and equipment or do we need specific equipment ?*

Questions ?

Title	**Conducting a Study in the Context of a Clinical Trial Application (CTA) in Canada**
Code	SOP-07
No. of Pages	9

History of Validated Versions

Date dd/mmm/yyyy	Version	Pages	Description of Change

History of SOP Implementation

Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy

Approval of Site SOP

	Signature	Date dd/mmm/yyyy

Table of contents

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 standard operating procedure 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. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP, ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

4.1 **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. [-5]

Two important points to remember:

4.1.1 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 participating subjects is ready to begin.

4.1.2 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 Ethics Committee should have been received before starting the recruitment of clinical trial participants.

4.2 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:

4.2.1 All Phase I to III studies on drug development;

4.2.2 Bioavailability comparison studies;

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

4.2.4 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 02.

4.2.5 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.

4.3 CTA Amendment

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.

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

4.3.2 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 participating subject or someone else, he may do so without waiting for Health Canada's review. However, he 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

4.3.3 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 subject;

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 subject;

IV. Protocol amendment affects the drug safety assessment;

V. Protocol amendment that extends the duration of the clinical trial;

VI. Amendments to information about drug chemistry and manufacturing affects the safety or quality of the drug.

4.4 Notification to Health Canada

For amendments to an already approved CTA and CTAM other than those described in 4.3, 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:

4.4.1 Changes to the protocol that do not compromise the safety of clinical trial participants and that are not viewed as amendments according to 4.3;

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

4.4.3 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.);

4.4.4 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 4.3.

4.5 Evaluation of a CTA Follow-up or Discontinuation

4.5.1 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.

4.5.2 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 participating subjects 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.

4.5.3 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.

4.5.4 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, see SOP 17.

4.5.5 Once a year 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.

4.6 Records Related to the CTA or CTAM

4.6.1 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.

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

4.6.3 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.

4.6.4 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.

4.6.5 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 Ethics Committee if any specific additional study related requirements exist (i.e. pediatric studies).

4.7 Research Ethics Board

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 Ethics Committee as described in Health Canada *Food and Drugs Act*.

4.7.1 The sponsor-investigator should submit to Health Canada the name of the REB who which 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.

4.7.2 The sponsor-investigator should keep in the files a statement issued and signed by the research Ethics Board which has approved the protocol and according to which he undertakes to fulfill his functions in compliance with *Good Clinical Practices*. The 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.

4.7.3 The sponsor-investigator should provide Health Canada with specifics regarding any refusal of a protocol or protocol amendment by an REB for any reasons whatsoever. (C.05.008 par. 1c [II])

4.7.4 It is strongly recommended that the notice of compliance from Health Canada to a CTA (no objection letter [NOL]) be submitted to the Ethics Committee.

The *Research Ethics Board Attestation Form* is to be provided to Health Canada only upon their request.

4.8 Qualified 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.

The *Qualified Investigator Undertaking* form is to be provided to Health Canada only upon their request.

To summarize, prior to each clinical study in Canada, the sponsor-investigator should complete:

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

4.8.2 The *Research Ethics Board Attestation* form. The 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.

4.8.3 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.

5. 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, General Considerations for Clinical Trials, ICH Topic **E8**, 1997.

Health Canada, Guidance for Industry, Clinical Safety Data Management Definitions and Standards for Expedited Reporting, ICH Topic E2A, 1995.

SOP-02 Organizing a Site for Clinical Research

SOP-17 Management of Adverse Events - Serious Adverse Events and Adverse Reactions – Serious Adverse Reactions

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

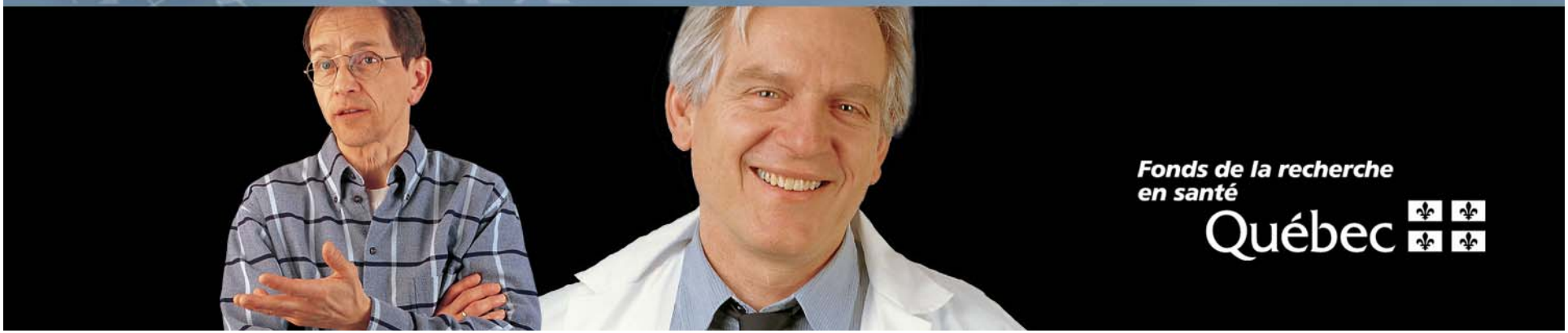
4. **Specific Responsibilities of the Institution**

5. **Procedures**

6. **References**

7. **Appendices**

Standard Operating Procedures (SOP)
SOP-07
Conducting a Study in the Context of a Clinical Trial Application (CTA) in Canada



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- **Objective**
  - 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.

- **Information**
  - Sponsors-investigators who want to conduct clinical drug trials in humans

- **Requirements**
  - Before initiating a clinical trial in Canada:
    - Fill a Clinical Trial Application (CTA)
  - CTA are required from sponsors-investigators for :
    - All Phase I to III studies on drug development
    - Bioavailability comparison studies
    - Clinical trials of marketed drugs whose use exceeds the parameters of the notice of compliance (NC) or the drug identification number (DIN)

- **CTA Amendment (CTAM)**
  - Amendments can be on the following modifications :
    - Drug manufacturing process modification
    - Approved protocol, altering the risk to the health of a subject
    - Selection criteria
    - Duration of the clinical trial
  - To modify a CTA under review, withdraw the active CTA and submit another one

- **Notification to Health Canada**
  - Amendments to an already approved CTA and CTAM
- **Evaluation of a CTA Follow-up or Discontinuation**
  - The sponsor-investigator should:
    - In the case of discontinuation, complete a notification

- **Records Related to the CTA or CTAM**
  - The sponsor-investigator should :
    - Keep complete and accurate record for a period of 25 years, available to Health Canada upon request

- **Research Ethics Board**
  - The proposed protocol and the Informed Consent Form should be reviewed and approved
  - The sponsor-investigator should :
    - Submit to Health Canada the name of the REB
    - Complete the section C of the Clinical Trial Site Information form

- **Qualified Investigators (only one qualified investigator per site)**
  - The Qualified Investigator Undertaking form is to be provided to Health Canada only upon their request
  - To summarize, prior to each clinical study in Canada, the sponsor-investigator should complete:
    - The Clinical Trial Site Information form
    - The Research Ethics Board Attestation form
    - The Qualified Investigator Undertaking form

Questions ?

Title	**Protocol and Protocol Amendment, Submission to Research Ethics Board**
Code	SOP-08
No. of Pages	15

History of Validated Versions

Date dd/mmm/yyyy	Version	Pages	Description of Change

History of SOP Implementation

Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy

Approval of Site SOP

	Signature	Date dd/mmm/yyyy

Table of contents

1. Policies

Within the framework of the principles inherent in Good Clinical Practice (GCP) of International Conference on Harmonisation (ICH), this standard operating procedure (SOP) describes the preparation, submission and approval of a clinical study protocol or protocol amendment. 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 subjects.

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/qualified investigator prepare and submit a clinical study protocol or a protocol amendment to the Ethics Committee.

3. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

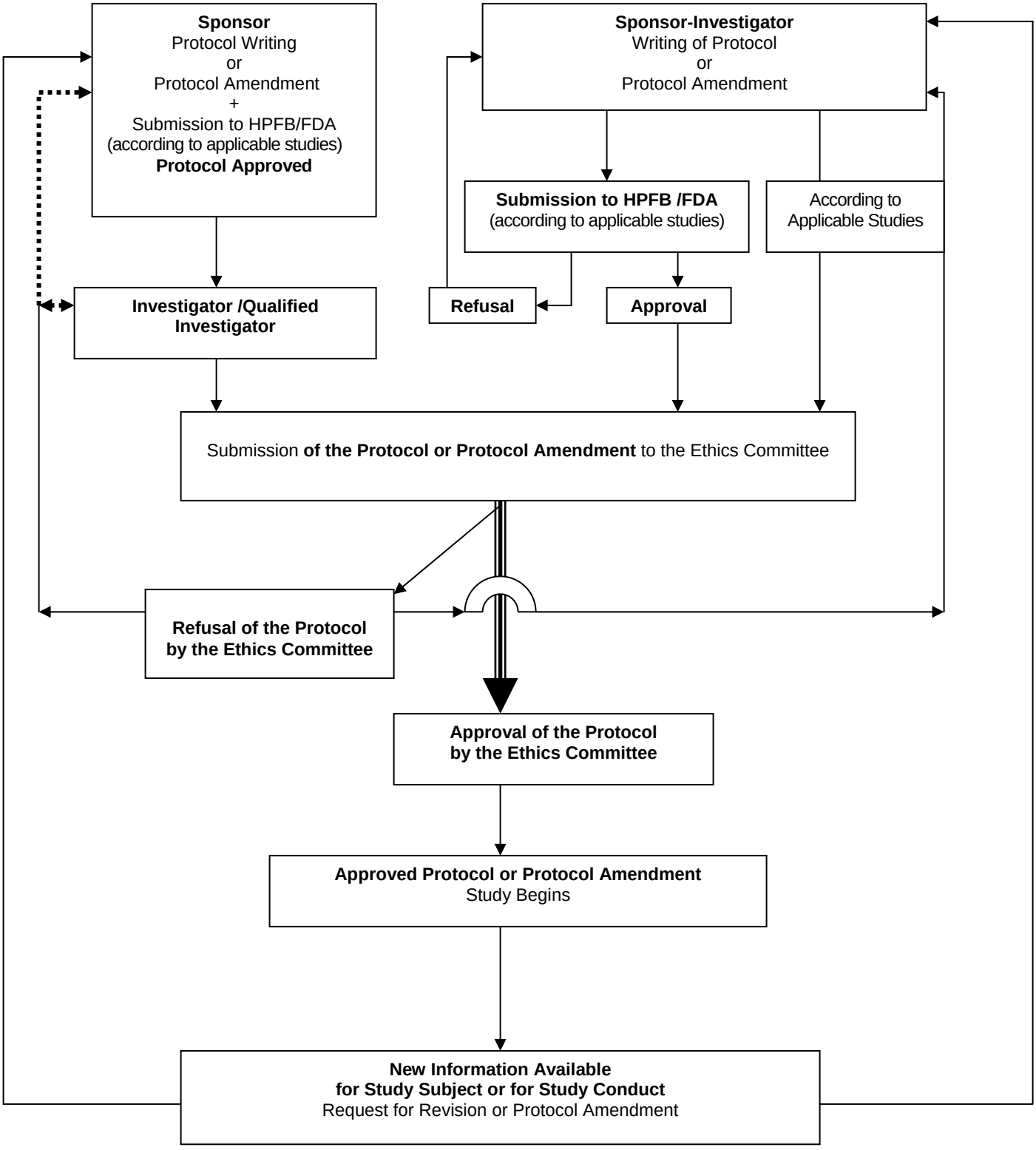
3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP, ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

Flow Chart



4.1 Submission of a Protocol by a Sponsor to an Investigator/Qualified Investigator

4.1.1 In preparing to submit the protocol to the Ethics Committee, the investigator/qualified investigator can use Appendix 2, *Reference for verification of protocol or protocol amendment* and Appendix 3, *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 this documentation be kept with the essential study documentation as described in SOP 02.

4.1.2 The investigator/qualified investigator is responsible for submitting the clinical study protocol or amendment to the Ethics Committee. This task may be delegated to another clinical study team member. It is recommended that this task delegation be documented as described in SOP 03.

4.1.3 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 Ethics Committee, SOP 09.

4.1.4 The investigator/qualified investigator is responsible for submitting to the sponsor, all modifications to the protocol required by the Ethics Committee.

4.2 Writing of a Protocol by a Sponsor-Investigator

4.2.1 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 03. To facilitate verification, Appendix 2, *Reference for verification of protocol or protocol amendment* and Appendix 3, *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 02.

4.2.2 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 03.

4.2.3 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 03.

4.2.4 The sponsor-investigator is responsible for the incorporation into the protocol, of all modifications or additions required by local or national regulatory authorities

4.2.5 The sponsor-investigator is responsible for submitting the clinical study protocol or protocol amendment to the Ethics Committee. This task may be delegated to another team member and should be documented as described in SOP 03

4.2.6 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 Ethics Committee, SOP 07.

4.2.7 The sponsor-investigator is responsible for the incorporation into the protocol or protocol modification all modifications or additions required by the Ethics Committee.

4.3 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

4.3.1 The date and version should be clearly indicated on each page of the protocol or protocol amendment as specified in Appendix 1, *Instructions Specific to the Site.*

4.3.2 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 as referred to in Appendix 1, *Instructions Specific to the Site.*

4.3.3 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 as described in Appendix 1, *Instructions Specific to the Site.*

4.4 Submission of a Study Protocol or Protocol Amendment

The sponsor or investigator/qualified investigator should submit the study protocol or protocol amendment to be used at the site to the Ethics Committee.

During the Study:

4.4.1 A protocol amendment dealing with a logistical or administrative change (i.e. change of phone number, auditor, etc.) should be submitted to the Ethics Committee for information. Approval of the Ethics Committee is not required to continue the study.

4.4.2 Comments (i.e. omissions or additions) from regulatory authorities or the Ethics Committee should be returned to the principal investigator/qualified investigator or by the author of the protocol or protocol amendment.

4.4.3 The investigator/qualified investigator may add a variation or modification to the protocol in order to eliminate any immediate danger to subjects participating in the clinical study without the Ethics Committee'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 Ethics Committee for review and approval;

II. To the sponsor for acceptance;

III. To regulatory authorities by the sponsor-investigator, if required. ICH 4.5.4

Safety of Subjects

4.4.4 Over the course of a clinical study, it is the responsibility of the sponsor-investigator or investigator/qualified investigator to decide, according to the information obtained and possibility of immediate danger to subjects, to stop subject recruitment until approval by the Ethics Committee and regulatory authorities, if required.

4.4.5 In case of termination or premature interruption of the clinical study by the sponsor or sponsor-investigator, the investigator/institution/qualified investigator is responsible for rapidly informing subjects participating in the study and ensuring that appropriate treatment and follow-up is provided to them, ICH 4.12. The investigator/institution/qualified investigator should notify the Ethics Committee 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 4.12.1.

4.5 Approval of a Study Protocol or Protocol Amendment

In the case of a sponsor-investigator

4.5.1 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/qualified investigator

4.5.2 For each clinical study, the protocol or protocol amendment should be submitted to the Ethics Committee. The Ethics Committee's requests should be sent by the investigator/qualified investigator to the sponsor or sponsor-investigator for corrections. The sponsor-investigator revises the protocol or protocol amendment according to the requirements of the Ethics Committee.

4.5.3 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 Ethics Committee by the investigator/qualified investigator.

4.5.4 The sponsor-investigator or investigator/qualified investigator should keep the original version of the protocol as well as any protocol amendments as described in Appendix 1, *Instructions Specific to the Site.* It is suggested that the sponsor-investigator keep and archive every draft of the protocol.

4.5.5 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 02.

5. 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.

Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, June 2003.

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 Organizing a Site for Clinical Research

SOP-03 Research Team: Role Definitions, Responsibilities and Task Delegation

SOP-07 Conducting a Study in the Context of a Clinical Trial Application (CTA) in Canada

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

4. **Specific Responsibilities of the Institution**

5. **Procedures**

6. **References**

7. **Appendices**

APPENDIX 2 PROTOCOL OR PROTOCOL AMENDMENT AUDIT

# Protocol or Investigational Product:	
# Protocol Version:	Version Date:
# Amendment Version:	Version Date:

Audit Date:	Quality Auditor: (name in block letters)	Quality Auditor: (signature)

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

No	1.0 General Information	Yes	N/A	* Note
1.1	Protocol title, protocol identifying number and, if applicable, date and number of all protocol modifications (amendments) should also be indicated. ** Add development phase			
1.2	Name and address of Sponsor/Sponsor-investigator and Monitor (if other than Sponsor/Sponsor-investigator, ex.: CRO)			
1.3	Name and title of person authorized to sign the protocol and protocol modifications (amendments) in the name of the Sponsor/Sponsor-investigator			
1.4	Name, title, address and phone number of Sponsor/Sponsor-investigator's medical expert for the clinical study			
1.5	Name and title of Investigator/qualified Investigator responsible for conducting the clinical study			
1.6	Name, title, address and phone number (s) of the qualified physician who will be responsible for all study related medical decisions			
1.7	Name, address and phone number of clinical study site			
1.8	Name (s) and address (es) of clinical laboratory (ies) and other technical department (s) or institution (s) involved in the clinical study			
1.9	**** Table of contents** Make sure that all protocol or modification pages are numbered and that each section information is properly indicated in the table of contents			
1.10	**** 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			

No	2.0 Basic Information	Yes	N/A	* Note
2.1	Name and description of investigational products			
2.2	Summary of non clinical studies conclusions likely to be significant on a clinical plan and study related clinical studies			
2.3	Summary of known and potential risks and benefits if any for human subjects			
2.4	Description and explanation of administration route, posology, dosage regimen and treatment period			

** Added items not included in ICH

***Note (See end of document)**

Protocol Number	Version Date	Amendment Number	Amendment Version Date

No	2.0 Basic Information (cont'd)	Yes	N/A	* Note
2.5	Statement to the effect that the study will be conducted in compliance with protocol, GCP and applicable regulatory requirements			
2.6	Description of target population			
2.7	Documentation and data references related to study and used as study general information			

No	3.0 Study Objectives and Purpose	Yes	N/A	* Note
3.1	Detailed description of primary and secondary objectives along with the study purpose			

No	4.0 Study Design	Yes	N/A	* Note
4.1	Precise statement of main and secondary results, if any, to assess in the course of the study			
4.2	Description of study type to conduct (i.e. double-blind, controlled versus placebo, parallel design, etc.) and a schematic diagram, procedure and study stages diagram			
4.3	Description of measures taken to reduce or avoid bias including: a) Randomization b) Blind test			
4.4	Description of treatment, posology and investigational product dosage regimen			
4.5	Description of dosage form, investigational product packaging and labelling			
4.6	Expected duration of subject participation and description of stages and duration of all study periods, especially the follow-up, if any			
4.7	Description of "stopping rules" or "proceeding criteria" regarding the subjects partial or total participation to the study			
4.8	Description of investigational product accountability procedures including placebos and comparators, if any			
4.9	List of codes used for treatment randomization and code key retention			
4.10	Description of code brreaking procedures and name of person responsible			
4.11	All data identification to log directly in the CRF (data not recorded on hard or electronic copy) and regarded as basic data			

No	5.0 Selection and Withdrawal of Subjects	Yes	N/A	* Note
5.1	Subjects inclusion criteria			
5.2	Subjects exclusion criteria			
5.3	Subjects withdrawal criteria (terminating investigational product treatment/study treatment) and withdrawal procedure specifications			
5.4	When and how to withdraw subjects or cancel investigational product treatment			

***Note (See end of document)**

Protocol Number	Version Date	Amendment Number	Amendment Version Date

No	5.0 Subject Selection and Removal (cont'd)	Yes	N/A	* Note
5.5	Type and timing of data to collect for withdrawn subjects			
5.6	Way of replacing subjects, if required			
5.7	Follow-up on subjects no longer treated with the investigational product or subjects withdrawn from the study			

No	6.0 Treatment of subjects	Yes	N/A	* Note
6.1	Description of treatment to be administered			
6.2	Name (s) of all products			
6.3	Dosage (s) of all products			
6.4	Dosing schedule (s)			
6.5	Administration route/mode (s)			
6.6	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			
6.7	Authorized and non authorized medication/treatments before or during the study			
6.8	Monitoring procedures regarding the study compliance			

No	7.0 Efficacy Assessment	Yes	N/A	* Note
7.1	Description of efficacy parameters			
7.2	Procedures and timing to assess, record and analyze efficacy parameters			

No	8.0 Safety Assessment	Yes	N/A	* Note
8.1	Description of safety parameters			
8.2	Procedures and timing to assess, record and analyze safety parameters			
8.3	Procedures to obtain reports of and record and signal adverse events and intercurrent illnesses			
8.4	Type and duration of follow-up of subjects after adverse events			

***Note (See end of document)**

Protocol Number	Version Date	Amendment Number	Amendment Version Date

No	9.0 Statistics	Yes	N/A	* Note
9.1	Description of statistical methods to be used including any planned periodical analysis (ses) schedule			
9.2	Anticipated number of subjects for multicentre studies, the anticipated number of subjects for each site should be indicated			
9.3	Reasons for choice of sample size including comments (or calculations) of the study power and clinical justification			
9.4	Significance level to be used			
9.5	Study termination criteria			
9.6	Procedures for accounting missing, unused or erroneous data			
9.7	Procedures for reporting any deviation (s) from the original statistical plan should be described and justified in the protocol or final report (if applicable)			
9.8	Selection of subjects to include in analysis (every randomized subject, subject having received one dose, all eligible and assessable subjects, etc.)			

No	10.0 Direct Access to Source Data/Documents	Yes	N/A	* Note
10.1	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.			

No	11.0 Quality Control and Quality Assurance	Yes	N/A	* Note
11.1	Details of monitoring, verifications and regulatory inspections			

No	12.0 Ethics	Yes	N/A	* Note
12.1	Description of study related ethical and legal considerations			

No	13.0 Data Processing and Record Keeping (Retention Period)	Yes	N/A	* Note
13.1	For study protocol, modifications, documentation and archiving procedures			

No	14.0 Financing and Insurance	Yes	N/A	* Note
14.1	The financing and insurance may be included if not addressed or specified in a separate document			

Note (See end of document)

*

Protocol Number	Version Date	Amendment Number	Amendment Version Date

No	15.0 Publication Policy	Yes	N/A	* Note
15.1	Describe the study protocol and report publication policy if not included in a separate document			
15.2	References: text consistency versus references and references versus text			

No	16.0 Signature	Yes	N/A	* Note
16.1	Appendices: check text consistency versus appendices and appendices versus text			
16.2	The complete protocol or protocol modification audit includes proof of reading and compliance to governing regulation and *good clinical practices.* Protocol and protocol modification should include some space dedicated to the proof of reading by the investigator (signature and date)			

No	17.0 Other (Detail please)	Yes	N/A	* Note
17.1	* Optional: required procedures presentation for each visit in a tabular format. Suggested by most auditors/inspectors			

***Note (See end of document)**

No	* Notes or comments

APPENDIX 3 PROTOCOL OR PROTOCOL AMENDMENT AUDIT CONFIRMATION

Name of Study, Project or Drug Number	
Protocol Version Number:	**Version Date:** dd/mmm/yyyy

DATE OF THIS AUDIT: _____
dd/ mmm / yyyy

REVIEWED BY:

_____ _____ _____
Name in block letters **Signature** **Title**

Appendix 2 – 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

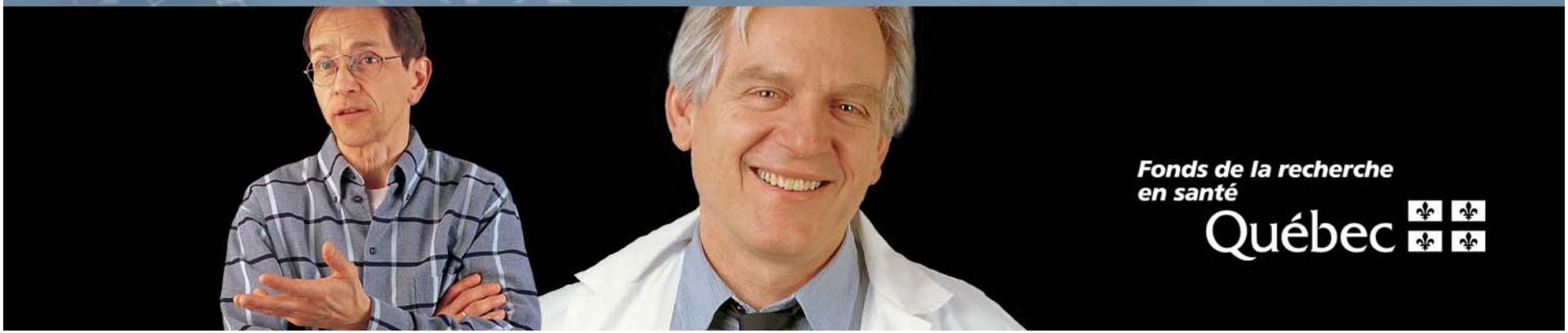
Protocol or Protocol Amendment to Submit

Protocol Version Date dd/mmm/yyyy	Signature of the Investigator/Qualified Investigator or His Delegate

Approved Protocol Versions

Date dd/mmm/yyyy	Version	No of Pages	Signature of Investigator/Qualified Investigator or His Delegate

Standard Operating Procedures (SOP)
SOP-08
Protocol and Protocol Amendment, Submission to Research Ethics Board



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- **Objectives**
  - Ensure that all clinical study protocols or amendments implemented within the institution are in compliance with ICH Good Clinical Practice and any applicable regulations .
  - Ensure that all institutional personnel working in clinical research comply with the protocol or protocol amendment .
  - Help the sponsor-investigator or investigator/qualified investigator prepare and submit a clinical study protocol or a protocol amendment to the Ethics Committee.

- **Submission of a Protocol by a Sponsor to an Investigator / Qualified Investigator**
  - The investigator/qualified investigator should :
    - Submit the protocol or amendment to the Ethics Committee
    - Submit to the sponsor all modifications to the protocol required by the Ethics Committee

- **Writing of a Protocol by a Sponsor-Investigator**
  - Responsible for writing/reviewing the clinical study protocol or amendment.
- **Writing of a Protocol by a Sponsor-Investigator**
  - Responsible for the incorporation into the protocol of all modifications or additions required by the local or national authorities

- **Preparation and Revision of a Protocol or Protocol Amendment**

- **Submission of a Study Protocol or Protocol Amendment**

  - Safety of subjects
    - It is the responsibility of the sponsor-investigator or investigator/qualified investigator to decide to stop recruitment according to possibility of immediate danger to subjects

  - In case of termination or premature interruption, the investigator/qualified investigator should:
    - Inform rapidly subjects participating and ensure that appropriate treatment and follow-up is provided to them

Questions ?

Title	Consent Process and Subject Informed Consent Form
Code	SOP-09
No. of Pages	16

History of Validated Versions

Date dd/mmm/yyyy	Version	Pages	Description of change

History of SOP Implementation

Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy

Approval of Site SOP

	Signature	Date dd/mmm/yyyy

Table of Contents

1. Policies

Within the framework of the principles inherent in International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), this standard operating procedure (SOP) defines the content of the subject 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.[1]

This SOP addresses all institutional personnel working in clinical research and should be observed by all those involved in clinical studies with human subjects.

[1] The principles established in the present document may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects. Refer to the ICH Guideline for Good Clinical Practice.

2. Objectives

One of the objectives of this standard operating procedure 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 subjects.

3. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

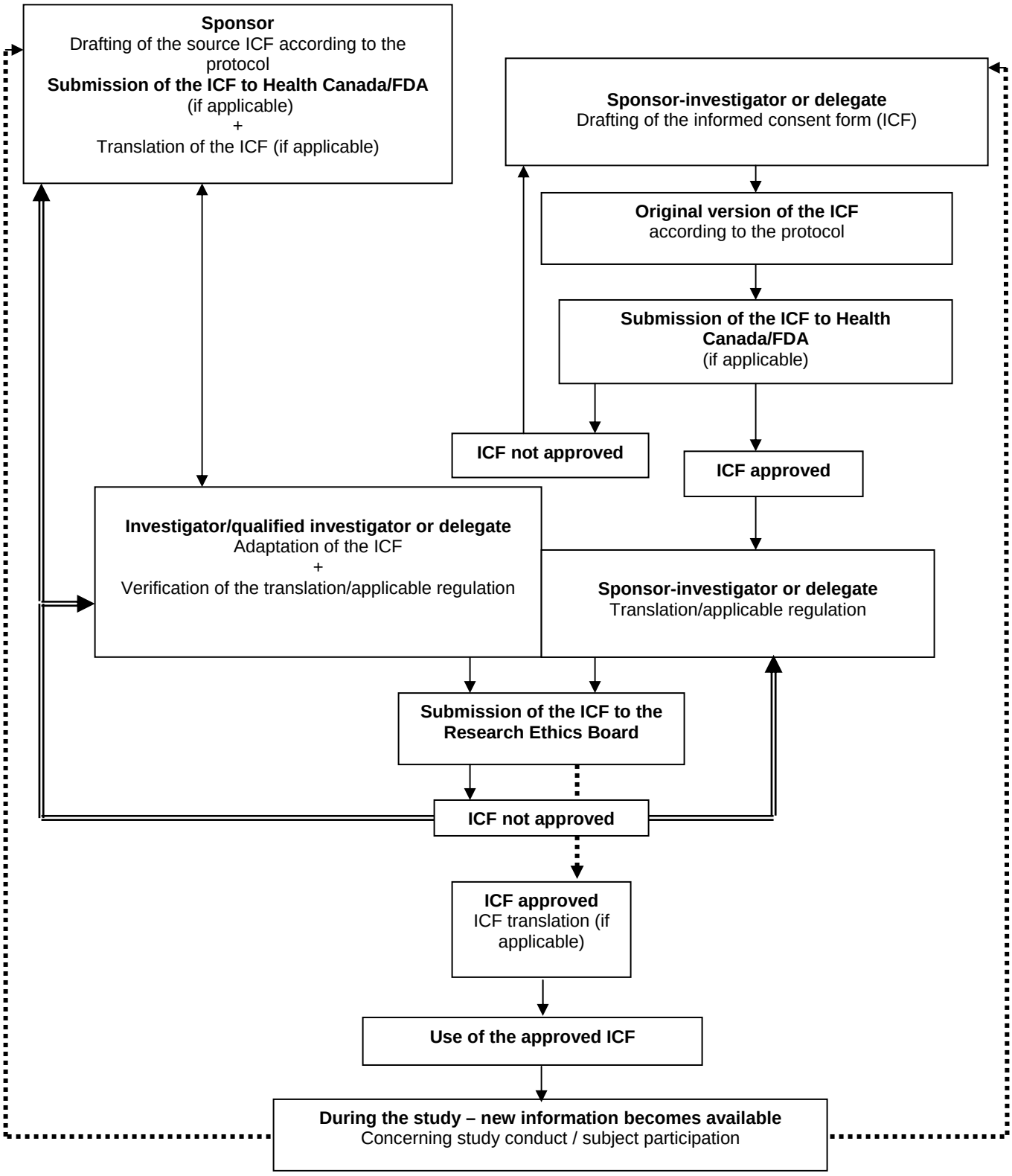
3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP, ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

Flow Chart



4.1 ICF submitted by a sponsor to the investigator/qualified investigator

The investigator/qualified investigator or his delegate is responsible for:

4.1.1 verifying the content of the ICF as outlined in GCP, section 4.8 of ICH. In order to conduct this verification, Appendix 2, *ICF Verification List* and Appendix 3, *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 02;

4.1.2 if applicable, checking and adapting the content to languages used at the site ;

4.1.3 advising the sponsor of any changes to the ICF before submission to the Research Ethics Board (REB);

4.1.4 submission of the ICF to the REB. This task may be delegated to another member of the clinical research team;

4.1.5 all revisions or additions to the ICF required by the REB;

4.1.6 sending the version of the ICF approved by the REB to the sponsor.

4.2 ICF prepared by the sponsor-investigator or his delegate

The sponsor/sponsor-investigator is responsible for:

4.2.1 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 as referenced in SOP 03. This form is to be kept with the other essential study documentation.

4.2.2 checking that the contents of the ICF are in agreement with the protocol and GCP.section– 4.8 of the ICH Guideline for GCP. This ICF verification should be documented as described in Appendix 1, *Instructions Specific to the Site*. In order to conduct this check, Appendix 2, *ICF Verification List*, and Appendix 3, *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 02;

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

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

4.2.5 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 03. This form is to be kept with the essential study documentation.

4.2.6 incorporation of any changes or additions to the ICF as required by local or national authorities, when applicable.

4.2.7 submission of the initial ICF to the REB, as well as any amendments to versions previously approved by the REB. 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 03. This form is to be kept with the essential study documentation.

4.2.8 incorporation of any changes or additions to the ICF as required by the REB.

4.3 Content and preparation of the ICF

4.3.1 The ICF describes all elements of the study protocol as described in SOP 08.

4.3.2 If by participating in a clinical study a subject is at risk, a copy of a summary of the research and the ICF will be included with the subject's medical record. The subject should have agreed to this procedure, as stated in the FRSQ, par. 2.26. When applicable, this element should be added to the ICF.

4.3.3 The language used in the ICF should not be technical and should be easily understood by the subject. The form cannot include explicit or implicit terms that could lead the subject or the subject'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.

4.3.4 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/qualified investigator prior to submission to the REB.

4.3.5 Each version of the ICF should be clearly identified with the number and date of the version on each page as specified in Appendix 1, *Instructions Specific to the Site*.

4.3.6 Identification of the ICF, i.e., the footer, should be coherent and appear uniformly throughout the entire document. The footer should also include a section for consent as described in Appendix 1, *Instructions Specific to the Site*.

4.4 Revision of the ICF

4.4.1 If changes to the protocol or new information (i.e. serious adverse event), are liable to influence the subject's decision to continue in the study, the sponsor-investigator or his delegate, the investigator/qualified investigator or his delegate, should make sure that the ICF contains this new information and that this information is submitted to the REB. All validated versions of the ICF used during the study should be kept with the essential study documents, as described in SOP 02.

4.4.2 Comments (i.e., omissions or additions) made by the regulatory authorities or by the REB, 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/qualified investigator should revise, authorize and submit to the REB, the ICF that will be used on site.

4.5 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 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 group approved and monitored by an 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 give 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 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.

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 subject 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 subjects, is read and explained to the subject or the subject's legal representative, and after the subject or the subject's legal representative has orally consented to the subject'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 subject or the subject's legal representative, and that informed consent was freely given by the subject or the subject's legal representative, part 3, B, 11.3.4, BPC art 4.8.9 .

Tri-Council Policy Statement, Research Ethics with respect to Human Subjects,:

The requirement for free and informed consent should not disqualify research subjects 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 REB, 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 subject, 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 subject.
- The intermediary has assisted the research subject in the discussion of the research study.
- The research subject 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.

4.5.1 The ICF should provide the subject 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 subject or the subject's legal representative, ICH 4.8.7.

4.5.2 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 provided-to the subject should be explained to the subject, ICH 4.8.10.

4.5.3 Only the version of the ICF that has been approved by the REB should be used for the subject for the duration of the study.

4.5.4 Prior to the subject'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 subject or the subject's legal representative, and by the person who conducted the informed consent discussion, as described in Appendix 1, *Instructions Specific to the Site*, ICH 4.8.8.

4.5.5 The original ICF, signed and dated by the subject and the designated signatories, should be kept with the essential study documents, as described in Appendix I, *Site Specific Instructions*.

4.5.6 Neither the investigator/qualified investigator nor the study staff should coerce or unduly influence a subject to participate or to continue to participate in a study, ICH 4.8.3.

4.5.7 If new information becomes available during the clinical study that may be relevant to the subject'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 REB, should be read, understood, signed and personally dated by all subjects who remain active in the study, as well as by all new subjects or their legal representatives. This new version should be signed by the person who conducted the discussion, as described in Appendix 1, *Instructions Specific to the Site*.

4.5.8 The investigator/qualified investigator or his delegate should inform the subject or, if the subject is unable to provide informed consent, the subject's legal representative, of all pertinent aspects of the study including the written information given approval by the REB, ICH 4.8.5.

4.5.9 If the subject or the subject's 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 subject or to the subject's legal representative, and after the subject or the subject's legal representative has orally consented to the subject's participation 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 subject or the subject's legal representative, and that the informed consent was freely given by the subject or by the subject's legal representative, ICH 4.8.9.

4.5.10 Prior to participating in the study, the subject or the subject's legal representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subject. During the subject's participation in the study, the subject or the subject'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 subjects, ICH 4.8.11.

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

4.5.11 In a clinical study (therapeutic or non-therapeutic) that includes subjects who can only be enrolled in the study with the consent of the subject's legal representative (subjects who are unfit or vulnerable), the subject should be informed of the study to the extent that it is compatible with the subject's understanding and, if capable, the subject 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.

4.5.12 Except as described in 4.5.13, a non-therapeutic study (i.e., a study in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects

who personally give their consent and who sign and date the informed consent form, ICH 4.8.13.

4.5.13 Non-therapeutic studies may be conducted in subjects 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 in subjects who can give informed consent personally.

II. The foreseeable risks to the subjects are low.

III. The negative impact on the subject's well-being is minimized and low.

IV. The study is not prohibited by law.

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

Such studies, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these studies should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed, ICH 4.8.14.

4.5.14 In the case of pediatric clinical studies (subjects under the age of 18), the investigator/qualified investigator should obtain the consent of the parents or legal representative as described in Appendix 1, *Instructions Specific to the Site*, and, if possible, the assent of the child according to local regulations.

5. 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.

Quebec, Civil Code of Quebec, 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.

Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, June 2003.

SOP-02 Organizing a Site for Clinical Research

SOP-03 Research team: Role Definitions, Responsibilities and Task Delegation

SOP-08 Protocol and Protocol Amendment, Submission to the Research Ethics Board (REB)

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. Filing System

2. Location of Filing System

3. Annual Approval or Revision

4. Specific Responsibilities of the Institution

5. Procedures

5. References

6. Appendices

APPENDIX 2 ICF VERIFICATION LIST

# Study, project or research product	Number of verified version	Date of verified version

1. Information concerning the informed consent procedure

No	Verified Items	Yes	No	Comments
1.1	Form confirming that the subject freely gave his consent.			
1.2	Form confirming that the subject had ample time and opportunity to find out about the details of the study.			
1.3	Form confirming that the subject will have ample time and opportunity to decide whether or not to participate			
1.4	Form confirming that the subject's participation is entirely voluntary.			
1.5	Form confirming that the subject's refusal to participate will not result in any penalty or loss of benefits.			
1.6	Form confirming that the subject has the right to withdraw at any time without prejudice of suffering any consequences.			
1.7	Form describing the foreseeable circumstances or reasons for terminating the subject's participation in the study.			
1.8	Form confirming that the subject will receive a written explanation and the signed and dated consent form for future reference.			

2. Study information

No	Verified Items	Yes	No	Comments
2.1	Explanation that the study involves research.			
2.2	Purpose of the study.			
2.3	Experimental vs. standard treatments (medications or devices).			
2.4	The study procedures description including all invasive procedures.			
2.5	Description of the study's experimental aspects.			

No	Verified Items	Yes	No	*NA	Comments
2.6	Description of the comparative study treatment (active treatment vs. placebo-controlled).				
2.7	Explanation on randomization procedure and the probability for assignment to different treatment.				

*** Not applicable**

# Study, project or research product	Number of verified version	Date of verified version

No	Verified Items	Yes	No	Comments
2.8	The expected duration of the subject's participation in the study.			
2.9	Description of consequences of the decision by the subject to withdraw from the study and the methods to end the subject's participation.			
2.10	The approximate number of subjects participating in the study, for the duration of the study as well as for the site.			
2.11	Description of the subject's responsibilities .			
2.12	It is suggested to specify the approximate duration of each visit. * See Appendix 1, *Instructions Specific to the Site*.			

3. Information concerning foreseeable risks and benefits

No	Verified Items	Yes	No	Comments
3.1	The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to the embryo, the fetus or the nursing infant.			
3.2	Form confirming that procedure or treatment may involve potential risks to the subject or, when applicable, to the unborn child.			
3.3	Description of the anticipated benefits; if no benefits are forthcoming, the subject should be informed.			
3.4	Description of the alternative treatment that may be available to the subject and their potential risks and benefits.			
3.5	Form confirming that subject or the subject's legal representative will be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to participate in the study.			
3.6	Explanation on the compensation or treatment that is available to the subject in the event of study-related loss or injury.			
3.7	Explanation on the availability of alternative treatment in the event of study-related loss or injury, and if applicable, what is the course of treatment and when other information will become available.			
3.8	The anticipated costs, if any, to the subject.			
3.9	Description of the anticipated proportional payment, in this occurrence, made to the subject for participating in the study.			

# Study, project or research product	Number of verified version	Date of verified version

4. Confidential data and new information

No	Verified Items	Yes	No	Comments
4.1	Form confirming that records identifying the subject 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 subject's identity will remain confidential.			
4.2	Explanation on the representatives of the sponsor/sponsor-investigator, the REB and the regulatory authorities will be granted access to the subject's medical records for verification of the clinical procedures or clinical data, without violating the confidentiality of the subject, and that by signing the informed consent form, the subject or the subject's legal representative is authorizing access.			
4.3	Form confirming that if the subject or the subject's legal representative has consented, the subject's personal physician will be kept informed of the subject's condition during the study.			
4.4	The name, address and telephone number of the person to contact for further information or in the case of a study-related injury.			

No	Verified Items	Yes	No	*NA	Comments
4.5	Identifying the study sponsor.				
4.6	Purpose of the clinical study.				
4.7	Description of the categories of individuals or research organizations under contract or regulatory authorities to whom will be granted access to study-related records.				
4.8	Explanation on other individuals have access to personal records, appropriate measures will be taken to protect the confidentiality of said data.				
4.9	Explanation on confidentiality requirements concerning the personnel directly or indirectly involved in data management permitting the identification of the subject.				

*** Not applicable**

# Study, project or research product	Number of verified version	Date of verified version

No	Verified Items	Yes	No	*NA	Comments
4.10	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.), A 19 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.				

*** Not applicable**

5. Formal Aspects

No	Verified Items	Yes	No	Comments
5.1	Identification of the subject: i.e., the subject's complete name and initials * see Appendix 1.			
5.2	A space for signatures of the subject or the subject'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.			
5.3	Site identification according to Appendix 1.			

6. Vulnerable Subjects

No	Verified Items	Yes	No	*NA	Comments
6.1	Confirm that when minors (<18 years of age) are involved in a study, that their parents' consent is required.				
6.2	Confirm that when minors are involved in a study, that the ICF is written in terms understood by the subject. A space should be set aside for the subject's signature.				

*** Not applicable**

7. Miscellaneous – to be added if applicable

No	Verified Items	Yes	No	Comments
7.1	The language used in this consent form should be non-technical and easily understood by the subject.			
7.2	Ensure that the ICF provided to the subject or to the subject's legal representative contains the information that the ICF was approved by the REB.			
7.3	The ICF should contain the names and addresses of the people to contact for information concerning the subject's participation in the study (ombudsman, subject's representative).			

APPENDIX 3 CONFIRMATION OF THE ICF VERIFICATION LIST

STUDY NAME, PROJECT OR NUMBER OF THE DRUG:	
ICF VERSION:	DATE OF THE VERSION: dd/mmm/yyyy
AUTHOR OF THE ICF:	

DATE OF THIS REVISION: _____
dd / mmm / yyyy

REVIEWED BY:

_____ _____ _____

Name in block letters **Signature** **Title**

Appendix 2 –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**

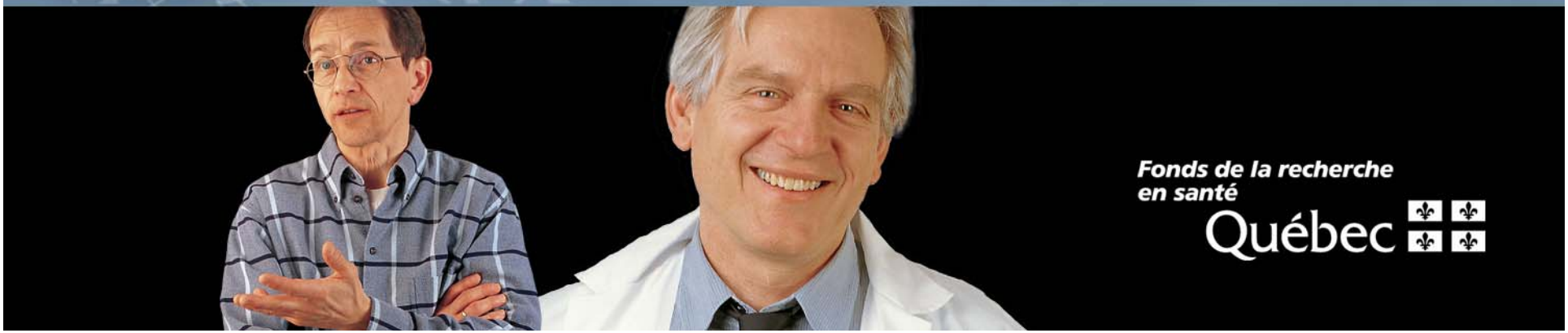
ICF for submission

Date of the ICF version dd/mmm/yyyy	Version	Signature of the investigator/qualified investigator or his delegate

ICF approved versions

Date dd/mmm/yyy	Version	Pages	Signature of the investigator/qualified investigator or his delegate

Standard Operating Procedures (SOP)
SOP-09
Consent Process and Subject Informed Consent Form



Fonds de la recherche en santé Québec

- **Objectives**
  - 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.
  - Ensure that the consent process used in the institution, follows applicable ethical standards in order to ensure the safety and protection of study subjects.

- **ICF submitted by a sponsor to the investigator/qualified investigator**

  – The investigator/qualified investigator or his delegate is responsible for :
    - Verifying the content of the ICF
    - Checking and adapting the content in both languages
    - Advising the sponsor of any changes to the ICF before submission to the REB
    - Submission of the ICF to the REB
    - All addition or revision required by the REB
    - Sending the version of the ICF approved to the sponsor

- **ICF prepares by the sponsor-investigator or his delegate**

  - The sponsor/sponsor-investigator is responsible for :
    - Drafting the initial version of the ICF
    - Checking the content of the ICF
    - Translation of the ICF
    - Revision of the ICF
    - Submission of the ICF to the REB as well as any amendments

- **Content and preparation of the ICF**
  - The ICF should describe all elements of the study protocol
  - The ICF should be included in the medical record if by participating in a clinical study, a subject is at risk; the subject should have agreed to this procedure
  - The language used in the ICF should not be technical and should be easily understood by the subject
  - Translation of the ICH should be validated

- **Revision of the ICF**
  - Keep all validated version of the ICF

- **The consent process**
  - Quebec Civil Code, L.Q., 1991, C. 64
  - FRSQ, Guide d'éthique de la recherche et d'intégrité scientifique, Standards en éthique de la recherche et en intégrité scientifique
  - Tri-Council Policy Statement, Research Ethics with respect to Human Subjects

Questions ?

Title	Rights and Protection of Study Subjects
Code	SOP-10
No of Pages	9

History of Validated Versions

Date dd/mmm/yyyy	Version	Pages	Description of change

History of SOP Implementation

Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy

Approval of Site SOP

	Signature	Date dd/mmm/yyyy

Table of contents

1. Policies

Within the framework of the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonisation (ICH), in compliance with the Tricouncil 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 Quebec 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 subjects 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 subjects.

2. Objective

The objective of this operating procedure is to describe the process which ensures the rights protection and well being of subjects participating in a clinical study.

3. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP, ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

4.1 **Generalities**

The rights, safety and well-being of the study subjects 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, subjects should always be the responsibility qualified physician, ICH 2.7.

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

<u>The Institution:</u>

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, **a. 59.1**. c. 78, a. 1;

Responsibility for respect for the rules of protection for human subjects, 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 complementarity

between both hospital and research files rests with the person with the highest authority within the public body.

The Ethics Committee:

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

Sponsor-Investigator and/or Investigator/Qualified Investigator:

The sponsor-investigator and procedures should address the costs of treatment of study subjects 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 the research activities of the sponsor-investigator or investigator-qualified being conducted on its premises. Each clinical study is subject to mandatory declaration and should be approved and followed by the Ethics Committee;

4.2 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:

4.2.1 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;

4.2.2 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:

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

4.2.4 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;

4.2.5 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

4.2.6 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:

4.2.7 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:

4.2.8 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 an Ethics Committee, for the period determined, where that is the case, by the Ethics Committee, **a. 19.1**.1999, c. 45, a.2.

4.2.9 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.

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.

4.3 Protection of Information and Respect for Subjects' Rights

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

4.3.1 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.

4.3.2 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.

4.3.3 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:

4.3.4 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;

4.3.5 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;

4.3.6 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;

4.3.7 Full age or the age of majority is 18 years, A. 153;

4.3.8 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;

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 an 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 mandatary, 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 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.

4.3.9 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.

4.4 Protection of Subjects

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

Indemnification to subjects:

4.4.1 It is in compliance with the law and ethics that the study subject is compensated for his participation in an experiment, however the indemnification to be legally valid should be limited to the losses and constraints sustained, Civil Code of Québec, 1991, C. 64, A. 25; What is written under the a. 25 indent 2 is : 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.

4.4.2 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 kand 3.1.8;

4.4.3 Each research team member is held to professional confidentiality. Each human subject has the right to professional confidentiality, should he be under age or of legal age, translated from FRSQ, Part 2, Section 14.

5. 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.

Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, June 2003.

Quebec, Civil Code of Quebec, 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-09 Consent Process and Subject Informed Consent Form

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

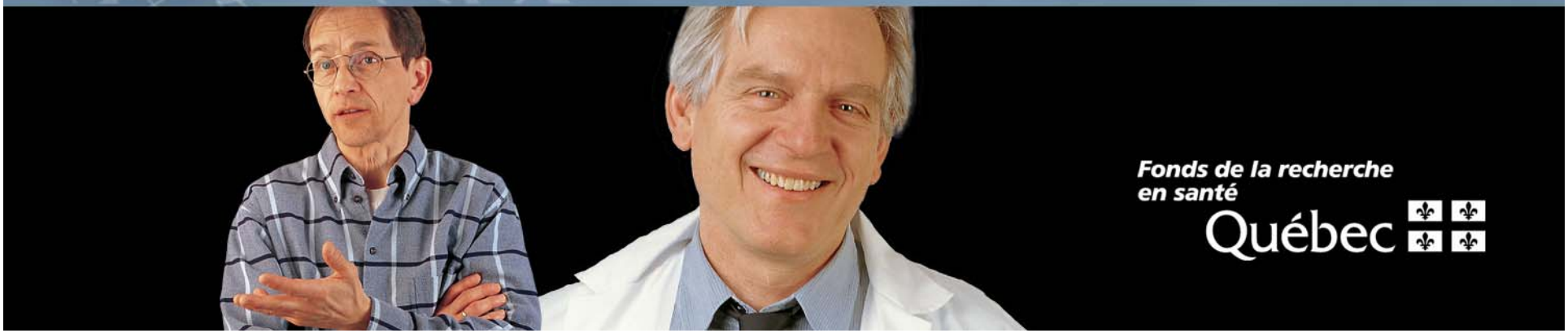
4. **Specific Responsibilities of the Institution**

5. **Procedures**

5. **References**

6. **Appendices**

Standard Operating Procedures (SOP)
SOP-10
Rights and Protection of Study Subjects



Fonds de la recherche en santé Québec

- **Objective**
  - Describe the process which ensures the rights protection and well being of subjects participating in a clinical study.

- **Generalities**
  - The Institution
  - The Ethics Committee
  - The Sponsor-Investigator and/or Investigator/qualified Investigator

- **Access to Documents**
  - Act Respecting Access to Documents Held by public Bodies and the Protection of Personal Information, 1982, c. 30
  - Act Respecting Health Services and Social Services, R.S.Q., Chapter S-42, section I, title II, chapter II, 1991

- **Protection of Information and Respect for Subjects' Rights**
  - Act Respecting Access to Documents Held by Public Bodies and the Protection of Personal Information, 1982, c. 30
  - Civil Code of Quebec, 1991, c. 64

- **Protection of Subjects**
  - The protection of human subjects ensures study participants the same rights as users benefiting from health care and social services
  - The compensation payment should be:
    - In compliance with the law and ethics
    - Absent of unjust allowance
    - Based on pro rata participation

Questions ?

Title	Conflict of Interest
Code	SOP-11
No of Pages	7

History of Validated Versions

Date dd/mm/yyyy	Version	Pages	Description of change

History of SOP Implementation

Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy

Approval of Site SOP

	Signature	Date dd/mm/yyyy

Table of Contents

1. Policies

Within the framework of principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonisation (ICH), in respect of the Tri-Council Policy Statement (TCPS): Ethical Conduct for Research Involving Humans and following the Guide d'éthique de la recherche et d'intégrité scientifique du 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 subjects.

2. Objective

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

Conflicts of interest can affect various parties in a clinical study. The sponsor-investigator, investigator/ qualified Investigator, ethics committee, institution and even a subject participating in the clinical study 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. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP, ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

4.1 **Generalities**

Investigators hold trust relationships with research subjects, 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.

Investigators and members of Research Ethics Boards (REB) shall disclose actual, perceived or potential conflicts of interest to the REB. REBs should develop mechanisms to address and resolve conflicts of interest, TCPS, article 4.1.

Procedures for declaration of conflicts of interest within the institution will be described in appendix 4, *Instructions Specific to the Site*, if this is the case.

4.2 **Investigator/ Qualified Investigator**

4.2.1 During the evaluation of a protocol by the Ethics Committee, the investigator may provide information on any aspect of a study, but should not participate in the

deliberations of the Ethics Committee or in the vote/opinion of the IRB/IEC, ICH 3.2.5.

4.2.2 The financial aspects of the clinical study should be documented in a written agreement between the sponsor-investigator and investigator/qualified Investigator and the institution, ICH 5.9.

4.2.3 The investigator/qualified 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 Ethics Committee, adapted form TCPS, article 4.1 A.

4.2.4 The investigator/qualified Investigator should disclose to subjects participating in a clinical study 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 patient, it is recommended that they be documented in the subject's source document.

4.2.5 An investigator/qualified Investigator should inform the Ethics Committee of any bonus, for example, fees or any other benefit agreed to in return for recruiting research subjects, translated and adapted from FRSQ, Part 2 section 12. No bonus or fee can be offered to members of a research team for recruiting subjects, translated and adapted from FRSQ, Part 2, section 11.

4.2.6 The investigator/qualified Investigator always remain responsible for the actions of team members who act in his name.

4.2.7 When the participation of an investigator/qualified 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/qualified 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.

4.3 Members of Research Ethics Boards

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

4.3.2 The REB should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the study subjects. The remuneration should be established on a pro rata basis and should not be paid only in the case of a subject who participates until the end of the study, ICH 3.1.8.

4.3.3 The REB should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payments to study subjects, is set forth in the written informed consent form and any other written information to be provided to subjects, The manner in which a payment will be prorated should be specified, ICH 3.1.9.

4.3.4 No member of a REB can accept an undue or excessive honorarium for their participation on a Board.

4.4 Institution/Institute

4.4.1 Ethics Committee's should act without constraints and maintain an independent relationship with the institution with which they are affiliated.

4.4.2 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 subjects, translated from FRSQ, part I, section 1.

4.5 Subjects participating in a clinical study

4.5.1 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 the subject's participation

4.5.2 Indemnification should not have the effect of exerting excessive influence on the subject.

4.5.3 The informed consent form should mention that a subject who withdraws from the research study will be compensated for his participation on a pro rata basis.

5. 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.
Quebec, Civil Code of Quebec, 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.

Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, June 2003.

SOP-09 Consent Process and Subject Informed Consent Form

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

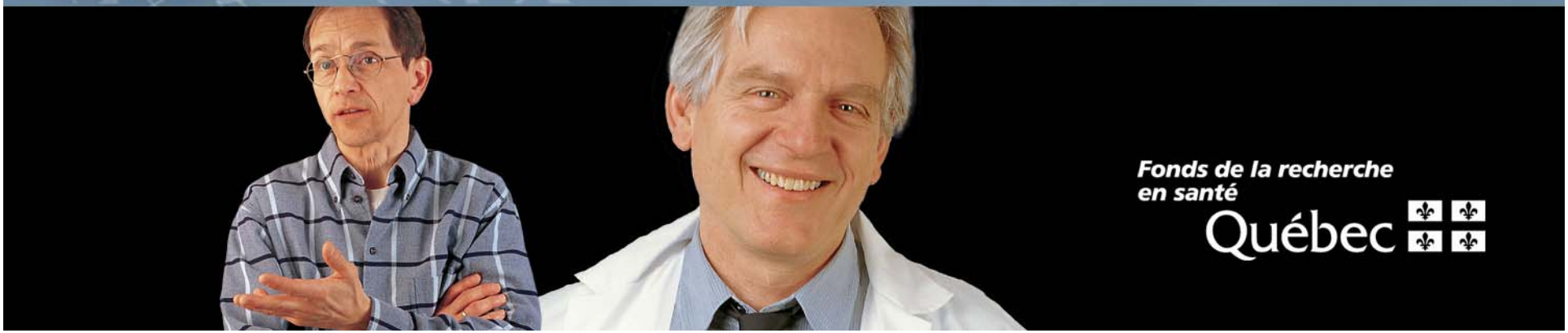
4. **Specific Responsibilities of the Institution**

5. **Procedures**

5. **References**

6. **Appendices**

Standard Operating Procedures (SOP)
SOP-11
Conflict of Interest



Fonds de la recherche en santé Québec

- **Objective**

  – Define the process of managing conflict of interest within an institution.

  All parties involved in clinical research should be independent, objective and loyal in their relation with subjects, sponsors, research establishments and professional corporations

- **Generalities**
  - Researchers hold trust relationships with :
    - Research subjects
    - Research sponsors
    - Institution
    - Professional bodies
    - Society
  - ALL parties are responsible for disclosing any conflict of interest

- **Investigator/Qualified Investigator**

  - Provide information on any aspect of the study but should not participate in the deliberations of the Ethics Committee
  - Disclose all details of his research activities to the Ethics Committee
  - Disclose to subjects all details concerning possible conflicts of interest
  - Inform the Ethics Committee of any bonus, fees or any other benefit agreed to in return for recruiting research subjects

    He always remains responsible for the actions of team members who act in his name

- **Members of Research Ethics Boards**
  - A member of the REB who has a personal interest must not be present when the REB is deliberating or making its decision
  - The reviewing of the amount and method of payment to subjects:
    - No coercion
    - Remuneration on a pro rata basis
    - Information regarding payment to subjects is set forth in the written consent form

- **Subjects participating in a clinical study**
  - A participant in a research project should receive compensation for loss and restriction suffered IF the compensation:
    - does not constitute an undue inducement
    - is paid on a pro rata basis
    - is not exerting excessive influence on the subject

Questions ?

Title	Subject Recruitment
Code	SOP-12
No. of Pages	8

History of Validated Versions

Date dd/mm/yyyy	Version	Pages	Description of Change

History of SOP Implementation

Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy

Approval of Site SOP

	Signature	Date dd/mm/yyyy

Table of Contents

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 process of recruitment of subjects 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 subjects.

2. Objective

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

3. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP, ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

4.1 Generalities

4.1.1 The investigator/qualified 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 products, medical devices or radiopharmaceuticals, 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.

4.1.2 With the goal of assuring compliance with GCP (ICH 4.2.4) and this SOP, it is necessary for the investigator/qualified 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 subjects to designated members of the research team be documented in the Task Delegation Form, reference: appendix 2, SOP 3. This document should be kept with documents essential to the study.

4.1.3 **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 an 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 the 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 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.

4.1.4 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.

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.

4.2 Recruitment Methods

4.2.1 Before initiating a study, the investigator/qualified investigator should inform and have approval from the Ethics Committee for the recruitment methods that he intends to use, as well as for subjects' remuneration and compensation, ICH 4.4.1 and ICH 4.8.10.

4.2.2 The investigator/qualified investigator should be able to demonstrate (based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period, outlined in the protocol, ICH 4.2.1.

Proof of this may be required by the sponsor, sponsor-investigator, Ethics Committee, Institution, as well as during monitoring or audit of the study by regulatory authorities.

4.2.3 The investigator/qualified 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 Ethics Committee and may include:

I. letters ;

II. telephone calls;

III. advertisement in television, radio, newspaper, etc..

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

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

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

III. Possible conflicts (i.e. attending physician, subject participating in other protocols).

4.2.5 The investigator/qualified investigator should define strategies to motivate potential subjects**,** taking into account that he cannot force or unduly influence a subject to participate in the study.

4.2.6. The investigator/qualified investigator should not permit subjects to participate unless they are eligible, according to criteria defined by the protocol.

4.3 Recruitment

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

4.3.1 Plan, when the protocol permits, a meeting with the subject and inform the investigator/qualified 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 subject 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/qualified investigator or the person designated by him must provide enough time to the subject or his 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 subject or his 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).

4.3.2 Verify eligibility criteria.

4.3.3 In conformity with section 4.5 of SOP 09, Consent Process, it should be ensured that the subject properly understands the nature of the clinical study that he 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 subject.

4.4 Recruitment Reports

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

I. **Screening Log:** this document identifies subjects figuring in the pre-study screening, ICH 8.3.20;

II. **Subject Enrolment Log:** this document lists enrolled subjects chronologically by study number, ICH 8.3.22;

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

Forms can be created for this information.

4.4.2 All of the following information should be kept by the Investigator/qualified investigator with the essential study documentation:

I. Advertisements used to recruit subjects, if applicable;
II. Dated approval from the Ethics Committee regarding advertisements for the recruitment of subjects, as the case may be;
III. The screening log identifying subjects screened as well as those who were included, or not, in the study;

IV. The confidential list of identification codes of all subjects who were given a study number;
V. The subject enrolment log that lists enrolled subjects chronologically by study number.

5. References

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

Health Canada, Guidance for Industry, Structure and Content of Clinical Study Reports, ICH Topic **E3**, 1996.

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**.

Health Canada, Guidance for Industry**,** Adoption of ICH Guidance: Statistical Principles of Clinical Trials, ICH Topic **E9**, February 2003.

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

SOP-02 Organizing a Site for Clinical Research.

SOP-03 Research Team: Role Definitions, Responsibilities and Task Delegation

SOP-09 Consent Process and Subject Informed Consent Form

SOP-10 Rights and Protection of Study Subjects

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

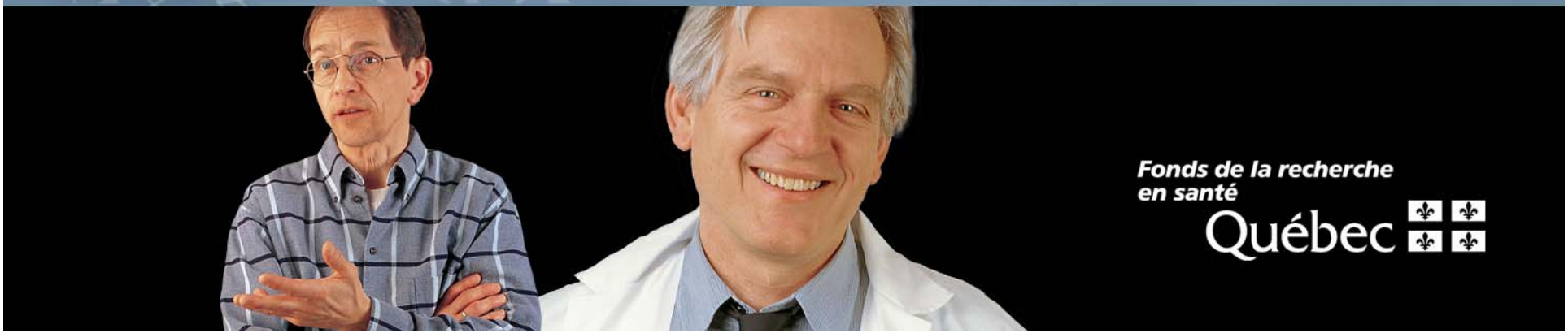
4. **Specific Responsibilities of the Institution**

5. **Procedures**

5. **References**

6. **Appendices**

Standard Operating Procedures (SOP)
SOP-12
Subject Recruitment



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- **Objective**
  - Describe the principles that govern the process of recruitment of subjects in a clinical study.

- **Recruitment Methods**
  - The investigator/qualified investigator should :
    - Inform and have approval form the Ethics Committee
    - Be able to demonstrate a potential for recruiting the required number of suitable subjects
    - Define recruitment strategies
    - Define strategies to motivate potential subjects

- **Recruitment**
  - No research activity in anticipation of a clinical study ca be conducted before the subject has signed the informed consent form
  - Recruitment should include the following steps :
    - Provide enough time to the subject or his legal representative to be informed
    - Answer all questions to the satisfaction of the subject or his legal representative
    - Ensure that the subject properly understands

- **Recruitment Reports**

  – Screening Log : identifies subjects figuring in the pre-study screening
  – Subject Enrolment Log : lists enrolled subjects chronologically by study number
  – List of subject identification codes
  – Advertisements used to recruit subjects
  – Approval from the Ethics Committee

  Keep with essential documentation

Questions ?

Title	Subject Follow-up
Code	SOP-13
No. of Pages	6

History of Validated Versions

Date dd/mm/yyyy	Version	Pages	Description of Change

History of SOP Implementation

Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy

Approval of Site SOP

	Signature	Date dd/mm/yyyy

Table of Contents

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 process of follow-up of subjects 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 subjects.

2. Objective

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

3. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP, ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

4.1 Generalities

4.1.1 As mentioned in GCP of the ICH 5.8.2, the investigator/qualified investigator should ensure that procedures or policies of the sponsor, sponsor-investigator address the costs of treatment of study subjects in the event of study-related injuries. In order to ensure protection of subjects taking part in the clinical study, he should ascertain that this information is found in the subject informed consent form, SOP 09.

4.1.2 The investigator/qualified investigator should ensure follow-up for subjects no longer using the investigational product or who were withdrawn from the study, ICH 6.5.3.d.

4.1.3 The investigator should inform the Ethics Committee when the recruitment and follow-up of subjects is finished or when the study is prematurely terminated, ICH 4.12.2. The process should be documented and records kept with the essential documentation of the study, SOP 2.

4.1.4 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 subjects, 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, biological products, medical devices or radiopharmaceuticals, as well as in all aspects of the study covered by the protocol, SOP 04 and 05. If they are not mentioned in the protocol, alternative treatments should be discussed (instructed) with the research team.

4.1.5 With the goal of ensuring better comprehension and greater compliance with this SOP, it is necessary that the investigator/qualified 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 subjects participating in the study.

4.2 Follow-up of Subject during the recruitment process

4.2.1 The sponsor-investigator or investigator/qualified investigator should ensure that subjects have received all necessary and pertinent information concerning the clinical study during the recruitment process, SOP 09 and 12.

4.2.2 In conformity with principle 4.8.7 of the ICH and as defined in SOP 09, the subject should have had enough time, before giving consent, to inform himself of the details related to the study and to decide whether to take part in the study or not.

4.3 Follow-up of the subject during the clinical study

4.3.1 The investigator/qualified investigator or his delegate should ensure that the subject adheres to all aspects of the protocol (medication taken, examinations done, questionnaires filled out...). This should be documented in the source documents, SOP 23.

4.3.2 In conformity with principle 4.12 of the ICH, if the study is abandoned or terminated prematurely for an unspecified reason, the investigator/institution/qualified investigator should inform the subjects taking part in the study promptly and ensure that suitable treatment and follow-up are provided to them.

4.3.3 In the event that the subject moves, the investigator/qualified investigator or his delegate should obtain the new contact information so as to ensure follow-up of the subject. All contacts with the subject in order to obtain this information (telephone, email, letter or other) should be documented in essential documentation, SOP 23.

4.3.4 If the subject no longer wants to participate in the study, the investigator/qualified investigator or his delegate should include this information in the source documents. If the reasons for this withdrawal are available (even if subject withdrew for no apparent reason), they should be noted in the source documents. In this case, the subject should be informed of other possible treatments and where they can be obtained. Subject follow-up should be according to the requirements of the protocol.

4.3.5 The investigator/qualified investigator should also inform the Ethics Committee of this any withdrawals. This information can be presented at the time of the submission of the annual report.

4.3.6 n the case of an adverse event, the subject should be followed until resolution of the event or according to the protocol. This follow-up should be documented in the source documents.

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

4.4 Follow-up of subjects after the end of the clinical study

4.4.1 The sponsor or the sponsor-investigator can define in the protocol a period of follow-up of subjects after the end of the study.

4.4.2 Following the end of the study, it is necessary to document follow-up of the subject 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.

5. References

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

SOP-02 Organization a Site for Clinical Research

SOP-04 Site Research Team: Competence, Knowledge and Training

SOP-05 Preparing the team for a Study

SOP-09 Consent Process and Subject Informed Consent Form

SOP-12 Subject Recruitment

SOP-23 Management of Data and Source Documents

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

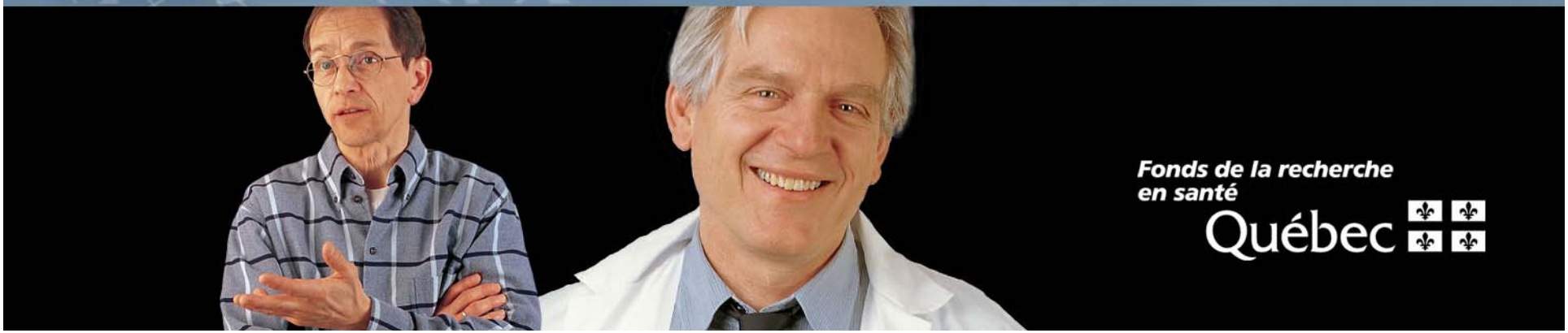
4. **Specific Responsibilities of the Institution**

5. **Procedures**

5. **References**

6. **Appendices**

Standard Operating Procedures (SOP)
SOP-13
Subject Follow-up



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- **Objective**
  - To ensure that the rights, the dignity and well-being of subjects are protected by proper follow-up.

- **Generalities**
  - The investigator/qualified investigator should :
    - Ensure that costs of treatment of study subjects in the event of study-related injuries are addressed
    - Ensure follow-up for subjects no longer using the investigational product or who where withdrawn
    - Inform the Ethics Committee when the recruitment is finished or when the study is prematurely terminated

- **Follow-up of the subject during the clinical study**
  - The investigator/qualified investigator should :
    - Inform the subject if the study is abandoned or terminated prematurely
    - Obtain the new contact information
    - Include in the source document if the subjects no longer wants to participate
    - Follow the subject until resolution in the case of an adverse event

- **Follow-up of subjects after the end of the clinical study**
  - Period of follow-up of subjects after the end of the study : upon the protocol

Questions ?

Title	Dealing with Scientific Misconduct and Protocol Deviations
Code	SOP-14
No of Pages	6

History of Validated Versions

Date dd/mmm/yyyy	Version	Pages	Description of Change

History of SOP Implementation

Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy

Approval of Site SOP

	Signature	Date dd/mmm/yyyy

Table of contents

1. Policy

Within the framework of the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonisation (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 subjects.

2. Objective

To ensure integrity of the data and validity of the final results of the clinical study, the investigator/qualified Investigator or those he 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. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP, ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

4.1 **Generalities**

To ensure adherence to ICH principle 4.5.1, the investigator / qualified 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 Ethics Committee has given its approval/favourable opinion. The investigator / qualified 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/qualified investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor/sponsor-investigator and approval/favourable opinion from the 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 subjects participating in the study 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/qualified investigator or a person he has designated, should document in writing and explain any deviations from the approved protocol.

4.1.1 The investigator/qualified investigator should comply with applicable regulatory requirements related to the obligation to inform the Ethics Committee of all instances of non-compliance including protocol variations or modifications to eliminate any immediate risk to subjects participating in the study, ICH 3.3.8.a. Such communications with the Ethics Committee should be documented and filed with the study-related essential documentation, ref. SOP 02.

4.1.2 The investigator/qualified 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.

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

4.2 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.

4.2.1 Any scientific misconduct by the investigator/qualified Investigator or a member of the research team should be reported to the investigator/qualified Investigator, the sponsor or sponsor-investigator and the 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 in Appendix 1, *Instructions Specific to the Site.*

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.

4.3 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).

4.3.1 Subjects should be informed of the importance of complying with the protocol as explained.

4.3.2 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.

4.4 Submission of Protocol Deviations to the Ethics Committee

4.4.1 The investigator/qualified Investigator should inform the Ethics Committee of all protocol deviations. If the deviation results in a protocol modification, approval by the Ethics Committee will be required before it can be applied, ICH 4.5.2 and SOP 08, except if

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

II. The modification has to be implemented immediately for the well-being of subjects.

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.

5. References

Health Canada, Guidance for Industry, Structure and Content of Clinical Study Reports, ICH Topic **E3**, 1996. [-2]

Health Canada, Guidance for Industry, Good Clinical Practice: Consolidated guideline, ICH Topic **E6**, 1997. [-3]

Health Canada, Guidance for Industry**,** Adoption of ICH Guidance: Statistical Principles of Clinical Trials, ICH Topic **E9**, February 2003. [-5]

Quebec, 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-02 Organizing a Site for Clinical Research

SOP-08 Protocol and Protocol Amendment, Submission to Research Ethics Board

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

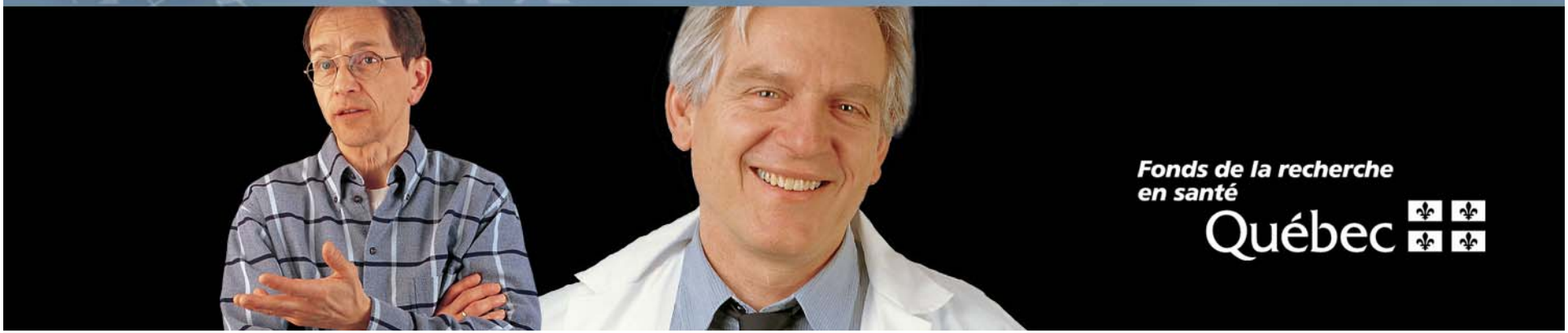
4. **Specific Responsibilities of the Institution**

5. **Procedures**

5. **References**

6. **Appendices**

Standard Operating Procedures (SOP)
SOP-14
Dealing with Scientific Misconduct and Protocol Deviations



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- **Objective**
  - Describe procedures for documenting scientific misconduct or protocol deviations and their submission to the appropriate bodies.

- **Generalities**
  - The investigator/qualified investigator should:
    - Document all incidents of scientific misconduct or deviation from protocol in the source documents and CRF

- **Scientific Misconduct**
  - Falsification of research data
  - Intentional omission of data

- **Protocol Deviation**
  - The Statistical Analysis Section prepared at the beginning of the study:
    - Indicate how protocol deviations will be analyzed

- **Submission of Protocol Deviations to the Ethics Committee**
  - The investigator/qualified investigator should :
    - Inform the Ethics Committee of all protocol deviations
  - A new approval by the Ethics Committee is required EXCEPT if :
    - The change is purely administrative
    - The modification has to be implemented immediately for the well-being of subjects
  - All documentation related to non-compliance with the protocol should be available for inspection

Questions ?

Title	Research Ethics Board (REB): Ongoing Communications
Code	SOP-15
No. of Pages	10

History of Validated Versions

Date dd/mmm/yyyy	Version	Pages	Description of Change

History of SOP Implementation

Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy

Approval of Site SOP

	Signature	Date dd/mmm/yyyy

Table of contents

1. Policy

Within the framework of the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonisation (ICH), the Tri-Council Policy Statement (TCPS) (*Ethics for Research Involving Human Subjects)*, as well as the "G*uide d'éthique de la recherche et d'intégrité scientifique"* from the *Fonds de la recherche en santé du Québec* (FRSQ), this standard operating procedure (SOP) outlines policies regarding Research Ethics Boards (REB) and describes procedures for the management of communications between the investigator/qualified Investigator and the Ethics Committee.

All research involving living human subjects, cadavers, human remains, tissues, body fluids, embryos or foetuses, will be assessed and approved by the REB according to the TCPS rule 1.1. prior to being initiated. Moreover, it is stated in the FRSQ document "G*uide d'éthique de la recherche et d'intégrité scientifique"* (2, page 20) that research conducted on gametes or based on personal information contained in medical files should also be submitted to an Ethics Committee.

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 subjects, the institutional Research Ethics Board is responsible for reviewing and periodically checking biomedical research projects involving human subjects. For all clinical studies, communications between investigator/qualified investigator and the REB start with the preparation of documents for submission, and continue 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/qualified investigator and Ethics Committee, during the course of clinical studies.

3. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision, will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP, ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

The Board of Directors of the institution is ultimately responsible for both the quality of the research and research ethics. The Board appoints a Research Ethics Committee for this purpose. The institution defines the responsibilities of the Ethics Committee 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.

An Ethics Committee should safegard the rights, safety and well-being of all subject. Special attention should be paid to studies that may include vulnerable subjects, ICH 3.1.1.

4.1 Documents to be Submitted to the REB

The investigator/qualified investigator is responsible for submitting the following documents to the Ethics Committee:

4.1.1 No objection letter (NOL) in the case of a CTA (Clinical Trial Application) submission or CTAM (Clinical Trial Application Modification) to Health Canada;

4.1.2 Study protocol and protocol modification. The complete protocol should be submitted and reviewed by the Ethics Committee;

4.1.3 Subject informed consent forms (ICF) and ICF modifications including all translations that will be used;

4.1.4 Subject recruitment methods (ads, posters, etc.);

4.1.5 Written documentation to be provided to subjects;

4.1.6 Investigator's Brochure (for studies with drugs) or product monograph, if applicable;

4.1.7 Other available information on the safety of the study investigational product, biological products, medical devices or radiopharmaceuticals, if applicable;

4.1.8 Information on subjects' compensation;

4.1.9 Curriculum Vitae of investigator/qualified investigator or update if applicable, and other documents pertaining to his competence;

4.4.1 Any other documents required by the Ethics Committee if applicable, as described in Appendix 1, *Instructions Specific to the Site*.

4.1.11 The investigator/qualified investigator should keep a copy of these documents in the file of study-related essential documents.

4.2 Preparation of Documents and Submission to the REB

The investigator/qualified investigator is responsible for submitting documents to the Ethics Committee. Tasks required for the submission may be delegated, but the responsibility rests with the investigator/qualified investigator.

4.2.1 The investigator/qualified 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;

4.2.2 The investigator/qualified investigator, to prevent any delays in the implementation of a clinical study, should be aware of the frequency and schedule of meetings of

the REB, as well as periods when the Board does not convene, as described in Appendix 1, *Instructions Specific to the Site*.

4.2.3 The investigator/qualified 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 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, as described in Appendix 1, *Instructions Specific to the Site*.

4.2.4 The investigator/qualified 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, as described in Appendix 1, *Instructions Specific to the Site*.

4.2.5 The investigator/qualified investigator should affirm his adherence to good clinical practice of the REB. Documents related to this adherence should be available for consultation and kept with the file of study-related essential documents.

4.2.6 The investigator/qualified investigator should know if specific forms are to be used to complete the submission, as described in Appendix 1, *Instructions Specific to the Site*.

4.2.7 The investigator/qualified investigator should know if there are any fees related to the submission to the Ethics Committee.

4.2.8 The investigator/qualified investigator should keep a copy of all submission documents together with any related correspondence, with the file of study-related essential documents.

4.2.9 The investigator/qualified investigator should ensure that all documents mentioned in item 4.1 of the present document are submitted to the Ethics Committee 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 2, *Example of Letter of Submission to the Research Ethics Board*.

4.2.10 The investigator/qualified investigator should keep a copy of this submission letter with the study related essential documentation file.

4.2.11 If the Institution's Ethics Committee has documented its policies and standard operating procedures, the investigator/qualified investigator should ensure that these are available for audits or inspections.

4.2.12 The investigator/qualified investigator should ensure compliance with the policies and procedures of the institution's Ethics Committee if applicable.

4.3 Response of the REB

4.3.1 The investigator/qualified investigator should ensure that the letter of response from the Ethics Committee includes the following information:

I. Clinical study identification, protocol number and title;

II. Name and version date of all documents reviewed by the Ethics Committee;

III. Date of review by the Ethics Committee;

IV. Decision/opinion/approval of the clinical study, including required modifications, if applicable;

V. Procedures for appealing the decision/opinion of the committee;

VI. Any other information, if applicable, as described in Appendix 1, *Instructions Specific to the Site*;

VII. Date of renewal of approval;

VIII. Signature of the Chair of the Ethics Committee and date of the response.

4.3.2 Following GCP (ICH 3.2.1 et 3.2.2) and according to the FRSQ's *(*page 40), a list of the members of the Ethics Committee and their qualifications, as well as the procedures of the said committee should be available.

4.3.3 The investigator/qualified investigator should keep a copy of the Ethics Committee's letter of response with the study related essential documentation file.

4.3.4 In Phase I, II and III clinical drug studies submitted to Health Canada, the investigator/qualified 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.

4.3.5 If any form other than the one provided by Health Canada is used to document approval of the study by the Ethics Committee 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. This information should be listed in Appendix 1, *Instructions Specific to the Site*.

4.4 Communication with the REB during the Study

To ensure study follow-up, the following communications with the Ethics Committee should be documented:

4.4.1 Modifications to the study protocol or subject informed consent form during the course of a clinical study may be submitted one by one to the Ethics Committee.

4.4.2 The investigator/qualified investigator **should report promptly** the following information to the Ethics Committee, as described in Appendix 1, *Instructions Specific to the Site*:

I. Any significant protocol change or deviation.;

II. Any serious adverse event involving a participating subject enrolled at the institutional site;

III. For multicentre studies, any serious, unexpected, adverse event involving a subject 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 subject or his willingness to continue participating in the study.

4.4.3 The following information **should be reported regularly, minimally annually,** to the Ethics Committee by the investigator/qualified 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 subjects 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 (see Appendix 1, *Instructions Specific to the Site*).

If the frequency of the Ethics Committee's review process is more than once a year, this information should be reported in Appendix 1, *Instructions Specific to the Site.*

4.5 Communication with the REB at the End of the Study

4.5.1 When the clinical study is finished (at the least when each subject has completed the study) according to Item 4.13 of IHC, the investigator/qualified investigator should submit a final study report to the Ethics Committee. The following items should be included in this report:

I. Total number of subjects: 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, (see Appendix 1, *Instructions Specific to the Site*).

4.5.2 The investigator/qualified investigator should keep a copy of those documents with the study related essential documentation file.

5. References

Health Canada, Guidance for Industry, Good Clinical Practice: Consolidated guideline, ICH Topic **E6**, 1997. [-3]

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

Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, June 2003.

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.

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

4. **Specific Responsibilities of the Institution**

5. **Procedures**

5. **References**

6. **Appendices**

APPENDIX 2 EXAMPLE OF LETTER OF SUBMISSION TO THE REB

Date of Submission

(Name of Ethics Committee)
(Address of Ethics Committee)

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 Ethics Committee.

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 REB 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. Subject Informed Consent Form – English Version, No 1 – December 10th 2004);
7. Subject 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 Ethics Committee.

Standard Operating Procedures (SOP)
SOP-15
Research Ethics Board (REB): Ongoing Communications

Fonds de la recherche en santé Québec

- **Objective**
  - Describe the communications process (submission, follow-up, etc.) between the investigator/qualified investigator and Ethics Committee, during the course of clinical studies.

- **Documents to be Submitted to the REB**

  - The investigator/qualified investigator is responsible for submitting to the Ethics Committee :
    - NOL (in the case of a CTA or CTAM submission to Health Canada)
    - Study protocol and modification
    - Subject informed consent forms (ICF)
    - Subject recruitment methods
    - Written documentation to be provided to subjects
    - Investigator's Brochure or product monograph

- **Documents to be Submitted to the REB**

  - Investigator's Brochure or product monograph
  - Information on subjects' compensation
  - Curriculum vitae

  Keep a copy of these documents with essential documentation

- **Response of the REB**
  - The investigator/qualified investigator should :
    - Keep a copy of the Ethics Committee's letter of response with the essential documentation

- **Communication with the REB during the Study**
  - Modifications to the study protocol or subject informed consent form

- **Communication with the REB at the End of the Study**
  - The investigator/qualified investigator should :
    - Submit a final report to the Ethics Committee
    - Keep a copy with the essential documentation

Questions ?

Title	Management of Communication During a Study
Code	SOP-16
No. of Pages	5

History of Validated Versions

Date dd/mmm/yyyy	Version	Pages	Description of Change

History of SOP Implementation

Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy

Approval of Site SOP

	Signature	Date dd/mmm/yyyy

Table of contents

1. Policy

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 communication procedures within the research team and with parties such as the sponsor (if applicable), Ethics Committee 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 subjects.

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 subjects. It also defines principles of communication between the investigator and the sponsor and, according to applicable regulatory requirements, communications with the sponsor-investigator, investigator, Ethics Committee and regulatory authorities.

3. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP, ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

To ensure the safety of subjects 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, participating subjects, the Ethics Committee, 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.

4.1 **Communications Within the Research Team**

4.1.1 While organizing the clinical study, the investigator should provide the research team with all information or data relevant to the safety of subjects and to the smooth conduct of the study, as described in SOP 05.

4.1.2 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. Subject recruitment;

II. Subjects or adverse events;

III. Administrative matters;

IV. Other study-related matters.

4.1.3 It is recommended that all communications, including the names of participants, meeting date, summary of discussions and resolutions adopted, be documented.

4.1.4 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.

4.2 Communications with Subjects Participating in the Study

4.2.1 As described in SOP 09, subjects should be provided with all relevant information, directly or through a representative/witness, prior to their consent, during the study and after, if applicable.

4.2.2 Subject or representative/witness should receive satisfactory answers to study questions, at all times.

4.2.3 Verbal communications with subject 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.

4.3 Communications with the Ethics Committee

4.3.1 As described in SOP 15, communication with the REB starts with the preparation of documents for submission, continues during the study and goes on until submission of the final study report.

4.3.2 All communications with the REB should be documented and kept with the source documents.

4.4 Communications with the Sponsor or Regulatory Authorities

4.4.1 As described in SOP 17, 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.

4.4.2 As described in SOP 14, information regarding protocol deviations should be forwarded to the sponsor.

5. References

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

SOP-05 Preparing the Team for a Study.

SOP-09 Consent Process and Subject Informed Consent Form

SOP-14 Dealing with Scientific Misconduct and Protocol Deviations

SOP-15 Research Ethics Board (REB): Ongoing Communications

SOP-17 Management of Adverse Events – Serious Adverse Events and Adverse Reactions – Serious Adverse Reactions

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

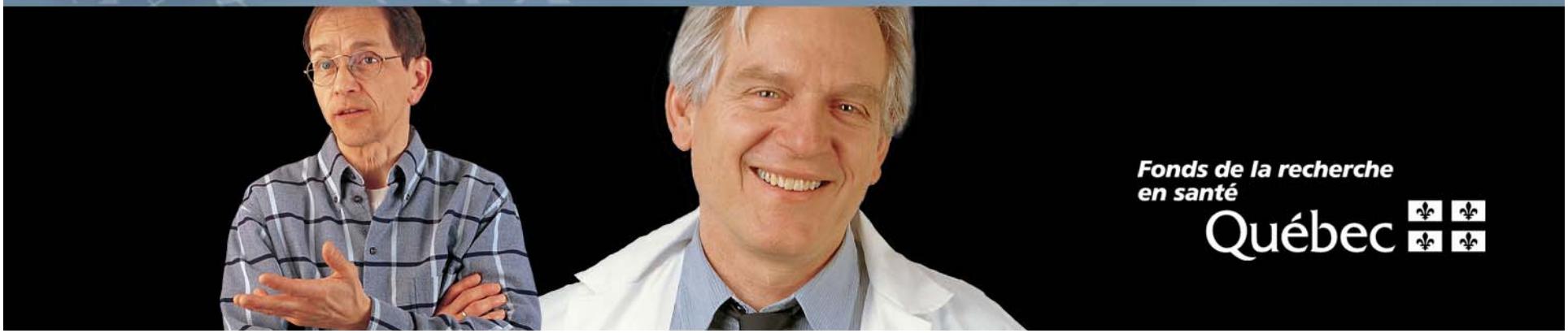
4. **Specific Responsibilities of the Institution**

5. **Procedures**

5. **References**

6. **Appendices**

Standard Operating Procedures (SOP)
SOP-16
Management of Communication During a study



Fonds de la recherche en santé Québec

SOP-16
Management of Communication During a Study

- **Objective**
  - Define channels of communication and exchange of information among the investigator, the research team and subjects. It also defines principles of communication between the investigator and the sponsor and, according to applicable regulatory requirements, communications with the sponsor-investigator, investigator, Ethics Committee and regulatory authorities.

- **Communication Within the Research Team**
  - It is recommended to :
    - Document all communications
    - Record the date of dispatch or receipt of all documents

- **Communication with Subjects Participating in the Study**
  - Ensure that verbal communication with subject is accurate, clear and understandable
    - Record communication and keep with the essential documentation

- **Communication with the Ethics Committee**
  - Communication continues during the study and goes until submission of the final report

- **Communication with the Sponsor or Regulatory Authorities**
  - The investigator should :
    - Inform the sponsor and regulatory authorities of any AE SAE

Questions ?

Title	**Management of Adverse Events - Serious Adverse Events and Adverse Reactions - Serious Adverse Reactions**
Code	SOP-17
No. of Pages	8

History of Validated Versions

Date dd/mmm/yyyy	Version	Pages	Description of Change

History of SOP Implementation

Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy	Version	Date dd/mmm/yyyy

Approval of Site SOP

	Signature	Date dd/mmm/yyyy

Table of contents

1. Policy

Within the framework of the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonisation (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 Ethics Committee 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 subjects.

2. Objectives

To ensure the safety of participants, the investigator/qualified investigator and research personnel are required to follow each subject 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/qualified investigator, as well as deadlines for reporting these AE/SAEs or AR/SARs.

3. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP, ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

4.1 **Generalities**

4.1.1 With respect to any adverse event, the investigator/institution/qualified investigator should ensure that appropriate medical treatment is provided to a subject during and after his participating in the study, ICH 4.3.2;

4.1.2 The investigator/institution/qualified investigator should inform the subject when medical care is needed regarding intercurrent illnesses, ICH 4.3.2;

4.1.3 The investigator/qualified investigator should promptly report to the Ethics Committee any adverse reaction that is serious and unexpected, as well as any new information that could adversely affect subjects' safety or the conduct of the study, ICH 3.3.8;

4.1.4 The investigator/qualified 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 Ethics Committee, ICH 4.11.1;

4.1.5 In the case of a death, the investigator/qualified investigator must provide, the sponsor, sponsor-investigator and Ethics Committee with all additional requested information (autopsy reports, medical reports, etc.), ICH 4.11.3;

4.1.6 The investigator/qualified 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;

4.1.7 The investigator/qualified 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;

4.1.8 The investigator/qualified investigator should accurately and regularly document **all** adverse events in the source documents and case report forms (CRFs).

4.1.9 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 subjects are the most important considerations and should prevail the interests of, science and society, ICH 2.3.

II. Medical care given to, and medical decisions made on behalf of subjects, 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*.

4.2 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 subjects 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 subjects involved in studies 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 subjects, Introduction of the ICH.

In the case of clinical studies without an investigational product, it is recommended that the sponsor-investigator and investigator/qualified investigator follow the same procedures for collecting clinical data related to adverse events and serious adverse events, assessing and reporting to their Ethics Committee and regulatory authorities, if applicable.

4.3 Collection of Clinical Data Related to AE/SAEs or AR/SARs

4.3.1 Subjects 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.

4.3.2 In the case of subject who is not competent, or minors, the investigator/qualified investigator or clinical study personnel should collect all data related to the AE or AR from the legal representative.

4.3.3 Whatever the AE or AR reported by the subject, research personnel involved in the clinical study should discuss it with the investigator/qualified investigator who is responsible for determining the causality of the AE or AR.

4.3.4 To ensure the subject'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 subject.

4.3.5 Each clinical event or worsening or deterioration of a clinical condition after inclusion of the subject in a clinical study should be reported to the investigator/qualified investigator and documented in the source documents and case report forms, unless otherwise specified in the protocol.

4.3.6 All laboratory abnormalities should be reported to the investigator/qualified investigator for assessment. Laboratory abnormalities deemed clinically significant should be documented as described in the protocol.

4.4 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:

4.4.1 **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.

4.4.2 **Severity:** events are classified as *serious* if associated with effects threatening the life or physiological functions of a subject. 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.

4.4.3 **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 Ethics Committee. The sponsor/sponsor-investigator is responsible for establishing if the reported adverse event is unforeseen or unexpected.

4.4.4 **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 nomenclature exists for this subject.

4.5 Report and Follow-up of AE/SAEs and AR/SARs

The investigator/qualified investigator is responsible for:

4.5.1 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;

4.5.2 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/qualified investigator will allow the sponsor/sponsor-investigator to fulfill regulatory obligations regarding prompt reports;

4.5.3 submitting immediately, to the Ethics Committee, 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 Ethics Committee, if applicable;

4.5.4 submitting to the Ethics Committee all SAE/SARs which occur at his site, at least annually or according to the frequency recommended by the Ethics Committee. Usually AE/ARs are not reported to the Ethics Committee. To that effect, each site should comply with the rules of its Ethics Committee;

4.5.5 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 Ethics Committee according to their requirements;

4.5.6 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.

4.5.7 **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, 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)**.

4.5.8 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 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. 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. 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.

5. References

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

Health Canada, Guidance for Industry, Clinical Safety Data Management Definitions and Standards for Expedited Reporting, ICH Topic **E2A**, 1995.

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

Health Canada, Guidelines for the Canadian Pharmaceutical Industry on Reporting Adverse Reactions to Marketed Drugs, July 2001.

Ministère de la santé et des services sociaux (MSSS), Comité central d'éthique du MSSS.

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. Filing System

2. Location of Filing System

3. Annual Approval or Revision

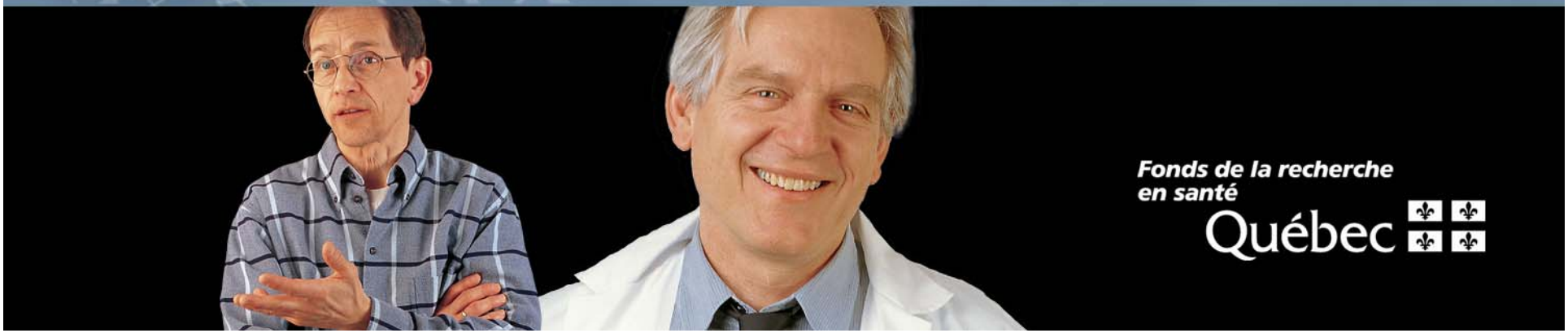
4. Specific Responsibilities of the Institution

5. Procedures

5. References

6. Appendices

Standard Operating Procedures (SOP)
SOP-17
Management of Adverse Events – Serious Adverse Events and Adverse Reactions – Serious Adverse Reaction



Fonds de la recherche en santé Québec

- **Objectives**
  - 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.
  - Defines AE/SAEs or AR/SARs, the responsibilities of the sponsor-investigator and investigator/qualified investigator, as well as deadlines for reporting these AE/SAEs or AR/SARs.

- **Generalities**
  - The investigator/qualified investigator should :
    - Ensure that appropriate medical treatment is provided to a subject during and after the study
    - Report to the Ethics Committee any AR that is serious and unexpected
    - Comply with applicable regulatory requirements related to the reporting of SADR
    - Provide requested information in the case of death
    - Report AEs or laboratory abnormalities
  - It is important to harmonize the collection, assessment and communication of AEs/SAEs or AR/SARs

- **Management of AEs and SAEs in studies with no Investigational Products**
  - The Good Clinical Practice
  - Studies without investigational product :
    - It is recommended to follow the same procedures

- **Collection of Clinical Data related to AE/SAEs or AR/SARs**
  - Subject is responsible to report all physical changes
  - Research personnel should :
    - Discuss the causality of the AE or AR with the investigator/qualified investigator
  - Clinical event :
    - Report to the investigator/qualified investigator worsening or deterioration or laboratory abnormalities

- **Assessment of AE/SAE or AR/SAR**
  - The investigator/qualified investigator will clinically assess :
    - Intensity
    - Severity
    - Incidence
    - Causality

- **Report and Follow-up of AE/SAEs and AR/SARs**

  – The investigator/qualified investigator is responsible for :
    - Reporting AE/SAEs or AR/SARs in source documents
    - Submitting the SAE/SARs to the sponsor/sponsor-investigator
    - Submitting to the Ethics Committee all initial and follow-up reports on SAE/SARs

- **Report and Follow-up of AE/SAEs and AR/SARs**

  - Fatal and life-threatening SAE/SARs
    - Case involving medication : within 7 days
    - The sponsor/sponsor-investigator should :
      - Provide a report of the SAE/SAR, within 8 days to Health Canada;

    - Case involving medical device : within 10 days

    - The sponsor/sponsor-investigator should :
      - Submit a summary report according the Minister's request (Health Canada)

- **Report and Follow-up of AE/SAEs and AR/SARs**
  - Non-fatal SAE/SARs
    - Case involving medication : within 15 days
    - Case involving medical device : within 30 days
    - The sponsor/sponsor-investigator should :
      - Submit a summary report according the Minister's request (Health Canada)
  - If a protocol is subject to foreign regulations, these should be scrupulously observed

Questions ?

Title	**Managing Investigational Products, Biological Products, Medical Devices or Radiopharmaceuticals Under Study**
Code	SOP-18
Pages	9

History of Validated Versions

Date dd/mm/yyyy	Version	Pages	Description of change

History of SOP Implementation

Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy

Approval of Site SOP

	Signature	Date dd/mm/yyyy

Table of Contents

1. Policy

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 policies which deal with the management of investigational products (drugs), biological products, medical devices, radiopharmaceuticals, etc. 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 or radiopharmaceuticals, under study.

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

2. Objectives

The objectives of this standard operating procedure are:

- To define standard operating procedures which describe how investigational products, biological products, medical devices or 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 investigational products, biological products, medical devices or radiopharmaceuticals specific to a sponsor/sponsor-investigator, are followed.

3. Site Responsibilities

3.1 The Research Centre Director or his delegate is responsible for:

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:

3.3.1 At the time of implementation of each SOP ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

4.1 Generalities

In order to ensure the safety of subjects, integrity of the data and conformity with regulatory requirements, it is important to recall that responsibility for investigational products accountability at the study site rests with the investigator/institution, ICH 4.6.1.

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

In general, the type of investigational product, biological product, medical device or radiopharmaceutical under study, as well as the site where the clinical study is carried out, dictates 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 du Québec – mesure 16*, it is recommended that investigational medications be subject to the same controls as medications available by prescription, in conformity with articles 116 and 117 (appendix 1) de la Loi sur les services de santé et les services sociaux.

4.1.1 The investigator/qualified investigator can delegate functions relating to investigational products to a pharmacist or another qualified person within the institution and biological products, medical devices or radiopharmaceuticals to a qualified person of the institution. It is suggested that, according to the structure of the institution, the pharmacy assumes the functions related to the investigational product in order to standardize management and documentation related to investigational products. It is important to document this delegation of tasks, as described in SOP 03 and to retain this documentation with the essential study documents, as described in SOP 02.

4.2 Receipt and Inventory of Investigational Products, biological products, medical devices or radiopharmaceuticals

The investigator/qualified investigator, the pharmacist or the person designated by the investigator/qualified investigator should:

4.2.1 At the time of delivery of the investigational products, biological products, medical devices or 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 or radiopharmaceuticals should be retained with the essential study documents, as described in SOP 02;

4.2.2 Within a short time, make an inventory of products/devices 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 02.

4.2.3 List any products/devices 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 or radiopharmaceuticals received. This

inspection should be documented and retained with the essential study documentation, SOP 02.

4.3 **Labeling and Coding of Investigational Products, biological products, medical devices or radiopharmaceuticals**

4.3.1 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)1(b)(vi), if the drug is a radiopharmaceutical as defined in section C.03.201. [-5]

4.3.2 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" and "Réservé uniquement à l'usage 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 (IVDD), 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.[-4]

4.3.3 The label on investigational products, biological products, medical devices or 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 he original label of the investigational product, biological product, medical device or

radiopharmaceuticals. In order to respect the confidentiality of subject information, when containers which hold medication are returned to the sponsor, no information which could identify a subject (nominative data) must appear on the label.

4.4 Storage of Investigational Products, biological products, medical devices or radiopharmaceuticals

Investigational products, biological products, medical devices or radiopharmaceuticals should be stored in a secure environment as defined in SOP 02 and ICH 5.13.

The investigator/qualified investigator, the pharmacist or the person designated by the investigator/qualified investigator should:

4.4.1 Establish and maintain controlled access for authorized personnel;

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

4.4.3 Store investigational products, biological products, medical devices or radiopharmaceuticals in a locked room;

4.4.4 Store investigational products (biological products, medical devices or radiopharmaceuticals if applicable) 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;

4.4.5 Store investigational products, biological products, medical devices or radiopharmaceuticals as specified by the sponsor and in accordance with applicable regulatory requirements, ICH 4.6.1 and 4.6.4.

4.5 Distribution of Investigational Products

The investigator/qualified investigator, the pharmacist or the person designated by the investigator/qualified investigator should:

4.5.1 inform each study subject about the correct use of the investigational product(s), biological products, medical devices or 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;

4.5.2 The investigator should ensure that investigational products, biological products, medical devices or 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 :

4.5.3 Document and identify the person who is authorized to prescribe the drug;

4.5.4 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 subject;

4.5.5 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;

4.5.6 Inform the subject 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;

4.5.7 Document any delegation of tasks, as defined in SOP 03. Documentation of delegation should be retained with the essential study documentation, as described in SOP 02.

4.5.8 Submit to the ethics committee all significant deviations from the drug dose/schedule that could have an impact on the health of the subject. The submitted documents should be kept with the documentation essential to the study, as described in SOP 02.

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

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

4.5.10 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 subject;

4.5.10 Document any delegation of tasks, as defined in SOP 03. Documentation of delegation should be retained with the essential study documents, as described in SOP 02.

4.6 Accountability for Investigational Products, biological products, medical devices or radiopharmaceuticals

The investigator/qualified investigator, the pharmacist or the person designated by the investigator/qualified investigator should, in the case of a clinical study utilizing a drug:

4.6.1 Document the quantity of drug used and returned for each subject;

4.6.2 Compare, the amount of drug returned/used versus the allotted drug, for each subject, if applicable;

4.6.3 Account for and document any inconsistency;

4.6.4 For the safety of the subject, perform a subject or pharmacy follow-up in the event of inconsistency in accounting, and document this inconsistency;

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

4.6.6 Retain this documentation with the study documentation, as defined in SOP 02.

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

4.6.7 Document and sign, if applicable, return of the device by the subject;

4.6.8 Under no circumstances, assign to another subject or to another site, a device assigned to a subject and not used;

4.6.9 Maintain this documentation with the essential study documents, as described in SOP 02.

4.7 Return/Destruction of Investigational Products, biological products, medical devices or radiopharmaceuticals

The investigator/qualified investigator, the pharmacist or the person designated by the investigator/qualified investigator should:

4.7.1 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 02;

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

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

4.7.4 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;

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

5. 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.

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

Quebec, 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.

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-02 Organizing a Site for Clinical Research

SOP-03 Research Team: Role Definitions, Responsibilities and Task Delegation

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

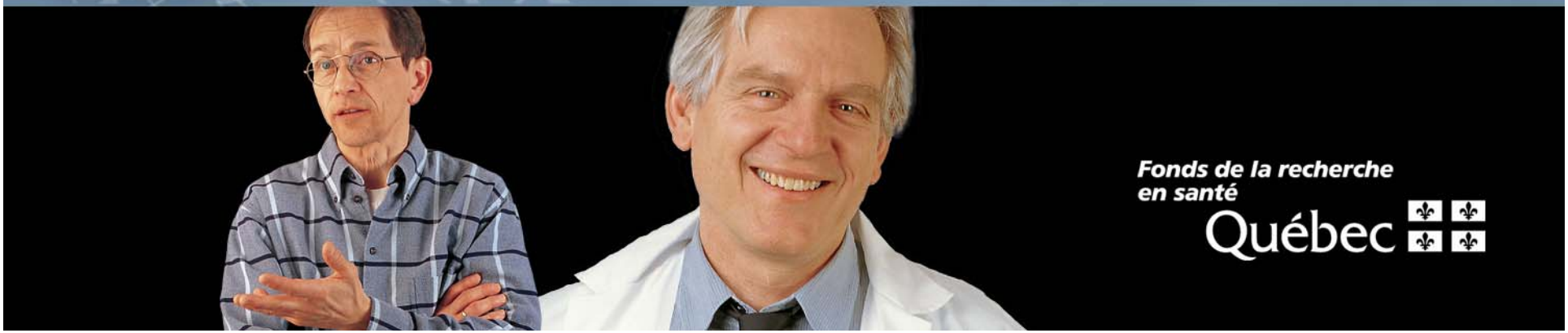
4. **Specific Responsibilities of the Institution**

5. **Procedures**

5. **References**

6. **Appendices**

Standard Operating Procedures (SOP)
SOP-18
Managing Investigational Products Under Study



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- **Objectives**
  - Define standard operating procedures which describe how investigational products are managed within the establishment;
  - Provide basic standards in order to ensure compliance with applicable regulatory requirements;
  - Ensure that procedures for management of research products specific to a sponsor/sponsor-investigator, are followed.

- **Generalities**
  - Responsibility for investigational products accountability at the study site rests with the investigator/institution
    - The investigational medications:
      - It is recommended to follow the same controls as medications available by prescription

- **Receipt and Inventory of Investigational Products**

  – The investigator/qualified investigator, the pharmacist or the person designated should:
    - Review the shipping instructions
    - Make an inventory of products received
    - List any product defects

    Retain document with essential documentation

- **Labelling and coding of Investigational Products**
  - The sponsor/sponsor-investigator shall ensure that the drug bears a label on which appears information in both official languages
  - A medical device for investigational testing should have a label with the appropriate information

- **Storage of Investigational Products**
  - Secure environment
  - The investigator/qualified investigator, the pharmacist or the person designated should :
    - Establish and maintain controlled access
    - Develop procedures to control access
    - Store investigational products in a locked room

- **Distribution of Investigational Products**
  - The investigator/qualified investigator, the pharmacist or the person designated should:
    - Inform subject about the correct use of the investigational product(s)

- **Distribution of Investigational Products**

  - Case of a study utilizing a drug:
    - Identify the person who is authorized to prescribe the drug
    - Document the assignment of the drug to the subject
    - Document any modification to or deviation from drug dosage
    - Submit to the Ethics Committee all significant deviations from the drug dose/schedule that could have an impact on the health of the subject

- **Distribution of Investigational Products**
  - Case of a study using an investigational device:
    - Specify the person who is authorized to prescribe the investigational device
    - Document the assignment of the investigational device to the subject

- **Accountability for Investigational Products**
  - In the case of a study utilizing a drug, the investigator/qualified investigator, the pharmacist or the person designated should:
    - Document the quantity of drug used/returned for each subject
    - Compare the drug returned/used versus the allotted drug
    - Document any inconsistency
    - Under no circumstances, assign to another subject a drug assigned to a subject and not used
    - Retain documentation

- **Accountability for Investigational Products**

  – In the case of a study utilizing an investigational device, the investigator/qualified investigator, the pharmacist or the person designated should:
    - Document return of the device
    - Under nor circumstances, assign to another subject a device assigned to a subject and not used
    - Retain documentation

- **Return/Destruction of Investigational Products**

  – The investigator/qualified investigator, the pharmacist or the person designated should:
    - Return to the sponsor/sponsor-investigator investigational products or follow the instructions in the protocol
    - Ensure that the institution or the pharmacy has appropriate procedures for destruction
    - Keep with the essential documentation

Questions ?

Fonds de la recherche en santé Québec

SOP19EN02

Title	**Management of Biological Specimens: Collection and Storage**
Code	SOP-19
Pages	6

History of Validated Versions

Date dd/mm/yyyy	Version	Pages	Description of Change

History of SOP Implementation

Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy

Approval of Site SOP

	Signature	Date dd/mm/yyyy

Table of Contents

1. Policy

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 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 subjects.

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. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

4.1 Generalities

In order to ensure the safety of subjects, the integrity of data and adhesion to regulatory requirements, it is important to recall that responsibility for the collection of biological specimens from subjects 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 equipment maintenance and calibration should be noted and kept by the research team.

4.1.1 The investigator/qualified 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 03 and to conserve this documentation with the essential study documentation, as described in SOP 02.

4.2 Collection of Biological Specimens

4.2.1 Before any specimen collection, the subject should be well informed regarding the purpose of this procedure and should have understood and signed the informed consent form, as described in SOP 09.

4.2.2 The investigator/qualified investigator or his 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.

4.2.3 Any documentation connected with maintenance of the equipment should be preserved with the essential study documentation, SOP 02.

4.2.4 The investigator/qualified investigator or delegate should ensure the safety and well-being of subjects during the collection of specimens.

4.2.5 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 subject, as well as the date when the collection was made should be included, according to the specifications in the protocol.

4.2.6 All specimens collected for the clinical study should be listed. This documentation should be kept with the essential study documentation, SOP 02.

4.3 Storage of Biological Specimens

The investigator/qualified investigator or his delegate should:

4.3.1 Ensure that storage of biological specimens takes place in a secure and suitable environment, as defined in SOP 02;

4.3.2 Establish and maintain controlled access for authorized personnel, in order to guarantee subject confidentiality;

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

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

4.3.5 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;

4.3.6 Make preparation for a backup system in the event of a power or equipment failure;

4.3.7 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;

4.3.8 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.

4.4 Analysis of Biological Specimens

4.4.1 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.

4.4.1 The investigator/qualified investigator should know, within a reasonable time, the results of the analysis related to the follow-up of a subject, with reference to the protocol.

4.4.1 The investigator/qualified 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 subject informed consent form.

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

4.5 Destruction of Biological Specimens

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

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

5. References

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

WHO, Standard Operating Procedures for Clinical Investigators, TDR

SOP-02 Organizing a Site for Clinical Research.

SOP-03 Research Team: Role Definitions, Responsibilities and Task Delegation

SOP-09 Consent Process and Subject Informed Consent Form

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. Filing System

2. Location of Filing System

3. Annual Approval or Revision

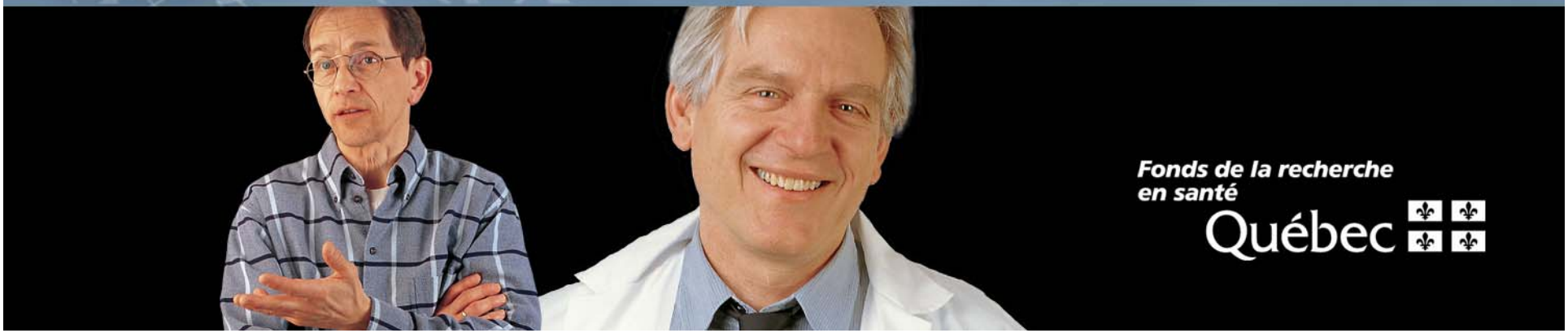
4. Specific Responsibilities of the Institution

5. Procedures

5. References

6. Appendices

Standard Operating Procedures (SOP)
SOP-19
Management of Biological Specimens: Collection and Storage



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- **Objective**
  - Describe the management of biological specimens, from their collection to their destruction, within the institution.

- **Collection of Biological Specimens**

  – The investigator/qualified investigator should:
    - Ensure that the equipment meets the requirements of the protocol
    - Ensure the safety and well-being of subjects during the collection of specimen
    - Identify as precisely as possible each specimen

  – List all specimens collected

    Keep with the essential documentation

- **Storage of Biological Specimens**
  - The investigator/qualified investigator or his delegate should:
    - Ensure that storage of biological specimens takes place in a secure an suitable environment
    - Establish a backup system in the event of a power or equipment failure
    - Establish an maintain controlled access for authorized personnel
    - Develop procedures to control physical access
    - Specify the storage time

- **Analysis of Biological Specimens**
  - Research personnel should be informed of any modification in laboratory norms or changes in calibration

- **Destruction of Biological Samples**
  - Requirements of the protocol and of the institution

  Keep documents with the essential documentation

Questions ?

Title	Preparation for Monitoring Visits
Code	SOP-20
Pages	6

History of Validated Versions

Date dd/mm/yyyy	Version	Pages	Description of Change

History of SOP Implementation

Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy

Approval of Site SOP

	Signature	Date dd/mm/yyyy

Table of Contents

1. Policy

This standard operating procedure (SOP) follows the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonisation (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/qualified 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 subjects.

2. Objective

The objective of this operating procedure is to guide the research team in its preparation for a monitoring visit.

3. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

4.1 Information

It is important to know that monitoring of the study is the responsibility of the sponsor/sponsor-investigator. 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.

ICH, 4.1.4 obliges the investigator/institution/qualified investigator to permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

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 subjects 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 subject participating in the study (nominative data) should leave the institution.

The elements described in this procedure are reference tools for the proper preparation for a monitoring visit.

4.2 Availability of the Investigator/Qualified Investigator

The investigator/qualified 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 02, section Study-related Essential Documents Management.

4.2.1 During monitoring visits, it is important that team members be available for discussions, for study updates and to answer questions.

4.2.2 It is strongly recommended that the investigator/qualified investigator be available at the time of visits, especially when issues concerning follow-up of subjects or the protocol are on the agenda.

4.2.3 The investigator/qualified investigator should be informed in advance of a monitoring visit.

4.3 Preparation for a Monitoring Visit

4.3.1 Ensure that the sponsor, the sponsor-investigator and the site 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.

4.3.2 Ensure the availability of all parties from different services, if applicable, at the time of the visit.

4.3.3 Ensure the identity of monitors upon arrival.

4.3.4 In order to respect confidentiality, ensure that monitors are accompanied by a team member during their visit to premises where confidential material is stored.

4.3.5 Verify that all the Case Report Forms required by the visit have been completed.

4.3.6 Verify that all patient files, data and source documents required by the monitoring visit are complete and available.

4.3.7 Verify that the essential documentation of the study is complete (i.e. recent correspondence, subject screening log, subject enrollment log, subject identification code lists, up-to-date medical licenses and documents related to the management of investigational products, biological products, medical devices or radiopharmaceuticals if applicable).

4.3.8 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 or radiopharmaceuticals are stored, if applicable.

4.3.9 Ensure that any questions or items that remained outstanding from the last monitoring visit, have been resolved.

4.3.10 Ensure, where a CRF or an electronic source document is used, that during the visit, the monitor has the necessary access.

4.3.11 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.

4.3.12 Have a suitable location equipped, if applicable, with the tools required for monitoring (telephone line, internet access, etc.).

4.4 **Documents Required for the visit**:

4.4.1 Case Report Forms and all related documents (i.e. laboratory reports, patient diaries, etc.);

4.4.2 Subject Informed Consent Form for each participating subject;

4.4.3 Subjects' medical files, if applicable;

4.4.4 Documentation related to the management of Investigational products biological products, medical devices or radiopharmaceuticals as well as decoding documentation;

4.4.5 Essential Study Documentation;

4.4.6 Documentation relative to biological specimens, if necessary;

4.4.7 All updates or new documentation that should be conveyed to the sponsor or sponsor-investigator;

4.4.8 All documentation related to the declaration of SAE/SARs submitted by or to the sponsor/sponsor-investigator or investigator/qualified investigator.

5. 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-03 Research Team: Role Definitions, Responsibilities and Task Delegation

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

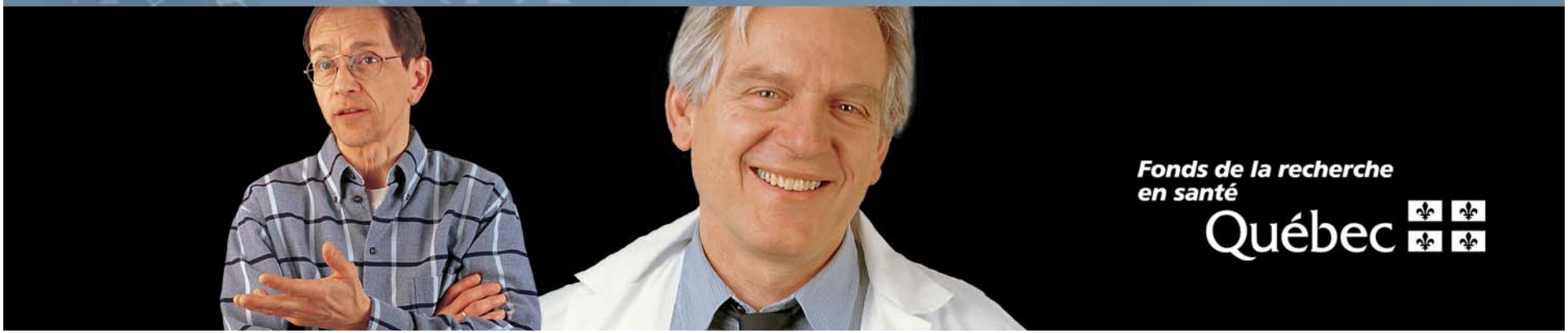
4. **Specific Responsibilities of the Institution**

5. **Procedures**

5. **References**

6. **Appendices**

Standard Operating Procedures (SOP)
SOP-20
Preparation for monitoring Visit



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SOP-20
Preparation for Monitoring Visit

- **Objective**
  - Guide the research team in its preparation for a monitoring visit

- **Information**

  – The investigator/qualified investigator must permit monitoring and auditing
  – The purpose of study monitoring is to verify that:
    - The rights and well-being of human subjects are protected
    - Reported data are accurate, complete and verifiable
    - The study is conducted in compliance with the protocol, GCP and applicable regulatory requirement

  No document (original or copy) which allows the identification of a subject participating in the study (nominative data) should leave the institution

- **Availability of the Investigator/Qualified Investigator**
  - He is entirely responsible for the study
  - He should be informed in advance of a monitoring visit

- **Preparation for a Monitoring Visit**
  - Ensure the availability of all parties
  - Ensure the identity of monitors upon arrival
  - Ensure that monitors are accompanied by a member team
  - Verify that all CRF are complete
  - Ensure that all patients files are complete and available
  - Verify that essential documentation is complete
  - Ensure a tracking document containing information
  - Have a suitable location for monitoring

- **Documents Required for the Visit**
  - Case Report Forms and all related documents
  - Subject Informed Consent Form
  - Subject's medical files
  - Document management for the Investigational product
  - Essential documentation
  - Documentation relative to biological specimens
  - All documentation related to the declaration of SAE/SARs

Questions ?

Title	Preparation for an Audit or Inspection Visit
Code	SOP-21
Pages	7

History of Validated Versions

Date dd/mm/yyyy	Version	Pages	Description of Change

History of SOP Implementation

Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy

Approval of Site SOP

	Signature	Date dd/mm/yyyy

Table of Contents

1. Policy

This standard operating procedure (SOP) follows the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonisation (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 subjects.

2. Objective

The objective of this operating procedure is to guide the research team in its preparation for an audit or inspection visit.

3. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

4.1 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 investigator/institution/qualified investigator must authorize the verification/audit and allow the appropriate regulatory organizations to carry out inspections, ICH 4.1.4.

4.2 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/qualified investigator's site.

The criterion most commonly cited for the selection of a site is the high number of subjects who participate in the study and 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 done on a site for no particular reason.

4.3 Preparation for a Verification/Audit or Inspection Visit

4.3.1 The investigator/qualified 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.

4.3.2 When there is a request for inspection, the investigator/qualified investigator should immediately inform the sponsor or the sponsor-investigator.

4.3.3 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.

4.3.4 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 02;

b) Case Report Forms (CRFs);

c) Informed Consent Forms for all subjects

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.

4.3.5 If there were retrospective entries or corrections, they should have been dated and signed by the person who made the entry or the correction.

4.3.6 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/qualified 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 subject participating in the study (nominative data) should leave the institution.

4.4 Conduct of a Verification/Audit or Inspection Visit

4.4.1 Verify the identity of the auditors or inspectors from the regulatory agency at the time of arrival.

4.4.2 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 ethics committee; compliance with the protocol; consent procedures; proof that every subject exists; eligibility of each subject; 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/qualified 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.

4.4.3 Following inspection by a regulatory agency, a written report is submitted to the sponsor or to the qualified 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").

4.4.4 The investigator/qualified 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, ICH 5.20.2) and the ethics committee that approved the trial, ICH 4.12.

5. 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-02 Organizing a Site for Clinical Research

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

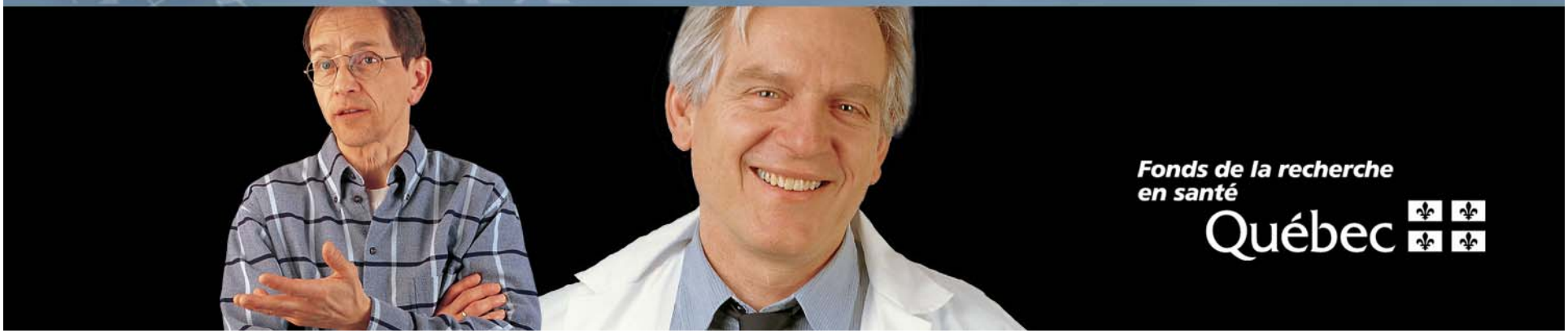
4. **Specific Responsibilities of the Institution**

5. **Procedures**

5. **References**

6. **Appendices**

Standard Operating Procedures (SOP)
SOP-21
Preparation for an Audit or Inspection Visit



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- **Objective**
  - Guide the research team in its preparation for an audit or inspection visit.

- **Information**
  - The verification/audit: a systematic and independent examination of the study-related activities and documents
  - The inspection: an official examination by regulatory authorities of documents, facilities, records and any other ressources
  - The investigator/qualified investigator must authorize the verification/audit

- **Scenario for a Verification/Audit or Inspection**
  - No particular reason is needed
  - Criteria most cited are:
    - High number of subjects
    - Problems with the site's data
    - An overly low or high rate of AE or AR

- **Preparation for a Verification/Audit or Inspection Visit**

  – The investigator/qualified investigator should:
    - Be informed in advance in writing of the visit
    - Inform the sponsor or sponsor-investigator when there is a request for inspection

    Keep communications with essential documentation

    It should be recalled that no document (original or copy) identifying a subject participating in the study (nominative data) should leave the institution

- **Preparation for a Verification/Audit or Inspection Visit**
  - The research team should verify that the following are available:
    - Essential documentation
    - Case Report Forms (CRFs) and Informed Consent Forms (ICFs)
    - Medical files and pharmacy files
    - Space for the visit
    - Photocopier and a phone
    - Research team and other departments involved
    - Arrangements to translate documents or to facilitate communication

- **Conduct of a Verification/Audit or Inspection Visit**
  - Verify the identity of the auditors/inspectors
  - Ensure that auditors/inspectors are accompanied by a member of the research team
  - Inspection visit:
    - Introductory meeting
    - Review of the study documentation
    - Visit of locations where study procedures are carried out
    - Meeting at the end of the visit

- **Conduct of a Verification/Audit or Inspection Visit**
  - Following inspection:
    - A written report is submitted to the sponsor or the qualified investigator
    - Implementation of corrective measures
  - Serious or persistent cases of non-compliance:
    - End the participation in the study

Questions ?

Title	Study Closure
Code	SOP-22
Pages	8

History of Validated Versions

Date dd/mm/yyyy	Version	Pages	Description of Change

History of SOP Implementation

Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy

Approval of Site SOP

	Signature	Date dd/mm/yyyy

Table of Contents

1. Policy

This standard operating procedure (SOP) follows the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonisation (ICH).

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 subjects.

2. Objective

The objective of this operating procedure is to guide the research team during the closing of a clinical study.

3. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP, ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

4.1 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 subject participating in the study has completed his 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 participating subjects 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 and the investigator/qualified investigator.

4.2 Monitoring

The sponsor or sponsor/investigator may have made provisions for a final monitoring visit once all participating subjects in the study have completed all the visits required by the protocol. For the closing of any study, the following steps should be completed:

4.2.1 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 17. 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 ethics committee. Follow-up procedures for the AE/SAEs and the AR/SARs that still ongoing at the time of the study closure should be in compliance with the protocol.

In compliance with the protocol and GCP, the investigator/qualified investigator should inform the sponsor/sponsor-investigator, the ethics committee and regulatory authorities, if applicable, of any unexpected SAE/SARs following the study closure that can be reasonably associated with the investigational product;

4.2.2 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;

4.2.3 All necessary corrections to the data, the source documents or the CRFs should be carried out according to the correction procedures described in SOP 23 and SOP 25;

4.2.4 The process of request for data clarification should be completed and confirmed by the investigator/qualified investigator;

4.2.5 All questions left outstanding from preceding monitoring, verification/audit or inspection visits should be resolved;

4.2.6 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.

4.2.7 Often the sponsor or sponsor-investigator will arrange a so-called closing visit to the site to ensure that all these procedures are completed.

4.2.8 Accounting for the investigational product, biological products, medical devices or radiopharmaceuticals, should be completed and, if applicable, the investigational product, its codes and the study-related material should be returned to the sponsor/sponsor-investigator.

4.3 Study-Related Material

4.3.1 At the end of the study, accounting for all investigational products, biological products, medical devices or radiopharmaceuticals, used and unused, should be recorded and this documentation retained with the essential documentation of the study, as described in SOP 18 and SOP 02.

4.3.2 When accounting/reconciliation is finished, and following the sponsor/sponsor-investigator's specifications, the investigational product, biological product, medical device or radiopharmaceutical should be returned or destroyed if permitted by the sponsor/sponsor-investigator. This destruction of the investigational product by the by local pharmacy should be done in accordance with the institution's written procedures regarding the destruction of investigational products. The codes of the investigational product should also be returned to the sponsor/sponsor-investigator or handled according to the requirements of the protocol.

4.3.3 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.

4.3.4 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/qualified investigator should ensure that they are stored in compliance with the protocol, SOP 19.

4.4 Ethics Committee and Regulatory Organizations

The ethics committee, 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/qualified investigator should inform the institution, if applicable, of the end of a study. The investigator/institution should also provide a summary of the study outcome to the, IRB/IEC as well as the reports required by regulatory organizations.

If the sponsor/sponsor-investigator submitted a clinical study application to Heath Canada, they should also be informed that the study has ended.

4.5 Clinical Study Report of study

As indicated in the guidelines of ICH E3, a study report is required for any study carried out on human subjects. 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/qualified investigator; the end date inclusion of subjects; the total number of subjects included; the number of subjects having completed the study; the number of subjects 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.

4.6 Archiving

Storage of all study documents should be planned at the beginning of the study in order to meet regulatory requirements.

4.6.1 Storage should guarantee safety and confidentiality of the information.

4.6.2 Storage should be adequately identified to the investigator/qualified investigator or sponsor-investigator.

4.6.3 In the case of a clinical study with medication or a medical device, the investigator / qualified 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.

4.6.4 In the case of a clinical study without drug or medical device, the investigator/qualified investigator should 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).

4.7 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/qualified investigator as well as the research team of this verification/audit or inspection. If the investigator/qualified investigator is notified of a verification/audit or an inspection, he should immediately notify the sponsor/sponsor-investigator, SOP 21.

5. 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, Structure and Content of Clinical Study Reports, ICH Topic **E3**, 1996.

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

Health Canada, Guidance for Industry**,** Adoption of ICH Guidance: Statistical Principles of Clinical Trials, ICH Topic **E9**, February 2003.

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

Quebec, 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-02 Organizing a Site for Clinical Research

SOP-17 Management of Adverse Events - Serious Adverse Events and Adverse Reactions - Serious Adverse Reactions.

SOP-18	Managing Investigational Products, Biological Products, Medical Devices or Radiopharmaceutical Under Study.
SOP-19	Management of Biological Specimens: Collection and Storage.
SOP-21	Preparation for an Audit or Inspection
SOP-23	Management of Data and Source Documents
SOP-25	How to Fill a Case Report Form and Modify Data.

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

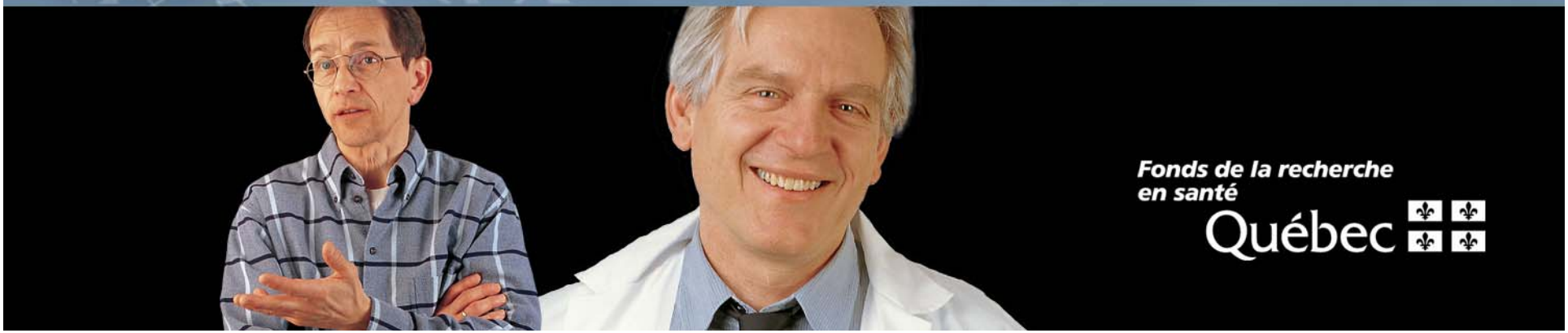
4. **Specific Responsibilities of the Institution**

5. **Procedures**

6. **References**

7. **Appendices**

Standard Operating Procedures (SOP)
SOP-22
Study Closure



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- **Objective**
  - Guide the research team during the closing of a clinical study.

- **Information**
  - Series of steps to be completed after the last subject has completed his last visit
  - Budgets verification:
    - Payments completed
  - Publication of results:
    - Participating sites are closed
    - All data analyzed

- **Monitoring**
  - The following steps should be completed:
    - Necessary corrections to CRF
    - Process of request for data clarification
    - Accounting of the investigational product

- **Study-Related Material**
  - Accounting for all investigational products used and unused
  - Following the sponsor/sponsor-investigator's specifications:
    - Investigational product is returned or destroyed
    - Used and unused CRFs and used and unused study – related material are returned or destroyed
  - Laboratory specimens should be returned to the sponsor/sponsor-investigator or stored on-site according to the protocol

- **Ethics Committee and Regulatory Organizations**
  - Should be informed of the end of the study
- **Clinical Study Report of study**
  - A study report is required for any study carried out on human subjects

- **Archiving**
  - In the case of clinical study with medication or a medical device:
    - 25 years and not to purge documents
  - In the case of a clinical study without drug or medical device :
    - « calendrier de conservation de l'établissement »

- **Verification/Audit and Inspection**
  - A visit is always possible even if the study is finished

Questions ?

Titre	Source Data and Document Management
Codification	SOP-23
Pages	8

History of Validated Versions

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History of SOP Implementation

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Approval of Site SOP

	Signature	Date dd/mm/yyyy

Table of Contents

1. Policy

Within the framework of the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonisation (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 procedure 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 subject's data precisely and that the said data are complete, accurate, precise and up-to-date.

3. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP, ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

4.1 **Confidentiality and Direct Access to Data and Source Documents**

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

4.1.2 Subjects authorize access to their data in the belief that all verified and collected information will be kept confidential by the sponsor, the sponsor-investigator, representatives authorized by sponsor/sponsor-investigator, auditors and inspectors of the regulatory authorities; reference SOP 09.

4.1.3 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 subjects and of the proprietary information of the sponsor/sponsor-investigator.

4.2 **Signature Sheet**

4.2.1 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 02.

4.3 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 participating subject 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/subject. Examples of communication: email, telephone messages, etc.;

e) Demographic data: subject'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 subject 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 handled and filed according to the applicable regulations.

4.4 Paper or Electronic Clinical Data

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

4.4.1 Reporting 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 subjects participating in the clinical study;

4.4.2 Re-examination of the clinical study data in agreement with the principles of the ICH;

4.4.3 Storage of data and source documents in agreement with SOP 02 and SOP 24;

4.4.4 The maintenance and accuracy of the data and the source documents for all participating subjects;

4.4.5 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 02;

4.4.6 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;

4.4.7 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 24;

4.4.8 Preserving a certified copy or the original for electronic data tracking.

4.5 Documentation of Source Data

4.5.1 All source data collected should be kept in the source document from the time of collection or observation.

4.5.2 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.**

4.6 Correction of Source Data

4.6.1 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 or appendix 1, *Instructions Specific to the Site,* should appear;

c) Corrections should be made, preferably, by the person who made the entry or by others authorized to do so (see item 4.2, signature document);

d) **The use of liquid corrector or correcting material is prohibited.**

4.7 Storage of Source Documents

The sponsor-investigator or the investigator/qualified investigator should:

4.7.1 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**;

4.7.2 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;

4.7.3 Clearly identify source documents (including the medical files of participating subjects) and the investigator's file for archiving, ICH 1.51 and 1.52;

4.7.4 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;

4.7.5 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;

4.7.6 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);

4.7.7 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.

5. References

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

Declaration of Helsinki, 2002

Food and Drug Administration (FDA), Electronic Records; Electronic Signatures Final Rule. 21 CFR Part 11, Federal Register Vol. 62, No 54, March 20, 1997.

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

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

Quebec, 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-02 Organizing a Site for Clinical Research.

SOP-09 Consent Process and Subject Informed Consent Form

SOP-24 Clinical Data Management, Paper or Electronic Format

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

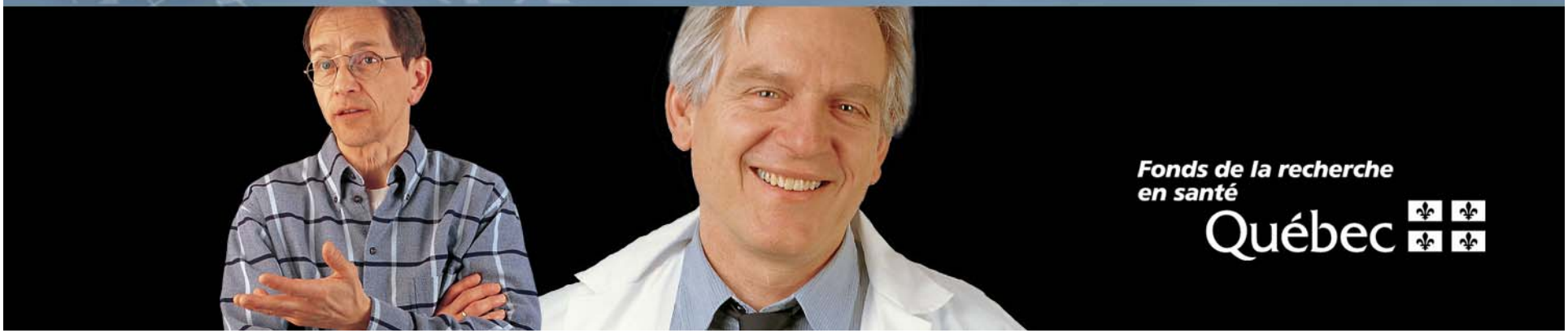
4. **Specific Responsibilities of the Institution**

5. **Procedures**

5. **References**

6. **Appendices**

Standard Operating Procedures (SOP)
SOP-23
Source Data and Document Management



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- **Objective**
  - 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 subject's data precisely and that the said data are complete, accurate, precise and up-to-date.

- **Confidentiality and Direct Access to Data and Source Documents**

  – Document or computerized system documentation to:
    - Make possible to compare the source data/documents and the CRF

  – Access to data:
    - All verified and collected information will be kept confidential

  – Confidentiality of the subject's identity

- **Signature Sheet**

  – Persons who have access
  – Persons who can enter or correct source data

  Document and keep with the essential documentation

- **Designation of Source Documents**
  - Process for obtaining informed consent (ICF), dated and signed
  - Medical file
  - Any communication between the various parties
  - Demographic data
  - Concomitant medications, current and previous
  - Inclusion, exclusion and randomization criteria
  - Dates of study visits

- **Designation of Source Documents**

  - Results of objective tests
  - Details of AEs or SAEs
  - Primary and secondary variables of effectiveness
  - Subject, randomization and CRF numbers

- **Paper or Electronic Clinical Data**

  – The sponsor-investigator or the investigator/qualified investigator is responsible for:
    - Re-examination of data
    - In the case of an electronic source data document, print, date and sign
    - Make track changes available

    Perceiving a certified copy or the original for electronic data tracking

- **Documentation of Source Data**
  - All source data should be kept in the source document
  - For documentation:
    - Date when the data were collected
    - Data written by hand should be legible and written with permanent ink
    - Use of liquid corrector or correcting material is prohibited
    - Work sheets or work forms can be created
    - Missing elements should be clearly reported
    - Data to be entered directly into the CRF should be mentioned in the protocol

- **Correction of Source Data**
  - A single line through the data to be corrected
  - Initialize and date the corrected data
  - The use of liquid corrector or correcting material in prohibited

- **Storage of Source Documents**

  – The sponsor-investigator or investigator/qualified investigator should:
    - In the case of study using a drug or medical device
      – 25 years and not to purge documents
    - In the case of data registered on thermal paper
      – Ensure that a dated and signed photocopy has been made
    - Identify clearly source documents and the file for archiving
    - In the case of study without drug or medical device
      – « calendrier de conservation de l'établissement »

Questions ?

Title	Clinical Data Management, Paper or Electronic Format
Code	SOP-24
Pages	8

History of Validated Versions

Date dd/mm/yyyy	Version	Pages	Description of Change

History of SOP Implementation

Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy

Approval of Site SOP

	Signature	Date dd/mm/yyyy

Table of Contents

1. Policy

Within the framework of the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonisation (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), wether 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 subjects.

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 (to be completed). 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 subject's data.

3. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

4.1 **Generalities**

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

4.1.1 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;

4.1.2 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;

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

4.1.4 Ensure the protection and security of clinical study data;

4.1.5 Ensure adherence to applicable regulatory requirements regarding confidentiality of the identity of subjects and their data by using unambiguous identification codes that allows identification of all data reported for each subject, ICH 5.5.5;

4.1.6 Precisely enter the data from the CRFs as required by the protocol. This data should correspond at every point with the data and source documents for all subjects participating in the clinical study;

4.1.7 Ensure that the electronic system used for clinical data management is valid and complies with regulatory requirements, ICH 5.5.3a, FDA and MSSS;

4.1.8 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;

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

4.1.10 Ensure that a summary of the study results is provided to the ethics committee, ICH 4.13;

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

4.2. Confidentiality and Direct Access to Clinical Data

4.2.1 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.

4.2.2 This document should be updated according to the roles and responsibilities delegated by the sponsor-investigator or the investigator/qualified investigator, as described in SOP 03.

4.3. Collection and Clinical Data Capture

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

4.3.2 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 .

4.3.3 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.

4.3.4 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:

4.3.5 Paper CRFs should be filled out according to SOP 25. 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 25. The CRF should be signed and dated by the investigator or his delegate, as described in the delegations/signatures document SOP 03 and in section 8.3 item 8.3.24 in ICH-GCP.

4.3.6 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.

4.3.7 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 03.

4.3.8 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:

4.3.9 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 5.5.3a. and FDA Guidance for Industry: Computerized System used in Clinical Trials.

4.3.10 Only persons authorized by the sponsor-investigator or the investigator/qualified 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).

4.3.11 In the case of online data entry, both methods of data entry are applicable.

4.3.12 The sponsor-investigator or the investigator/qualified investigator should ensure that those using the clinical data processing system are trained in the use of the electronic system and follow the instructions described in Appendix 1 of SOP 02.

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

4.4 Quality Control and Modifications to Clinical Data

4.4.1 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.

4.4.2 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.

4.4.3 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.

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

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

4.4.6 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/qualified investigator or his delegate. The original document should be retained by the sponsor/sponsor-investigator and a copy should be retained by the investigator/qualified investigator, ICH 8.3.15.

4.4.7 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.

4.5 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

4.5.1 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.

4.5. The IDMC should have written operating procedures and maintain written records of the minutes of all their meetings, ICH 5.5.2.

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

4.6 Storage of Clinical Data

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

4.6.2 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, C.05.012 (4), of **25 years.**

4.6.3 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).

4.6.4 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.

5. References

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

Food and Drug Administration (FDA), Electronic Records; Electronic Signatures Final Rule. 21 CFR Part 11, Federal Register Vol. 62, No 54, March 20, 1997.

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

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

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.

SCDM, Good Clinical Data Management Practices, Version 3, September 2003.

SOP-02 Organizing a Site for Clinical Research.

SOP-03 Research Team: Role Definitions, Responsibilities and Task Delegation

SOP-25 How to Fill In a Case Report Form and Modify Data

SOP-26 Security and Confidentiality of Data

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

4. **Specific Responsibilities of the Institution**

5. **Procedures**

6. **References**

7. **Appendices**

Standard Operating Procedures (SOP)
SOP-24
Clinical Data Management, Paper or Electronic Format

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- **Objectives**
  - 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.
  - Ensure that the collection, follow-up, control and confidentiality of all clinical data entered in a CRF, paper or electronic, conforms 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 subject's data.

- **Generalities**

  – The sponsor-investigator who is responsible for the management of clinical data for the study should:
    - Develop instructions in the case where data management is performed directly by a service within the institution
    - Manage authorizations for access to clinical data
    - Ensure the protection and security of data
    - Ensure confidentiality of the identity of subjects

- **Generalities**

  – The sponsor-investigator who is responsible for the management of clinical data for the study should:
    - Precisely enter data from the CRF
    - Ensure that the electronic system used for clinical data management is valid
    - Retain the original or a certified copy of the certified data backup

- **Confidentiality and Direct Access to Clinical Data**

  – Document identifying person authorized to access

- **Collection and Clinical Data Capture**

  – Study information should be recorded, processed, stored, interpreted and verified
  – Data capture can be done by single or double data entry
  – A system for tracking data entry and modification should be available

  Paper CRFs

  Electronic CRFs

- **Quality Control and Modifications to Clinical Data**
  - Quality control systems should be:
    - Applied to each stage
    - Established during the data capture
    - Applied once data capture is completed
  - CRF modifications
    - Data clarification form (DCF)
  - Tracking system

- **Storage of Clinical Data**

  – In the case of a clinical study using a drug or medical device:
    - 25 years

  – In the case of a clinical study without drug or medical device:
    - « calendrier de conservation »

Questions ?

Title	How to Fill In a Case Report Form and Modify Data
Code	SOP-25
Pages	7

History of Validated Versions

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History of SOP Implementation

Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy

Approval of Site SOP

	Signature	Date dd/mm/yyyy

Table of Contents

1. Policy

Within the framework of the principles inherent in Good Clinical Practice (GCP) of the International Conference on Harmonisation (ICH) and published by Health Canada, this standardized operating procedure (SOP) describes how a case report form (CFR) 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 subjects 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 standard 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. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP, ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

4.1 **Generalities**

The sponsor-investigator or the investigator/qualified 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.

4.2 **Recording Data on CRFs**

4.2.1 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/qualified investigator or his delegate.

4.2.2 CRFs should be completed only by authorized persons. This authorization should be documented, as defined in SOP 03.

4.2.3 The sponsor-investigator or the investigator/qualified 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 04.

4.2.4 For reasons of security and confidentiality of subjects and their data, only non-ambiguous subject identification codes should be used for identification of all data reported in the CRF for each subject, ICH 5.5.5 and SOP 26.

4.2.5 The CRF should be completed as soon as the data are available or during the subject's evaluation or follow-up visit.

4.2.6 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.

4.2.7 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.

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

4.3 Modifying CRF Data

4.3.1 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.

4.3.2 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 CRFs

4.3.3 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.

4.3.4 **The use of corrector fluid or other correction material is not authorized**.

4.3.5 Any modifications made to paper CRFs should be justified, reviewed, authorized and approved by the investigator/qualified investigator. To confirm this approval, it is recommended that the investigator/qualified 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.

4.3.6 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 24. The original DCF is retained by the sponsor/sponsor-investigator and one copy given to the investigator/qualified investigator, ICH 8.3.15.

Electronic CRFs

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

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

4.3.9 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.

4.3.10 The sponsor-investigator or the investigator/qualified investigator should maintain a copy of the certified data backup, ICH 5.5.3.f.

4.3.11 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.

4.4 Confirming and Signing CRFs

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

4.4.2 The CRF should be signed and dated by the sponsor-investigator or the investigator/qualified investigator, as defined by the delegation/signature form. reference SOP 03. This delegation should be retained with the essential study documents, SOP 02.

5. References

Health Canada, Guidance for Industry, Good Clinical Practice: Consolidated guideline, ICH Topic **E6**, 1997. -3

Food and Drug Administration (FDA), Electronic Records; Electronic Signatures Final Rule. 21 CFR Part 11, Federal Register Vol. 62, No 54, March 20, 1997. -1

Food and Drug Administration (FDA), Guidance for Industry: Computerized systems used in clinical trials, April 1999, -2

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. -1

SOP-02 Organizing a Site for Clinical Research.

SOP-03 Research Team: Role Definitions, Responsibilities and Task Delegation

SOP-04 Site Research Team: Competence, Knowledge and Training

SOP-24 Clinical Data Management, Paper or Electronic Format

SOP-26 Security and Confidentiality of Data

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

4. **Specific Responsibilities of the Institution**

5. **Procedures**

6. **References**

7. **Appendices**

Standard Operating Procedures (SOP)
SOP-25
How to Fill in a Case Report Form and Modify Data

Fonds de la recherche en santé Québec

- **Objectives**
  - 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.
  - 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.

- **Generalities**

  – Data should be recorded, handled, stored, interpreted and verified

- **Modifying CRF Data**

  – Tracking mechanism

  Paper CRF

  – The use of corrector fluid or other correction material is not authorized
  – Corrections made to the CRF after it is retrieved from the site
    - Use the data clarification form (DCF)

- **Modifying CRF Data**

  Electronic CRFs
  - Modification or addition to the information
  - Electronic system and tracking guarantee
  - Copy of the certified data backup
  - Validation and secure data transfer

- **Confirming and signing CRFs**

Questions ?

Title	Security and Confidentiality of Data
Code	SOP-26
Pages	7

History of Validated Versions

Date dd/mm/yyyy	Version	Pages	Description of Modification

History of SOP Implementation

Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy	Version	Date dd/mm/yyyy

Approval of Site SOP

	Signature	Date dd/mm/yyyy

Table of Contents

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 Harmonisation (ICH), 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 subjects.

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. Site Responsibilities

3.1 **The Research Centre Director or his delegate is responsible for:**

3.1.1 Approving or updating site SOPs that will be used in the institution according to internal institutional validation procedures;

3.1.2 Informing members of the Ethics Committee that this site SOP will be implemented within the institution;

3.1.3 Implementing and managing this site SOP within the institution;

3.2 **The Sponsor-Investigator or Investigator/Qualified Investigator is responsible for:**

3.2.1 Ensuring that, during the clinical study, the research team, which will be under his/her supervision will comply with this site SOP.

3.3 **Under the supervision of the Research Centre Director or his delegate, the person responsible for site SOPs should:**

3.3.1 At the time of implementation of each SOP, ensure that clinical study personnel at the institution are trained in procedures and comply with this SOP.

3.3.2 In the event that an SOP is modified, provide training for institutional clinical study personnel regarding the change(s) and ensure their compliance with any changes.

4. Procedures

4.1 **Generalities**

4.1.1 The sponsor-investigator or the investigator/qualified 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 03.

4.1.2 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, subject 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.

4.2 **Data Security**

4.2.1 A mechanism for control of access to secure premises should be established and documented, SOP 03 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.

4.2.2 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 8.3.24.

4.2.3 **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.

4.2.4 **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 03;

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/qualified investigator, SOP 03;

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 03.

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 03;

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.

4.3 Data confidentiality

As mentioned in SOP 23 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. 3; 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.

4.3.1 In conformity with the requirements of the applicable regulations concerning protection of personal information, confidentiality of files in which subjects may be identified must be protected, ICH 2.11 and the MSSS “Cadre global de gestion des actifs informationnels – Volet Sécurité”.

4.3.2 A subject who authorizes access to data relating to him should be reasonably assured that the sponsor/sponsor-investigator, the investigator/qualified investigator, representatives authorized by the sponsor/sponsor-investigator, the ethics committee and auditors and inspectors of the regulatory authorities have all taken precautions so that verified and collected data remain confidential, ICH 5.15.1 and SOP 09.

4.3.3 Confidentiality of data should be maintained and respected in the course of and after the clinical study, SOP 10

5. 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.

Food and Drug Administration (FDA), Electronic Records; Electronic Signatures Final Rule. 21 CFR Part 11, Federal Register Vol. 62, No 54, March 20, 1997.

SOP-02 Organizing a Site for Clinical Research

SOP-03 Research Team: Role Definitions, Responsibilities and Task Delegation

SOP-09 Consent Process and Subject Informed Consent Form

SOP-23 Management of Data and Source Documents

APPENDIX 1 INSTRUCTIONS SPECIFIC TO THE SITE (EXAMPLES)

1. **Filing System**

2. **Location of Filing System**

3. **Annual Approval or Revision**

4. **Specific Responsibilities of the Institution**

5. **Procedures**

6. **References**

7. **Appendices**

Standard Operating Procedures (SOP)
SOP-26
Security and Confidentiality of Data

Fonds de la recherche en santé Québec

- **Objectives**
  - Describe the process that ensures the quality, integrity and confidentiality of clinical data collected within the framework of a clinical study.
  - Describe procedures for the protection of data from any risk of accidental or involuntary destruction.

- **Generalities**
  - The sponsor-investigator or investigator/qualified investigator is responsible for authorizing access to the clinical data
  - Authentification of the person who has access to the data constitutes the most important aspect of security

- **Data Security**

  - Access to secure premises
  - Tracking document
  - Physical security
  - Logical security
    - Authorized access to members of the research team
    - Physical access or electronic access to data
    - System administrator
    - Cancellation of authorized access
    - Identification code
    - Plan for saving and recovering data
    - Standardized procedures for logical security

- **Data Confidentiality**
  - Release of nominative information
  - Confidentiality of files
  - Subject and authorization to data access

Questions ?

www.frsq.gouv.qc.ca

500, rue Sherbrooke Ouest, bureau 800
Montréal (Québec) H3A 3C6

Téléphone (514) 873-2114
Télécopieur (514) 873-8768
courrier@frsq.gouv.qc.ca

Fonds de la recherche en santé
Québec