Title	**Serious Adverse Drug Reaction Reporting in Clinical Trials**
SOP Code	SOP012_08
Effective Date	15-May-2019

Site Approval/Authorization to Adopt

Name and Title of Local Personnel (typed or printed)	Signature	Date dd/Mon/yyyy

1.0 PURPOSE

This Standard Operating Procedure (SOP) outlines the processes for reporting adverse drug reactions (ADRs), and serious adverse drug reactions (SADRs) to the Research Ethics Board (REB), study sponsor (if applicable), and regulatory authorities, including Health Canada, US Food and Drug Administration (FDA), and the European Medicines Agency (EMA).

2.0 SCOPE

This SOP is applicable to all interventional clinical studies undertaken at the site, and to those clinical research personnel responsible for receiving, reviewing, processing, and submitting adverse drug reaction, and serious adverse drug reaction reports.

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 guidances.

3.0 RESPONSIBILITIES

The Sponsor-Investigator or Qualified Investigator (QI)/Investigator is responsible for ensuring that the adverse event, adverse reaction, and serious adverse reaction reporting meet all of the applicable regulatory, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), sponsor, and local requirements.

Unless otherwise indicated, any or all parts of this procedure may be delegated to appropriately trained study team members, but remain the ultimate responsibility of the Sponsor-Investigator or Qualified Investigator (QI)/Investigator.

4.0 DEFINITIONS

Adverse Event (AE): 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.

Adverse Drug Reaction (ADR): In the pre-approval clinical experience with a new medicinal/natural health product or its new usages, particularly as the therapeutic doses may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug/natural health product 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.

For marketed medicinal/natural health products: a response to a drug/natural health product 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.

Serious Adverse Drug Reaction (SADR): An adverse drug/natural health product 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 Unexpected Adverse Drug Reaction: A serious adverse drug/natural health product 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/natural health product.

Unexpected Adverse Drug Reaction: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator Brochure for an unapproved investigational product or package insert/summary of product characteristics, e.g. Product Monograph for an approved product).

See Glossary of Terms.

5.0 PROCEDURE

5.1 General

5.1.1 It is essential to continue to educate subjects about adverse events/reactions, and the importance of reporting them to the coordinator or investigator at study visits and/or during telephone contact.

5.1.2 Adverse events include all events related and not related to the investigational drug/natural health product. Non-related adverse events are NOT considered as adverse reactions, and are NOT reportable; however, all AEs must be captured in source documents and Case Report Forms (CRFs), as described in the protocol.

5.1.3 Ensure that the protocol outlines recording and reporting requirements for adverse drug reactions (ADRs) and serious adverse drug reactions (SADRs).

5.1.4 Postmarketing (Phase IV) studies: Report adverse reactions, as per the regulations and requirements of the Marketed Health Products Directorate (MHPD) (Canada).

5.2 Recording Serious Adverse Reaction Reports

5.2.1 Document the details of any adverse events/reactions at each study visit/telephone contact, using the protocol-defined terminology. Anyone within the study research team who becomes aware of a serious adverse reaction must report this information to the Qualified Investigator (QI)/Investigator.

5.2.2 The minimum information for the submission of a report to regulatory health authorities includes at least one identifiable patient/subject, one identifiable reporter, one serious reaction, and one suspect product.

5.2.3 Qualified Investigator/Investigator: Break the blinding code, if necessary, to ensure optimal subject care. Refer to study protocol (or equivalent document) for detailed un-blinding procedure.

5.2.4 Collect and follow prospective and retrospective Exposure *in Utero* (EIU) reports, in order to obtain outcome information. The absence of an adverse reaction does not preclude collection of this data.

5.2.5 Maintain an adverse reaction log/database/tracking system for all protocol-specified serious adverse reaction reports occurring in the clinical trial.

5.3 Reporting Responsibilities of Qualified Investigator/Investigator (External Sponsor)

5.3.1 Forward serious adverse event and serious adverse reaction reports directly to the Sponsor or Sponsor-Investigator, immediately (within 24 hours) of learning about a serious adverse reaction, or as otherwise specified in the protocol using the appropriate forms. Means of reporting include online, telephone and/or fax according to the sponsor's specified reporting procedures and instructions. Follow up with additional information, as soon as it becomes available.

5.3.2 The Sponsor or Sponsor-Investigator is responsible for reporting to the regulatory authorities (unless otherwise stated in the study contract, or other document).

5.3.3 Inform the Research Ethics Board (REB)/Independent Ethics Committee (IEC) of all serious and unexpected adverse reactions, or as per local REB/IEC procedures.

5.3.4 Document the need to break the randomization code, and communicate to the appropriate authorities, as needed.

5.3.5 Maintain all adverse reaction documentation, reports, and communications, including faxes, telephone calls, and instructions given, in the study files.

5.3.6 The Sponsor or Sponsor-Investigator is responsible for distributing expedited reports to each investigator (of a multi-centre trial) for submission to local ethics committees, as appropriate, within 15 days. Each investigator receives blinded serious adverse reaction reports.

5.3.7 Establish a procedure for receiving and processing safety reports received from the sponsor. Submit all safety reports/summaries and follow-up information to the local REB/IEC. Maintain all safety reports and associated REB correspondence in the study files.

5.4 Reporting Responsibilities of Sponsor-Investigator

5.4.1 The Sponsor or Sponsor/Investigator must comply with the regulatory requirements of Health Canada regarding prompt reporting of unexpected

serious adverse reactions, and for which a causal relationship with the investigational product cannot be ruled out.

5.4.2 Lead Investigator (multi-centre trial, no external sponsor): Distribute expedited reports to each investigator for submission to local ethics committees, as appropriate, within 15 calendar days. Each investigator receives blinded serious adverse reaction reports.

5.4.3 Establish a procedure for receiving and processing safety reports received from the Lead Investigator. Submit all safety reports/summaries and follow-up information to the local REB/IEC. Maintain all safety reports and associated REB/IEC correspondence in the study files.

5.5 Mandatory Problem Reporting Timelines

5.5.1 The timeline for reporting to Health Authorities begins when the Sponsor or Sponsor-Investigator or CRO learns about the reaction.

5.5.2 Submit preliminary information on fatal and life-threatening reactions from a clinical trial within 7 calendar days, verbally if appropriate, and complete written follow-up submitted within another 8 calendar days.

5.5.3 Submit all other SUADR reports within 15 calendar days.

5.5.4 Post marketing studies: Submit reports, as per applicable national regulations.

5.5.5 Fatal and life-threatening Mandatory Problem Reporting of SADRs:

- Investigational drug/natural health product: File initial report within 7 calendar days following awareness of the event. Provide Health Canada with a detailed follow-up report, within 8 calendar days from the date that the initial report was filed.
- Investigational medical device: File report within 10 calendar 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. 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.

5.5.6 Non-fatal SADRs:

- Investigational drug: File report within 15 calendar days following awareness of the event.
- Investigational medical device: File report within 30 calendar 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. 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.

5.6 Assessment of Severity and Causality by a qualified physician who is a QI/Investigator or Sub-Investigator for the trial

5.6.1 Clinically assess the event and provide the subject with appropriate medical care.

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

5.6.3 Assess the report for severity, seriousness, expectedness, and causality/relatedness. See descriptions below:

- 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 study. The terms serious and severe are not synonymous.
- Seriousness: Events/reactions are classified as serious if associated with effects threatening the life or physiological functions of a subject. 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.
- 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.
- Causality/Relatedness: Events/reactions are assessed, according to the investigator's clinical judgement, 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 called Adverse Drug Reactions (ADRs).

5.6.4 Confer with Sponsor or Sponsor-Investigator, as/if required. Sign off the final assessment.

5.7 Submission to Regulatory Authorities

5.7.1 Prepare a CIOMS I form (or MedWatch for US reports) for submission to national health authorities (Health Canada, FDA, EMA, etc.), as appropriate. Unblind the related unexpected SADR Reports for the purposes of expedited reporting, especially for reports submitted in Europe.

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

5.7.3 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).

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

5.8 Management of AEs and SAEs in Studies with No Investigational Products

5.8.1 In the case of clinical studies without an investigational product, it is recommended that the Sponsor or Sponsor-Investigator and QI/Investigator follow the same procedures for collecting clinical data related to adverse events and serious adverse events, assessing and reporting to their REB/IEC.

6.0 REFERENCES

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

Government of Canada, Medical Devices Regulations, Part 3 Medical Devices for Investigational Testing involving Human Subjects, SOR/98-282, May 7, 1998; last amended February 13, 2017, current to March 20, 2017.

Government of Canada, Natural Health Products Regulations, Part 4 Clinical Trials Involving Human Subjects, SOR/2003-196, June 5, 2003; last amended October 17, 2018, current to February 14, 2019.

Health Canada, Guidance Document for Industry - Reporting Adverse Reactions to Marketed Health Products, March 2, 2011.

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.

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 (2014), December 2014.

Department of Justice (Canada), Personal Information Protection and Electronic Documents Act (PIPEDA), last amended November 1, 2018, current to February 13, 2019.

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

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.

7.0 REVISION HISTORY

SOP Code	Effective Date	Pages	Summary of Changes
SOP12_01	24-Mar-2008	8	original version
SOP12_02	15-May-2009	8	5.1.4: delete – duplicate of 5.1.1; renumber old 5.1.5 to new 5.1.4; 5.5.5: revise wording for submission deadlines; 6.0: revised reference #1 title for clarity; minor typographical corrections.
SOP12_03	15-May-2010	9	Revised terminology to reflect Division 5 vs. non-Division 5-regulated trials: QI/Investigator and Sponsor or Sponsor-Investigator; revised terminology: REB/IEC; revised patient(s) to subject(s); updated agency name to EMA; 5.8 new section on trials with no investigational products.
SOP12_03.1	15-May-2010	9	6.0 Added Medical Device Regulations to reference list.
SOP012_04	15-May-2011	9	Changed SOP numbers to three digits in header/footer, title box, and section 7; 6.0: re-ordered references; added TCPS to references; updated ICH E2A reference format.
SOP012_04.1	15-May-2011	9	3.0: Added in: Unless otherwise indicated 5.6: Added in: by a qualified physician who is a QI/Investigator or Sub-Investigator for the trial 5.6.4 : Deleted : Qualified Investigator or authorized medically qualified designee:

SOP Code	Effective Date	Summary of Changes
SOP012_05	15-May-2013	Removed total number of pages from header and section 7.0; 6.0: added NHP regulation and marketed product reporting references.
SOP012_06	15-May-2015	Added ‘Authorization to Adopt’; update reference versions for MDR, NHP, TCPS; added drug to title; revised to ‘drug’ reaction and ADR throughout document; 2.0: added interventional; 5.7.3: added regulatory agency, re-worded.

SOP Code	Effective Date	Summary of Changes
SOP012_07	15-May-2017	5.2.2: Added regulatory; 5.4.2, 5.5.5, 5.5.6: added calendar; updated MDR, NHP, ICH E6, and PIPEDA references; changed Annex 11 to FDA Guidance.
SOP012_08	15-May-2019	References updated. Minor clarifications with acronyms.