***Management and Reporting of Adverse Events, Serious Adverse Events, Unanticipated Adverse Device Effects, and Unanticipated Problems***

1. **PURPOSE**

This Standard Practice Guideline (SPG) describes the procedures, processes, and responsibilities for identifying, assessing, recording, and reporting Adverse Events (AEs), Serious Adverse Events (SAEs), Unanticipated Adverse Device Effects (UADEs), and Unanticipated Problems (UaPs).

(**MANDATORY LANGUAGE**)

1. **SCOPE**

This Standard Practice Guideline applies to all clinical trial staff, including the Principal Investigator (PI), Sponsor-Investigator (SI), Co-Investigator(s) (Co-I), Study Coordinator(s), and other research professionals that may be involved in the identification, management and reporting of AEs, SAEs, UADEs and UaPs. (**MANDATORY LANGUAGE**)

*[Optional: Insert any additional details necessary to further define the scope of this SPG]*

1. **POLICY**

**Good Clinical Practices (ICH GCP)**

**Principal Investigator (PI)**

This Standard Practice Guideline (SPG) supports the Good Clinical Practice (ICH GCP) guidelines established by the International Council on Harmonization (ICH), Section 4.11.2:

*Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.*

In addition, ICH Section 4.11.1 provides guidance on Serious Adverse Events (SAE) and states that: *all SAEs should be reported immediately to the sponsor, except for those SAEs that the protocol or other document identifies as not needing immediate reporting.*

**Sponsor-Investigator (SI):**

Per ICH section 5.16, the sponsor is responsible for the ongoing safety evaluation of the investigational product(s) (5.16.1).

Per section 5.16.2 the sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favourable opinion to continue the trial (5.16.2).

Per section 5.17.1 Adverse Drug Reaction Reporting the sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

**FDA Regulation(s)** (if applicable)

**Principal Investigator (PI)**

Code 21 of Federal Regulations 312.53(c)(1) (vi(e)) indicates that a commitment by the investigator is required that he/she *will report to the sponsor adverse experiences that occur in the course of the investigation(s), in accordance with 312.64 (Investigator reports).*

Similarly, IDE regulation 812.150(a)(1) indicates: *an investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.*

21 CFR 812.150(7)(1) provides additional guidance regarding reporting of unanticipated adverse device effects. *Unanticipated adverse device effects.* *A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.*

Investigators are also responsible for assuring IRB reviews are completed per 21 CFR 312.66:

*An investigator shall assure that an IRB that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.*

**Sponsor-Investigator (SI):**

Per code 21 Code of Federal Regulations Part 312.32 (c)(1):

*The sponsor must notify FDA and all participating investigators in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15*

*calendar days after the sponsor determines that the information qualifies for reporting under paragraph (c)(1)(i), (c)(1)(ii), (c)(1)(iii), or (c)(1)(iv) of this section. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.*

Additionally, 312.32 (2) states that *the sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor’s initial receipt of the information*.

**University of Michigan Institutional Review Board (IRBMED)**

According to the University of Michigan Institutional Review Board (IRB), *It is a federal and university requirement that investigators of all human subjects research (whether FDA-regulated or not) report to the IRB any ‘unanticipated problems involving risks to the subjects or others' (hereafter referred to as ‘unanticipated problems’).*

In addition, the IRB requires clinical research teams to follow the IRBMED Standard AE Reporting Guidelines or the clinical research team’s own IRB approved study-specific reporting guidelines for reporting internal AEs to the IRB. The reporting obligations for external AEs to the IRB are different from these and the IRBMED has unique reporting guidance for these as well.

**Additional Regulations or Policies** [ ]  **N/A**

**(MANDATORY LANGUAGE)**

*[Optional: Insert any additional project, department, sponsor, institution, state, or federal policies that apply]*

1. **DEFINITIONS**

ADVERSE EVENT (AE): Any experience or abnormal finding that has taken place during the course of a research project and was harmful to the subject participating in the research, or increased the risks of harm from the research, or had an unfavorable impact on the risk/benefit ratio. The event may or may not be caused by an intervention (e.g., headache following spinal tap, death from the underlying disease, car collision). Adverse Events also include psychological, social, emotional, and financial harms.

CO-INVESTIGATOR (Co-I): Any individual member of the clinical trial team designated and supervised by the principal investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions.

DATA and SAFETY MONITORING BOARD (DSMB): An appointed independent group consisting of at least three (3) members assigned to conduct interim monitoring of accumulating data from research activities to assure the continuing safety of research participants, relevance of the study question, appropriateness of the study, and integrity of the accumulating data. Membership should include expertise in the relevant field of study, statistics, and research study design.

EXPECTED EVENT**:** An event that is expected in that it has been addressed or described in one or more of the following: Informed consent document(s) for this study, IRB application for this study, grant application or study agreement, protocol or procedures for this study, investigators' brochure or equivalent (for FDA regulated drugs or devices), DSMB Reports, published literature, other documentation, or characteristics of the study population.

INSTITUTIONAL REVIEW BOARD (IRB):

An independent body constituted of medical, scientific, and non-scientific members that is responsible for ensuring 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 (ICH-GCP R2 definition)

INVESTIGATIONAL DEVICE EXEMPTION (IDE):

Approval by FDA for investigational device exemption (IDE) permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully across state and international boundaries for the purpose of conducting investigations of that device. (FDA 21CRF812)

INVESTIGATIONAL NEW DRUG APPLICATION (IND): a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms “investigational drug” and “investigational new drug” are deemed to be synonymous for purposes of this part.

IND means an investigational new drug application. For purposes of this part, “IND” is synonymous with “Notice of Claimed Investigational Exemption for a New Drug.” (FDA part 312)

INVESTIGATOR'S BROCHURE (IB): The Investigator's Brochure is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance

with, many key features of the protocol, such as the dose, dose frequency/interval,

methods of administration, and safety monitoring procedures. (ICH-GCP R2 definition)

INTERNATIONAL COUNCIL ON HARMONISATION (ICH): A joint initiative involving both regulators and research-based industry representatives of the European Union, Japan, and the USA in scientific and technical discussions of the testing procedures required to assess and ensure the safety, quality and efficacy of medicines

LIFE-THREATENING ADVERSE EVENT: An adverse event is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patients or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

MEDWATCH FORM 3500A: FDA Form for clinically important safety information and reporting serious problems with human medical products.

RELATED ADVERSE EVENT: An Adverse Event believed to be caused by a procedure, drug, biologic or device used in the clinical trial.

SERIOUS ADVERSE EVENT (SAE): Any adverse experience occurring at any dose or level of participation that results in any of the following outcomes: death, a life-threatening experience, hospitalization, or prolongation of existing hospitalization, a persistent or significant disability or capacity, or a congenital anomaly or birth defect.

SEVERITY OF AE: An assessment regarding the intensity of an Adverse Event (rating the event mild, moderately severe, severe, life threatening or fatal). Severity is independent of seriousness assessments.

SPONSOR: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

SPONSOR-INVESTIGATOR: 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. (ICH-GCP R2 definition)

SUSPECTED ADVERSE REACTION (SUSAR) (21 CFR 312.32 (a)): Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, ‘reasonable possibility’ means there is evidence to suggest a causal relationship between the drug and the adverse event.

UNANTICIPATED ADVERSE DEVICE EFFECT (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan of application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

UNANTICIPATED PROBLEM INVOLVING RISKS TO SUBJECTS OR OTHERS (UPIRSO / UaP): Often referred as an Unanticipated Problem. An unanticipated problem may be either an actual harmful or unfavorable occurrence or any development that potentially increased the likelihood of harm occurring in the future. Assessment Criteria:

1. Unanticipated Severity:  The nature, severity, or frequency of the event(s) or information was NOT expected, given descriptions in the study documents or the characteristics of the subject population being studied.
2. Related:  There is a reasonable possibility that the procedures involved in the research caused the problem.
3. Increased Risk:  The event(s) or information suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized (including physical, psychological, economic, or social harm).

Note: Some of the definitions above were obtained from the IRBMed Glossary. These definitions were current as of 01-Oct-2022 and are subject to change. Please see the [IRBMed Glossary](https://research.medicine.umich.edu/office-research/institutional-review-boards-irbmed/guidance/glossary) for the most current definitions and additional guidance.”

(**MANDATORY LANGUAGE**)

*[Optional: Insert any additional definitions for technical or special terms used within the Standard Practice Guideline that may not be familiar to the lay reader]*

1. **ROLES AND RESPONSIBILITIES**

**Principal Investigator**

An individual filling the role of Principal Investigator (PI) is responsible for making sure AEs, SAEs, UADEs, and UaPs occurring during a clinical trial are appropriately reviewed, recorded, and reported. The PI shall be responsible for the following activities: (**MANDATORY LANGUAGE**)

* Protects the rights, safety, and welfare of subjects participating in the clinical trial
* Designates the mechanism that will be used for monitoring subjects and identifying AEs, SAEs, UADEs, and UaPs
* Manages AEs, SAEs, UADEs, and UaPs and follows up until resolved or the follow-up requirements of the protocol have been met
* Determines the relatedness, expectedness, severity and seriousness of the AE, SAE, UADE, or UaP
* Determines whether the AE meets the definition of a SUSAR, when the clinical trial is FDA-regulated
* Ensures that AEs, SAEs, UADEs, and UaPs are reported to the sponsor (and to the FDA if the clinical trial is investigator-initiated), to the IRB, and to the Data Safety Monitoring Board, if applicable
* Ensures that the IND/IDE Safety Report information is reported to the co-investigators on the clinical trial
* Submits notification of AEs, SAEs, UADEs, and UaPs to the DSMB, local and central IRBs, sponsor, etc., This includes the preparation and submission of annual and/or progress reports.
* Reports SAEs utilizing Medwatch in FDA-regulated clinical trials
* Manages and reviews safety reports received from the sponsor and submits to the IRB as deemed necessary
	+ Submits amended/updated protocols or other documents received from the sponsor to the IRB as necessary
* Delegates activities to other research team members, as appropriate

(**MANDATORY LANGUAGE**)

*[Optional: Insert any additional details regarding the responsibilities of the Principal Investigator/Designee*]

**Sponsor-Investigator**

An Investigator filling the role of the Sponsor-Investigator assumes the responsibilities of the Principal Investigator as described above and in addition, is responsible for the following: **(MANDATORY LANGUAGE)**

* Ensures that the IND/IDE Safety Report information is reported to the FDA according to the timelines specified within pertinent federal regulations
* Ensures that all unexpected, fatal, or life-threatening suspected adverse reactions are reported to the FDA as soon as possible and within the timeframes specified in the applicable federal regulations
* Amends the protocol and/or the Investigator’s Brochure (IB), etc. when serving as the Sponsor-Investigator ([See reporting guidelines from the IRBMED](https://research.medicine.umich.edu/office-research/institutional-review-boards-irbmed/guidance/adverse-events-aes-other-reportable-information-and-occurrences-orios-and-other-required-reporting/adverse-event-reporting) below)
* Ensures that the IND/IDE Safety Report information is reported to all participating investigators on the clinical trial
* Notifies FDA and all participating investigators in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under paragraph FDA CFR21.32 (c)(1)(i), (c)(1)(ii), (c)(1)(iii), or (c)(1)(iv) of this section. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.
* Delegates activities to other research team members, as appropriate
* Work with the MICHR IND/IDE Investigator Assistance Program (MIAP) team for all FDA IND and IDE trials

(**MANDATORY LANGUAGE**)

 *[Optional: Insert any additional details regarding the responsibilities of the Sponsor- Investigator*]

**Study Coordinator(s)/Designee**

An individual filling this role may be responsible for the following activities: (**MANDATORY LANGUAGE**)

* Screens for AEs, SAEs, UADEs, and UaPs on an ongoing basis using subject-reported history, physical examination, laboratory data, chart review and other available data for each patient enrolled in a clinical trial
* Provides follow-up information on all AEs, SAEs, UADEs, and UaPs until resolution or an appropriate end point is reached
* Manages and maintains documentation related to AEs/SAEs/UADEs/UaPs submissions to the IRB and other regulatory authorities
* Facilitates the management, review, and submission of external sponsor safety reports to the IRB

(**MANDATORY LANGUAGE**)

*[Optional: Insert any additional details regarding the responsibilities of the Study Coordinator/Designee*]

**Co-Investigator(s)**

An individual filling this role may be responsible for the following activities:

* Notifies the PI and applicable research team members of any AEs, SAEs, UADEs or UaPs reported during interactions with clinical trial subjects
* Determines the relatedness, expectedness, severity and seriousness of the AE, SAE, UADE, or UaP

(**MANDATORY LANGUAGE**)

*[Optional: Insert any additional details regarding the responsibilities of the Co-Investigator/Designee]*

**Additional Roles and Responsibilities** [ ]  **N/A**

**(MANDATORY LANGUAGE)**

*[Optional: Insert any additional role(s) and responsibilities that apply to this SPG]*

1. **PROCEDURE**

**Assessing AEs/SAEs/UADEs/UaPs**

*[Describe the process for assessing AEs/SAEs/UADEs/UaPs.]*

**Managing AEs/SAEs/UADEs/UaPs**

*[Describe the process for managing AEs/SAEs/UADEs/UaPs, based on the follow-up requirements specified in the protocol or other study documentation.]*

**Recording and Maintaining Documentation of AEs/SAEs/UADEs/UaPs**

*[Describe the process for recording AEs/SAEs/UADEs/UaPs, including determination of relatedness, expectedness, severity, and seriousness.]*

**Reporting Non-Serious Adverse Events**

*[Describe the process for reporting non-serious AEs. This should include the process for notification of the DSMB, local and central IRBs, sponsor, etc.]*

**Reporting Serious Adverse Events**

*[Describe the process for reporting SAEs. This should include the process and timeframes for notification of the DSMB, local and central IRBs, sponsor, etc. Please see the IRBMED link below for reporting requirements.]*

**Reporting Unanticipated Adverse Device Effects**

*[Describe the process for reporting UADEs. This should include the process and timeframes for notification of the DSMB, local and central IRBs, sponsor, FDA, etc.]*

**Reporting Unanticipated Problems**

*[Describe the process for reporting UaPs. This should include the process for notification of the DSMB, local and central IRBs, sponsor, etc. ]*

**External Safety Reporting**

*[Describe the process for the management, review, and submission of External Safety Reports. This may include the process for notification to the DSMB, local and central IRBs, sponsor, etc.]*

**Additional Procedures** [ ]  **N/A**

*[Optional: Insert any additional relevant procedures. Provide enough detail to ensure the procedure is consistently carried out, without providing so much detail that violations occur due to normal or expected variations in the work.]*

1. **REFERENCES**

FDA - Guidance for Industry and Investigators: Safety Reporting Requirements of INDs and BA/BE (Bioavailability and bioequivalence) Studies:

<https://www.fda.gov/media/85124/download>

FDA - Investigational New Drug (IND) or Device Exemption (IDE) Process (CBER) <http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/InvestigationalNewDrugINDorDeviceExemptionIDEProcess/>

FDA - Investigational Device Exemptions - Definitions:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.3>

FDA - IRB Functions and Operations:

[CFR - Code of Federal Regulations Title 21 (fda.gov)](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=56)

FDA – Investigation New Drug -General provisions 312.32 (c) (1)

[eCFR :: 21 CFR Part 312 -- Investigational New Drug Application](https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312)

FDA - 312.53 Selecting investigators and monitors

[CFR - Code of Federal Regulations Title 21 (fda.gov)](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=312.53)

FDA – 312.66 Responsibilities of Sponsors and Investigators

[CFR - Code of Federal Regulations Title 21 (fda.gov)](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.66)

FDA - IDE regulation 812.150

[eCFR :: Title 21 of the CFR -- Food and Drugs](https://www.ecfr.gov/current/title-21)

FDA - Reporting Serious Problems to FDA:

[Reporting Serious Problems to FDA | FDA](https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program/reporting-serious-problems-fda)

International Council for Harmonisation:

<http://www.ich.org/>
<https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf>

MIAP services:

<https://az.research.umich.edu/medschool/policies/university-michigan-medical-school-policy-requirement-use-michr-miap-services>

US Department of Health and Human Services Office for Human Research Protections - Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events:

<http://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems>

University of Michigan IRBMED - Adverse Events (AEs), Other Reportable Information and Occurrences (ORIOs), and Other Required Reporting:

<https://research.medicine.umich.edu/office-research/institutional-review-boards-irbmed/guidance/adverse-events-aes-other-reportable-information-and-occurrences-orios-and-other-required-reporting/other-reportable-information-or-occurrence-orio>

University of Michigan IRBMED - Adverse Events (AEs), Other Reportable Information and Occurrences (ORIOs), and Other Required Reporting, External Adverse Event (AE) Reporting- External Events:

<https://research.medicine.umich.edu/office-research/institutional-review-boards-irbmed/guidance/adverse-events-aes-other-reportable-information-and-occurrences-orios-and-other-required-reporting/adverse-event-reporting/external-adverse-event-ae-reporting>

University of Michigan IRBMED - Study - Specific Adverse Event (AE) Reporting Plans:

<https://az.research.umich.edu/medschool/guidance/study-specific-ae-reporting>

(**MANDATORY LANGUAGE**)

*[Optional: Insert any additional SPG references]*

1. **APPENDICES**

(**MANDATORY LANGUAGE**)

*[Optional: Insert any additional SPG appendices]*