Vancouver CoastalHealth Research Institute

# STANDARD OPERATING PROCEDURE

## Safety Reporting Requirements for Research Involving Participants

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### Site Approval

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| **Date** | 10-May-2021 | **Date** | 10-May-2021 |

### Authorization to Adopt

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## Document History

| Version | Summary of Changes Made | Effective Date |
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| 1 | Original document. | 09-JUL-2010 |
| 2 | This version has undergone extensive revision for administrative, educational, regulatory, and clinical changes by individual content experts and the VCHRI SOP Committee. This document has also had substantial formatting, grammatical and glossary updates. It has been classed as a rewritten document. | 10-JAN-2016 |
| 3 | This version has undergone revision for administrative, education, regulatory and clinical changes by individual content experts and VCHRI SOP Committee. There have been substantial changes made throughout the SOP and is therefore classed as a rewritten document. References and definitions have been updated. | 01-Jun-2021 |
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## 1. PURPOSE

1.1. This Standard Operating Procedure (SOP) outlines the processes for recording and reporting Adverse Events, Adverse Drug Reactions and Serious Adverse Drug Reactions, Medical Device Incidents and Unanticipated Problems to the Research Ethics Board (REB), Sponsor/Sponsor-Investigator (if applicable), and Regulatory Authorities, including Health Canada, US Food and Drug Administration (FDA), and the European Medicines Agency (EMA).

## 2. SCOPE

2.1. This SOP is applicable to all interventional Clinical Trials/Studies undertaken at the Institution, and to those Research Team Members responsible for receiving, reviewing, processing, and submitting Adverse Events, Adverse Drug Reactions, Serious Adverse Drug Reaction and Medical Device Incidents and Unanticipated Problems reports.

2.2. Serious Adverse Drug Reaction reporting is in accordance with the International Conference on Harmonisation (ICH) Guidelines E2A, *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*, and applicable national regulations and guidance.

## 3. RESPONSIBILITIES

3.1. The Principal Investigator or Sponsor-Investigator is responsible for ensuring that the Adverse Event, Adverse Drug Reaction, Serious Adverse Drug Reaction and Medical Device Incidents reporting meet all of the applicable regulatory, International Conference on Harmonisation (ICH), Good Clinical Practice (GCP), Sponsor, and local requirements. The Principal Investigator or Sponsor-Investigator must ensure the Protocol outlines how Adverse Events and Adverse Drug Reactions, Serious Adverse Drug Reactions and Medical Device Incidents will be defined, documented and monitored at the Clinical Trial/Study site, and subsequently reported to the appropriate parties.

3.2. Delegated Research Team Members may be involved in capturing the Adverse Events, Adverse Drug Reactions, Serious Adverse Drug Reactions, Medical Device Incidents and Unanticipated Problems in the source documents and Case Report Forms. However, the ultimate responsibility lies with the Principal Investigator or Sponsor-Investigator.

## 4. RELATED SOPS/DOCUMENTS

4.1. International Conference on Harmonisation (ICH) Guidelines E2A, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
4.2. VCHRI Tool: Patient Adverse Event Assessment Form
4.3. VCHRI Tool: Serious Adverse Event Safety Letter Tracking Log

## 5. DEFINITIONS

*Note: There is considerable variation in the terminology utilized for Adverse Event reporting. It is recommended that Research Team Members be familiar with the terms used in the study specific Protocol and in the applicable regulatory reporting jurisdiction. The terms and definitions below (and in the VCHRI glossary) are consistent with Health Canada.*

5.1. **Adverse Drug Reaction (ADR):** In the pre-approval clinical experience, with a new Investigational Product or its new usages, particularly as the therapeutic doses may not be established: all noxious and

unintended responses to an Investigational Product related to any dose should be considered adverse drug reactions. A causal relationship between the Investigational Product and an Adverse Event is at least a reasonable possibility, that is, the relationship cannot be ruled out.

5.1.1. For Clinical Trials/Studies including marketed drug products (e.g. Phase IV): 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.

5.2. **Adverse Event (AE):** Any untoward medical occurrence in a research Participant administered an Investigational Product which does not necessarily have a causal relationship with this Investigational Product. An Adverse Event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporarily associated with the use of an Investigational Product, whether or not related to the Investigational Product.

5.2.1. **Local (Internal) Adverse Event:** Those adverse events experienced by a research Participant enrolled by the Investigator(s) at one or more centres under the jurisdiction of the REB of Record. In the context of a single-centre Clinical Trial/Study, all Adverse Events would be considered local AEs.

5.2.2. **Non-Local (External) Adverse Event**: From the perspective of the REB overseeing one or more centres engaged in a multi-centre Clinical Trial, external adverse events are those adverse events experienced by research Participants enrolled by the Investigator(s) outside the REB's jurisdiction.

5.3. **Medical Device Incident:** An incident related to a failure of a medical device or a deterioration in its effectiveness, or any inadequacy in its labelling or in its directions for use that has led to the death or a serious deterioration in the state of health of a patient, user or other person, or could do so were it to recur. A serious deterioration in the state of health means a life-threatening disease, disorder or abnormal physical state, the permanent impairment of a body function or permanent damage to a body structure, or a condition that necessitates an unexpected medical or surgical intervention to prevent such a disease, disorder or abnormal physical state or permanent impairment or damage.

5.4. **Serious Adverse Drug Reaction (SADR):** An adverse drug reaction that requires in-patient hospitalization or prolongation of existing hospitalization, that causes congenital malformation, that results in persistent or significant disability or incapacity, that is life threatening, or that results in death.

5.5. **Serious Adverse Event (SAE)**: Any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgement, is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

5.6. **Serious Unexpected Adverse Drug Reaction (SUADR)**: 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. Reportable to Health Canada.

5.7. **Unanticipated Problem**: Any incident, experience or outcome that meets all the following criteria:

- Unexpected (in terms of nature, severity or frequency) given the research procedures that are described in the Protocol-related documents, such as the REB-approved research protocol and Informed Consent documents, or the Investigator's Brochure; and the characteristics of the research Participant population being studied; and
- Related or possibly related to participation in the research (meaning there is a reasonable possibility that the incident, experience or outcome may have been caused by the Investigational Product or procedures involved in the research; and
- Suggests that the research places Participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

5.8. See also VCHRI Glossary of Terms.

## 6. PROCEDURE

### 6.1. General

6.1.1. Adverse Events (AE) means any adverse occurrence in the health of a Clinical Trial/Study Participant who is administered a drug, that may or may not be caused by the administration of the drug and includes an adverse drug reaction. Non-related AEs are not considered as Adverse Drug Reactions and are not reportable. However, all AEs must be captured in source documents and Case Report Forms (CRFs), as described in the Protocol.

6.1.2. Ensure that the Protocol outlines recording and reporting requirements for Adverse Drug Reactions, Serious Adverse Drug Reactions and Medical Device Incidents.

6.1.3. *Post-marketing products*: Report serious unexpected Adverse Drug Reactions and Medical Device Incidents to the Institution and it is recommended to report them to the Marketed Health Products Directorate (MHPD) at Health Canada.

6.1.4. *Sponsor-Investigator initiated studies*: Sponsor-Investigators should develop risk-based Adverse Events reporting guidelines and for multi-site trials and distribute to sites involved in the Clinical Trial/Study.

6.1.5. It is important to continually educate and support research Participants about recognizing potential Adverse Events, Adverse Drug Reactions and Medical Device Incidents, and the importance of reporting them to the Principal Investigator, Sponsor-Investigator or Clinical Research Coordinator at study visits and/or during telephone contact.

6.1.6. The Principal Investigator is responsible for establishing a process for receiving and processing safety reports received from the Sponsor or Sponsor-Investigator at the Clinical Trial/Study site level. Submit applicable safety reports/summaries and follow-up information to the local REB as per local requirements. Maintain all safety reports and associated REB correspondence in the Clinical Trial/Study files. Your procedure must include and address the following:

6.1.6.1. As soon as the Clinical Trial/Study site is aware of a new safety report from the Sponsor/Sponsor-Investigator, this must be brought to the attention of the Principal Investigator. The Principal Investigator must then notify all relevant Research Team Members, and others associated with the Clinical Trial/Study, as needed.

6.1.6.2. Document evidence of staff training/awareness of safety information with research team training documentation.

## 6.2. Recording Adverse Events, Serious Adverse Events, Adverse Drug Reactions, Medical Device Incidents and Unanticipated Problems

6.2.1. Document the details of any serious Adverse Events, Serious Adverse Events or Medical Device Incidents at each study visit/telephone contact, using the Protocol-defined terminology, at the Clinical Trial/Study level.

6.2.2. Anyone within the research team who becomes aware of a Serious Adverse Event, Serious Adverse Drug Reaction or Unanticipated Problem must report this information to the Principal Investigator or Sponsor-Investigator within the appropriate timelines.

6.2.3. It is good practice to maintain a site-level log, database or tracking system for all Protocol-specified Serious Adverse Drug Reaction reports occurring in the Clinical Trial/Study.

6.2.4. The Sponsor or Sponsor-Investigator is responsible to keep records of all Adverse Events in respect of the Investigational Product used in a Clinical Trial/Study, whether those events occur inside or outside of Canada, including information that specifies the indication for use and the dosage form of the drug at the time of the Adverse Event.

## 6.3. Principal Investigator Reporting Responsibilities

6.3.1. To the Sponsor: As soon the Principal Investigator is made aware, he/she is responsible for submitting Serious Adverse Events, Serious Adverse Drug Reactions, or Medical Device Incidents to the Sponsor or Sponsor-Investigator, within the time specified in the Protocol, using the appropriate forms. Use the Sponsor's or Sponsor-Investigator's specified reporting procedures and instructions and follow up with additional information as soon as it becomes available. It is critical that any relationship between a serious event and the Investigational Producent is indicated in the submission form.

6.3.1.1. The immediate and follow-up reports should identify study Participants by unique code numbers assigned to the Clinical Trial/Study Participant rather than by the Participant's name, personal identification number and/or address.

6.3.2. To the REB: The Principal Investigator is required to inform the REB of local Adverse Events, Serious Adverse Event, Adverse Drug Reactions that are deemed to be Unanticipated Problems (unexpected, related/possibly related and involving greater risk) as per local REB procedures.

6.3.3. Maintain all relevant Adverse Event documentation, reports, and communications, including faxes, telephone calls, and instructions given, in the study files.

6.3.4. The Principal Investigator must document the need to break the randomization code, and communicate to the appropriate authorities, as needed.

## 6.4. Sponsor/Sponsor-Investigator Reporting Responsibilities

6.4.1. To Regulatory Agencies: The Sponsor/Sponsor-Investigator is responsible for reporting to the Regulatory Authorities, unless otherwise stated in the research contract or other documentation.

6.4.2. For multi-centre trials: The Sponsor or Sponsor-Investigator is responsible for distributing expedited reporting of all Serious Unexpected Adverse Drug Reactions to all Investigators collaborating in the Clinical Trial/Study for submission to local ethics committees, as appropriate, within 15 calendar days.

6.4.2.1. Such expedited reports should comply with the applicable regulatory requirements and with the ICH guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2A) (ICH E6 5.17.2)

6.4.2.2. The Sponsor/Sponsor-Investigator should also submit to the Regulatory Agency all safety updates and periodic reports, as required by applicable regulatory requirements.

### 6.5. Mandatory Problem Reporting Timelines for Drugs

6.5.1. Reporting to Health Canada is a Sponsor/Sponsor-Investigator responsibility. The timelines for reporting to Regulatory Authorities begins when the Sponsor or Sponsor-Investigator or Contract Research Organization (CRO) becomes aware of the event or reaction.

6.5.2. Serious Unexpected Adverse Drug Reactions are subject to expedited reporting to Health Canada. Submit all Serious Unexpected Adverse Drug Reaction reports within fifteen (15) calendar days to Health Canada, whether the event is fatal or non-life threatening, and whether or not the event occurred inside or outside of Canada.

6.5.3. Serious but expected reactions, and Serious Adverse Events that are considered unrelated to the study Investigational Product should not be reported to Health Canada.

6.5.4. If the event is fatal or life-threatening, Health Canada must be advised of the event within seven (7) calendar days following awareness of the event. Additionally, advise the VCHRI Clinical Research Quality Assurance Specialist.

6.5.4.1. In cases where the event is fatal or life-threating, the Sponsor/Sponsor-Investigator must submit a complete report to Health Canada within eight (8) calendar days from the date that the first notification (initial report) was filed.

6.5.4.2. Follow up reports of fatal or life-threating reactions must include an assessment of the importance of the event at the implications of any findings, including relevant previous experience with the same or similar drugs.

6.5.4.3. The Sponsor should expedite reporting of all Serious Unexpected Adverse Drug Reactions to all concerned Principal Investigators, Institutions, and the REB where required.

6.5.5. Post marketing products (e.g., Phase IV): Submit reports, as per applicable national regulations.

### 6.6. Mandatory Problem Reporting Timelines for Medical Devices

6.6.1. The timelines for reporting to Regulatory Authorities begins when the Sponsor or Sponsor-Investigator or Contract Research Organization (CRO) becomes aware of the Medical Device Incident.

6.6.2. Investigational medical device: The manufacturer is to file a report within ten (10) calendar days to Health Canada, following awareness of an event that has occurred in Canada, and caused a fatal outcome or serious deterioration in the health of a Participant, user or another person. The obligation to report promptly to Health Canada, an event which has occurred abroad, applies only if the manufacturer has notified Regulatory Authorities in the country at issue, of its intention to adopt remedial actions or if these Regulatory Authorities have asked the manufacturer to do so.

6.6.2.1. Additionally, advise the VCHRI Clinical Research Quality Assurance Specialist in this case.

6.6.3. Non-fatal Serious Adverse Event/Incident

6.6.3.1. Investigational medical device: The manufacturer is to file a report within thirty (30) calendar days after becoming aware of the event that has occurred in Canada and did not cause death or serious deterioration to the health of a Participant, user or another person, but may do so if it reoccurs. The obligation to promptly report to Health Canada an event which has occurred abroad applies only if the manufacturer has notified regulatory authorities in the country at issue of their intention to adopt remedial actions, or if these regulatory authorities have asked to do so.

6.6.3.2. Additionally, advise the VCHRI Clinical Research Quality Assurance Specialist.

**6.7. Assessment of Severity and Causality by a Qualified Physician Who is a Principal Investigator or Sub-Investigator for the Clinical Trial/Study**

6.7.1. Clinically assess the event and provide the Participant with appropriate medical care.

6.7.2. Prepare/receive Individual Case Safety Reports (ICSR), including minimum information for the submission of a report to regulatory authorities, i.e., at least one identifiable Participant, one identifiable reporter, one serious reaction, and one suspect product.

6.7.3. Assess the report for severity, seriousness, expectedness, and causality/relatedness:

6.7.3.1. Severity (intensity): Events/reactions are usually classified as mild, moderate or severe. General definitions for severity categories are often provided in the Protocol, and specific definitions for particular types of events (e.g. for mild, moderate or severe hepatitis) may also be provided depending on the Clinical Trial/Study. The terms serious and severe are not synonymous.

6.7.3.2. Seriousness: Events/reactions are classified as serious if associated with effects threatening the life or physiological functions of a Participant. Seriousness criteria include death, hospitalization (initial or prolonged), persistent or significant disability, life threatening, congenital anomaly, or medically relevant adverse reaction. The seriousness of a reaction determines if it should be reported to the Sponsor or Sponsor-Investigator or regulatory authorities.

*NOTE: A grade of severe is not the same as serious. Serious is a specific term used in determining whether SAEs must be reported to a Sponsor, Sponsor-Investigator or regulatory authority. SAEs, regardless of severity, demand immediate action and attention.*

6.7.3.3. Expectedness: Events/reactions are classified as unforeseen or unexpected if, by nature or intensity, are not reported in the Investigator Brochure, or Product Monograph. The Sponsor or Sponsor-Investigator is responsible for determining if the reported Adverse Event is to be considered unforeseen or unexpected.

6.7.3.4. Causality/Relatedness: Events/reactions are assessed, according to the Principal Investigator/Sub-Investigator's clinical judgment, if there is a reasonable doubt as to causal relationship. Attribution may be related, not related, or unknown. Adverse events that have been judged to have at least a possible relationship with the Investigational Product (drug, natural health product or device) are always called Adverse Drug Reactions (ADRs).

*NOTE: Causality refers to the likelihood and extent that the Investigational Product being studied contributed to the development of an Adverse Event and involves medical decision making and discretion. An Investigator who has the medical expertise should be making the causality determination. If the Investigator determines that an AE is related to the Investigational Product, additional reporting may be required by the Sponsor.*

6.7.4. Consult with Sponsor or Sponsor-Investigator, as/if required. Final assessment must be signed off by Principal Investigator/Sub-Investigator.

### 6.8. Submission to Regulatory Authorities by Sponsor or Sponsor–Investigator

6.8.1. Prepare a CIOMS safety form (or MedWatch for US reports) for submission to Health Canada, as per the Protocol or risk-based safety reporting plan. Unblind the related unexpected Serious Adverse Drug Reaction reports for the purposes of expedited reporting, especially for reports submitted in Europe.

6.8.2. Ensure that the unblinding information is limited to biometrics personnel, and other normally unblinded study staff, as needed.

6.8.3. Submit related unexpected Serious Adverse Drug Reaction reports to the Regulatory Authorities, as per national regulations, for the Clinical Trial Application (CTA), or the Investigational New Drug Application (IND).

6.8.4. Submit periodic, quarterly or annual reports, as per national regulations.

### 6.9. Management of Adverse Events and Serious Adverse Events with no Investigational Products

6.9.1. In the case of Clinical Trial/Studies without an Investigational Product, it is recommended that the Sponsor or Sponsor-Investigator and Principal Investigator follow the same procedures for collecting clinical data related to Adverse Events and Serious Adverse Events, assessing and reporting to the REB.

## 7. REFERENCE(S)

BC Freedom of Information and Protection of Privacy Act, [RSBC 1996, c. 165], as amended from time to time.

Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, TCPS 2 (2018), December 2018.

Department of Justice (Canada), Personal Information Protection and Electronic Documents Act (PIPEDA), last amended June 21, 2019, current to February 15, 2021.
Government of Canada, Medical Devices Regulations, Part 3 Medical Devices for Investigational Testing involving Human Subjects, SOR/98-282, May 7, 1998; last amended December 16, 2019, current to February 15, 2021.

Government of Canada, Natural Health Products Regulations, Part 4 Clinical Trials Involving Human Subjects, SOR/2003-196, June 5, 2003; last amended September 28, 2020, current to February 15, 2021.

Health Canada, Food and Drug Act, Part C, Division 5, Drugs for Clinical Trials Involving Human Subjects, (Schedule 1024), June 20, 2001.

Health Canada, Guidance Document: Part C, Division 5 of the Food and Drug Regulations "Drugs for Clinical Trials Involving Human Subjects". GUI-0100. August 20, 2019.

Health Canada, Guidance for Industry – Reporting Adverse Reactions to Marketed Health Products, March 2, 2011

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

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), ICH Harmonised Guideline, Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice, E6(R2), November 9, 2016.

Network of Networks (N2) Management of Investigational Products SOP010_09, Effective 15 May 2021.

Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-operation Scheme, Annexe 11, Computerised Systems.

US Food and Drug Administration, Code of Federal Regulations, Title 21, Volume 1:

- Part 11, Electronic Records; Electronic Signatures, (21CFR11).
- Part 50, Protection of Human Subjects, (21CFR50).
- Part 54, Financial Disclosure by Clinical Investigators, (21CFR54).
- Part 56, Institutional Review Boards, (21CFR56).
- Part 312, Investigational New Drug Application (21CFR312).
- Part 314, Applications for FDA Approval to Market a New Drug (21CFR314).

US Department of Health and Human Services, Code of Federal Regulations, Title 45, Part 46, Protection of Human Subjects (45CFR46).

US Department of Health and Human Services, Guidance for Industry: Computerized Systems Used in Clinical Investigations, May 2007.

## 8. ATTACHMENT(S)

None.