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## Part 1: Introduction



### **Inherent Complexities of Client Safety and Adverse Events**

Participant safety is a broad topic that cuts across all aspects of Good Clinical Practice (GCP) as is discussed in the document the [ICH Guideline for Industry: Clinical Safety Data Management](#). Among other issues, ensuring participant safety encompasses protocol design, quality-assurance monitoring, government regulations, and ethical issues. It may also involve the use of clinical judgment, and entail situations/decisions on which no two clinicians may be in complete agreement. As a result, new researchers may feel frustrated when questions arise about participant safety.

This module focuses on ways of protecting participants' safety and well-being as well as how adverse events should be recorded and reported for clinical studies.

Because of the complexity of the topic, this module cannot cover every participant safety issue that might arise in a clinical trial. Researchers are advised to seek further guidance as needed from the study investigator or other knowledgeable team members. The role of investigators in protecting the safety and well-being of research participants is discussed further in this module.



# Key Points About the Protection of Participant Safety

- The obligation to protect the well-being of study participants does not end when a study receives Institutional Review Board (IRB) or Data and Safety Monitoring Board (DSMB) approval, or when a participant signs the informed consent form. The interests of study participants must be safeguarded at all times—and by many entities—throughout a clinical research study.
- Ultimately, no single individual or institution can provide complete protection for trial participants. A systematic plan must be followed for each trial to ensure that everyone involved understands and fulfills his or her responsibilities.
- Research team members with adequate knowledge of clinical trials, statistics, and the clinical disorder and the Investigational Product being studied must review the study data regularly to ensure that events are properly interpreted and reported.
- Ongoing communication among all study staff is an essential part of ensuring participant safety.

## [Who is responsible for assuring the safety of study participants?](#)

### Investigator

In accordance with ICH GCP, the investigator or a sub-investigator that is a qualified physician (or dentist, when appropriate) is responsible for all trial-related medical decisions. The investigator must ensure that adequate medical care is provided to a subject for any adverse events and inform the subject when care is needed for an intercurrent illness that the investigator becomes aware of. (ICH GCP E6(R2), 4.3)

## [Who is responsible for assuring the safety of participants in studies of investigational new drugs?](#)

In studies conducted under the [Investigational New Drug](#) (IND) regulations, responsibility for ensuring compliance with FDA regulations on participant safety rests with the sponsor of the IND under which the study is conducted.

### **The investigator is responsible for:**

"protecting the rights, safety, and welfare of study participants under the investigator's care."

The U.S. Food and Drug Administration (FDA) requires the investigator to:

"promptly report to the IRB ([Institutional Review Board](#)) all unanticipated problems involving risk to human subjects or others"

and to report to both the sponsor and the IRB:

"any serious adverse event, whether or not considered drug related and must include an assessment of whether there is a reasonable possibility that the drug caused the event" .

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## Responsibilities of Role Players in CTN

### Role of the Lead Investigator



For each CTN protocol, the [Lead Investigator](#) (LI) is responsible for the accurate documentation, investigation, and follow-up of all safety reports. In addition, the LI must ensure that each Institutional Review Board (IRB) involved in the study is fully informed of safety issues that may arise from the protocol.

### **Role of the Site Principal Investigator**

In CTN studies, the [Node Principal Investigator](#) (PI) is responsible for assuring the safety of study participants at research sites within his or her Node. This includes responsibility for assuring the proper monitoring of study progress and the evaluation and reporting of adverse events at the Node.

For any given protocol, the Node PI may delegate any of these tasks to other appropriately qualified persons, such as the Protocol Principal Investigator (below), affiliated with his or her Node. Such delegation of authority should be formally designated in a delegation of responsibilities log.

### **Role of the Protocol Site Principal Investigator**

In CTN studies, the [Protocol Principal Investigator](#) (PI) is charged with assuring the safety of study participants at the research sites within the Node for which he or she is responsible.

The Site PI is also expected to be knowledgeable about the policies of all local IRBs concerning the reporting of adverse events and to adhere to these policies.



### **Role of the Study Medical Monitor**

In CTN studies, the Study Medical Monitor is appointed by the Lead Investigator and is responsible for reviewing reports of adverse events (AEs) and serious adverse events (SAEs) that are submitted by study sites. He or she must ensure that participants receive good clinical care and that safety concerns are identified quickly and addressed appropriately. The Study Medical Monitor must:

- Review each AE/SAE and consider whether it may be related to study participation.
- Determine if the safety event meets reportability criteria as per federal regulations.
- Propose changes in the [protocol](#) or [consent form](#), if warranted by the severity or frequency of adverse events.

## Role of the NIDA Study Medical Officer

In CTN studies, the NIDA [Study Medical Officer](#) has overall responsibility for evaluating, monitoring, and reporting on the safety of participants.



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## Ongoing Informed Consent

As discussed in the [Informed Consent module](#), informed consent is a process as well as a legally required document. Throughout any study, researchers must continue to keep study participants informed about any new information with regard to the safety of the product and, in particular, about any new developments or findings that may affect participants' willingness to remain in the study.

Researchers must:

- Inform participants, in a language that they understand, about emerging developments in the study, related studies utilizing the same Investigational Product(s), or pertinent pre-clinical studies that are significant to participant safety.
- Offer participants the opportunity to ask questions about the information they have been given.
- Ensure that participants understand they may withdraw from the study at any time and cannot be penalized for doing so.
- Be satisfied that each participant understands what he or she has been told and is making a voluntary, informed decision to remain in the study.



## Part 2: Participant Safety & Adverse Events

### [What is an adverse event?](#)



The Good Clinical Practice (GCP) guidelines of the International Council for Harmonization (ICH) define an adverse event (AE) as: “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment” (ICH GCP, E6(R2) 1.2).

The term adverse event is defined in the U.S. Code of Federal Regulations (CFR) Title 21 Section 312.32(a) as follows: "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related."

ICH guidelines for [Clinical Safety Data Management: Definitions and Standards for Expedited Reporting](#) uses the ICH GCP definition.

An AE may be “any unfavorable or unintended” sign, symptom, or disease that occurs in a person who has taken a medication. The occurrence does not need to be related to the drug treatment.

An adverse event (AE) may be:

- A physical event (e.g., a rash).
- A psychological event (e.g., depressed mood).
- A laboratory event (e.g., elevated blood sugar).
- An increase in the severity or frequency of a pre-existing symptom or condition (e.g., increased pain in a painful tooth)

An adverse event may also be referred to as an “adverse experience.”

[Click here](#) for examples of situations involving the use of a drug in humans in which an AE may occur.

[Click here](#) for examples of events that should or should not be reported as AEs.

### [What is an adverse event in a behavioral study?](#)



As defined in the previous section, an AE is commonly understood to be an event that occurs during treatment with a drug or device. However, the definition can also be applied to any “untoward occurrence” that occurs in any clinical trial, including behavioral studies.

For trials that are not regulated by the FDA, the [Investigators](#) and protocol teams may define the term adverse event to reflect what is clinically and scientifically relevant to their study.

Thus, for a behavioral trial that does not involve treatment with a drug, an AE may be defined as:

“Any unfavorable, unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome, or disease that occurs during the study, having been absent at baseline, or—if present at baseline—appears to worsen.” (Interim Guidelines for NIH Intramural Principal Investigators and for NIH Institutional Review Boards on Reporting Adverse Events)

In certain studies, including some behavioral studies, it may be important to capture the occurrence of nonmedical events such as arrest, imprisonment, and violence to others, which may be contributing factors to an AE or may indicate that an AE has occurred. As an example of the latter, a participant’s increased drug abuse—an AE—could result in an arrest.

[Investigators](#) may elect to capture nonmedical events that may be behavioral (e.g., violence) or social (e.g., arrest, imprisonment) on the AE Case Report Form (CRF), or such events may be captured elsewhere.

### [What is an adverse drug reaction?](#)



The terms adverse event and adverse drug reaction are easily confused, but they have distinctly different meanings. As discussed in earlier sections, an adverse event (AE) is any “untoward occurrence” in a patient or clinical study participant that need not be related to treatment.

By contrast, an adverse drug reaction (ADR) implies an adverse event that results from a medicine or treatment (i.e., there is a degree of relatedness between the adverse reaction and the treatment).

FDA regulations define an ADR as

“an undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence” (21 CFR 201.57(c)).

Remember: Although every ADR is also an AE, only some AEs will also be ADRs. Therefore, it is very important to collect clear and complete information about every AE.

### What is a serious adverse event?



An AE is considered serious if it poses a threat to the patient’s life or functioning. The FDA defines a serious adverse event (SAE) as any untoward medical occurrence that:

- Results in death, or



- Is life-threatening (places the patient at risk of death), or
- Requires hospitalization or prolongs an existing hospitalization, or
- Causes persistent or significant disability or incapacity, or
- Is a birth defect, or
- Requires medical intervention to prevent one of the above outcomes (e.g., an asthma attack that requires intensive treatment in an emergency room, a seizure that does not result in hospitalization but requires medical treatment).

An AE needs to meet only one of the above criteria to be considered serious. A change in vital signs, diagnostic tests (e.g., an electrocardiogram), or laboratory test results may be an SAE if the change is of sufficient magnitude to meet one of the above criteria.

An adverse event is judged “serious” on the basis of the threat it poses to a patient’s life or functioning. For example, a patient could be diagnosed with pneumonia in his or her doctor’s office and given antibiotics to take at home. The pneumonia is an AE, but not an SAE

However, if the patient is hospitalized for the pneumonia, that is considered an SAE. (The SAE is pneumonia resulting in hospitalization.)

It is also imperative to clarify between severe and serious. While the intensity of an event may be severe, it may not meet the criteria for serious (e.g. Severe Migraine). Severity is discussed in this module.

Elective surgery (i.e. surgery that is planned prior to entry into the study) is not a Serious Adverse Event. For example, removal of bunions on feet, nose reconstruction, planned hysterectomy, etc.

### [What is a serious adverse event in a behavioral study?](#)



The definition of an SAE in the previous section is commonly understood to relate to clinical studies of drug treatments. However, the definition can be applied to any kind of clinical study, including behavioral studies.

The [Investigator](#) of a study may, for the purposes of the study, limit or expand the FDA criteria for an SAE to reflect the specific risks of the study intervention and the characteristics of the study population.

The Investigator may describe in the [research protocol](#) other AEs that in that particular study are to be considered serious, although the AE may not meet the FDA criteria. For example, all suicide attempts may be considered SAEs in a specific research protocol, whether or not they require hospitalization or place the patient at immediate risk of death. On the other hand, certain occurrences that would be considered

SAEs under the standard definition, such as hospitalizations for normal childbirth or voluntary admissions for detoxification, may be explicitly defined not to be reportable as AEs and/or SAEs, if the Investigator so chooses. Any such modifications to the definition of an SAE must be approved during the protocol review process and by the appropriate IRBs.

### What is an unexpected adverse event?

For clinical studies that involve the use of marketed drugs (as opposed to investigational new drugs), FDA defines an unexpected AE as:

- An AE that is not listed in the drug's current labeling, or
- An AE that is more severe or more specific than indicated in the labeling.

For clinical studies in which [investigational new drugs](#) are used, the FDA defines an unexpected AE as:

- An AE that is not consistent with the information about the drug's risks that appears in the relevant source document(s) (e.g., [protocol](#), [Investigator's Brochure](#), and consent documents), or
- An AE that is not consistent with the risk information, or
- An AE that has occurred within the class of drugs, but not specifically with the Investigational Product.

### What is an unexpected adverse event in a behavioral study?

In studies conducted under the [Investigational New Drug](#) regulations, the known risks and expected benefits of an investigational new drug are described in the [Investigator's Brochure](#).

However, an Investigator's Brochure is often not prepared for behavioral studies. For this reason, researchers who conduct behavioral studies are expected to describe in the [research protocol](#) any adverse events that might be expected to occur in the study population as a result of the experimental behavioral intervention. They must also briefly describe these events in the consent documents.

In a behavioral study, therefore, an unexpected adverse event would be an AE that is not mentioned in the protocol or consent documents or an AE that has not been seen before. Additionally, unexpected AEs in a behavioral study can be considered as unanticipated problems (discussed further below) and are thereby regulated under 45 CFR46.

### What is an unanticipated problem?

The Office of Human Research Protections (OHRP) defines *unanticipated problems involving risks to study participants and others* as an event that meets all of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

**Suspected unanticipated problems must be promptly reported to the IRB, who will make the subsequent determination to report it to the proper regulatory authority.**

Although unanticipated problems are found but not defined in 45 CFR 46, all NIH funded studies are required to comply with 45 CFR 46. For OHRP's current guidance on unanticipated problems, follow the

link [here](#).

## Part 2: Participant Safety & Adverse Events

### Interactive: Participant Safety & Adverse Events

A new research coordinator has started working on a clinical study comparing the effectiveness of two marketed drugs to treat facial acne. There are 37 participants enrolled at the research site. She is tasked with entering all safety events for these participants into the electronic Case Report Form.

#### Users are instructed as follows:

Below is a list of seven safety events that study participants experienced. The research coordinator has to crosscheck her understanding of each safety event with the safety monitor to ensure that the data she enters is accurate. Evaluate each safety event and choose whether it is an **Adverse Event by choosing AE** or a **Serious Adverse Event by choosing SAE**. After assessing each event, you will be given feedback on your response.

#### Scenario 1

Severe cramps in arms and legs. *Is this an AE or SAE?*

*Feedback: Is this an AE or SAE?* This is an AE-Adverse Event – this is an untoward event experienced by the participant.

#### Scenario 2

Nausea and vomiting at day 7 of dosing. *Is this an AE or SAE?*

*Feedback: Is this an AE or SAE?* This is an AE-Adverse Event – this is an untoward event experienced by the participant.

#### Scenario 3

Severe bronchospasms that resulted in ER visit for intervention. *Is this an AE or SAE?*

*Feedback: Is this an AE or SAE?* This is a SAE-Serious Adverse Event – it meets the criteria of important medical event.

#### Scenario 4

Tinnitus (ringing in ears) after taking an anti-histamine. *Is this an AE or SAE?*

*Feedback: Is this an AE or SAE?* This is an AE-Adverse Event – this is an untoward event experienced by the participant.

### **Scenario 5**

An intercurrent infection resulting in death. *Is this an AE or SAE?*

*Feedback: Is this an AE or SAE?* This is a SAE-Serious Adverse Event – In this case, the diagnosis will be infection and Death is the outcome.

### **Scenario 6**

Broke right arm while riding a bike. *Is this an AE or SAE?*

*Feedback: Is this an AE or SAE?* This is an AE-Adverse Event – This is an untoward event experienced by the participant irrespective of its relation to the investigational product.

### **Scenario 7**

Emergency hysterectomy during the study. *Is this an AE or SAE?*

*Feedback: Is this an AE or SAE?* This is a SAE-Serious Adverse Event – This is emergency surgery and not planned.



## Part 3: Assessing an Adverse Event



Every protocol should list specific AEs that are to be addressed at every visit. Generally, this will be a very short list of lab values and clinical signs and symptoms. The protocol should also specify the duration that information on AEs will be collected.

All AEs that occur in any clinical study participant should be assessed for:

### Severity

The severity of an AE is not the same as its seriousness. Severity refers to the intensity of a specific event (e.g., mild, moderate, or severe pain). However, the event itself may be of minor medical significance (e.g., a severe toothache). (Click [here](#) to see sample definitions of the grades of severity of an AE.)

By contrast, the seriousness of an AE is assessed by the extent to which it poses a threat to the patient's life or functioning. Thus, an AE may be severe (e.g., severe pain from a toothache) without being serious (threatening the patient's life or functioning).

Determining the severity of an AE is largely a matter of individual clinical judgment. No universally accepted scale exists for describing or measuring the severity of AEs. The severity of an AE should be determined with input from a qualified physician or licensed medical staff.

### Relatedness

An AE may or may not be causally related to the study intervention. A causal relationship means that the intervention caused (or is reasonably likely to have caused) the AE. This usually implies a relationship in time between the intervention and the AE (e.g., the AE occurred shortly after the participant received the intervention).

For all AEs, it is the responsibility of the clinician who examines and evaluates the patient to determine the relatedness of the event to the study intervention. Data managers who have no role in patient clinical assessment must not perform this important task.

Acceptance that an AE is related to the intervention usually requires a plausible mechanism of action—that

is, a believable sequence of events by which the intervention brought about the AE. It may be helpful to seek the opinion of the Study Medical Monitor on this point. It can also be helpful to ask the participant whether he or she thinks the intervention could have brought about the AE. (Click [here](#) to see terminology utilized in protocols to assist clinicians in their assessment of the relatedness of an event.)



If an AE is thought to have a causal relationship with the intervention, and the AE raises concern about the safety of the participant, serious consideration must be given to temporarily halting or permanently discontinuing the intervention. Additionally, rechallenging the participant (that is, giving the intervention again to test the causal relationship to see if the AE occurs again) is not often done because of safety concerns. For this reason, it is often impossible to say with certainty that an experimental intervention caused an AE.

The causal relationship between an intervention and an AE may be tested by discontinuing the intervention and then rechallenging the participant (giving the intervention again) to see if the AE occurs again. However, this is rarely done because of safety concerns. For this reason, it is often impossible to say with certainty that an experimental intervention caused an AE.

When an AE is labeled “associated with the use of the intervention,” therefore, this means there is a reasonable possibility that the AE may have been caused by the intervention and is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

Early in the development of a drug or other intervention, when little is known of its safety profile, it is especially important to maintain a high level of suspicion for AEs and to report all AEs that may in any way be causally related to an experimental drug or intervention.

Any AE reported by a participant should be followed up at each subsequent study visit until the AE has resolved. It is important to document both the duration (e.g., minutes, hours, days) and severity of an AE. An AE that persists from one study visit to the next should be documented as one event. For AEs that are sustained past the study duration, follow-up may occur until resolution or for a reasonable period of time defined by the protocol.

The initial report of an AE is usually made by the participant; however, an AE may also be reported by a family member, friend, nurse or other caregiver, or someone else. For example, a family member or friend may call to report that a participant has been hospitalized. Or another participant may report hearing from a third party that a participant is seriously ill.

Regardless of who reports an AE, the event should always be documented in the participant’s [source documents](#) including [progress notes](#). When an AE is reported by a third party, the Research Assistant

should make every effort to contact the participant directly to verify the report. In some cases, a report of an AE may turn out to be false. As more information about the event is gathered and assessed, the Research Assistant must ensure that [source documents](#) and reports are updated with accurate information about the AE.

## Part 4: Adverse Event Reporting



AE reporting is an essential part of participant safety protection during a clinical study. Determining whether an incident is a reportable AE—and if so, what should be reported about it, to whom, and when—depends on many factors, including:

- Previous experience and knowledge of the drug or intervention,
- The disease being treated, and
- Regulatory requirements.

In addition to the factors listed above, investigators must consider incident reporting requirements for NIH-funded studies, including reportable AEs and unanticipated problems (UPs). All NIH-funded studies are required to comply with 45 CFR 46 for safety event reporting. For OHRP’s current guidance on UPs involving participant safety risks, follow the link [here](#).

Not all AEs require reporting, as they might not directly impact participant risk or present significant new findings. Inundating the study IRB with individual, unanalyzed UPs is an uninformative process, and UPs that don’t impact participant risk can be covered during the IRB’s continuing review. Requirements for the reporting of AEs are defined in each protocol.

The investigator and research team must consider these factors when writing the sections of the [protocol](#) and the operations manual that discuss adverse event reporting. The investigators and the study sponsor jointly determine the extent and type of AE data that will be collected for a specific trial.

They may decide that minor complaints of daily living will not be considered AEs. An event such as the worsening of symptoms of a current illness could be captured in the patient’s [progress notes](#) or on a [case report form](#).

### ICH GCP requirements for AE reporting

The investigator must report all Serious Adverse Events to the sponsor immediately. The immediate reports should be followed promptly by detailed, written reports.

In the event of a death, the investigator should supply the sponsor and the IRB with any additional requested information.

In addition, the investigator must comply with the applicable regulatory requirements as well as protocol specific requirements related to the reporting of safety issues. In some instances, the local laws or network requirements may request more stringent reporting of emergent or safety events.



## Part 4: Adverse Event Reporting

### FDA Requirements

For IND studies FDA guidelines (21 CFR 312.32) require expedited reporting by the sponsor of all AEs that are associated with the use of the drug, serious, unexpected and reasonably related to the investigational product.

- Related and unexpected fatal or life-threatening AEs (severity grade 4 or 5) that are associated with the use of the drug must be reported to FDA by telephone or fax no later than 7 calendar days after the sponsor first learns of the event. This initial report must be followed within 8 additional calendar days by a written safety report that is as complete as possible.
- FDA must be notified of serious, related and unexpected AEs associated with the use of the drug that are not fatal or life-threatening in a written safety report no later than 15 calendar days after the sponsor first learns of the event.
- The sponsor should report pertinent follow-up information for previously submitted reports to the FDA as soon as it is available, including for AEs that were not initially deemed reportable if the follow-up information causes a change in assessment.

Aggregate analyses of adverse events observed from a clinical trial, or from other studies outside the sponsor's scope, that detail new information regarding the investigational product (i.e. new side effects, or increasing frequency of side effects) should be reported to the FDA. Significant non-clinical findings are also reportable if they're suggestive of increased risk for human studies. The FDA also accepts voluntary reporting for marketed drugs in studies exempt from FDA reporting requirements with their MedWatch system.

Under these guidelines, expedited reporting to the FDA is generally not necessary for AEs that are:

- Serious but expected.
- Serious but not related to the study drug, whether expected or not (e.g., a patient who dies of a cancer that was present prior to entry into a study of an antidepressant).
- Non-serious, whether expected or not.

For studies of investigational new drugs, FDA requires the sponsor to notify all participating investigators in a written safety report of any serious and unexpected AE that is associated with the use of the study drug. The sponsor may add additional requirements to this notification. Consider how NIDA fulfills this obligation. NIDA has directed Lead Investigators to distribute such reports within 24 hours of learning of an AE that:

- Is considered serious, related and unexpected, or
- Requires revision of the protocol or the informed consent form, or
- Requires termination of the study or suspension of enrolment.

If a serious related and unexpected AE represents an increased risk to study participants, investigators must inform participants of this increased risk as soon as possible.

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### CTN Requirements

ICH GCP guidelines (E6) state that all serious adverse events (SAEs) should be reported immediately to the sponsor. An exception is made for SAEs that are identified in the protocol or other document (e.g., Investigator's Brochure as not requiring immediate reporting).

For CTN studies (whether conducted under an Investigational New Drug application or not), any AE that meets FDA's criteria for a serious adverse event (SAE) must be reported within 24 hours to the NIDA Study Medical Officer and all parties specified in the protocol. The FDA's definition of an SAE is to be used unless the protocol specifically limits or expands the FDA definition.

Following the initial report of the SAE by phone, fax, or e-mail all efforts will be made to gather additional information available on the SAE. Once received, this information will be sent to NIDA within the time frame specified in the research study protocol.

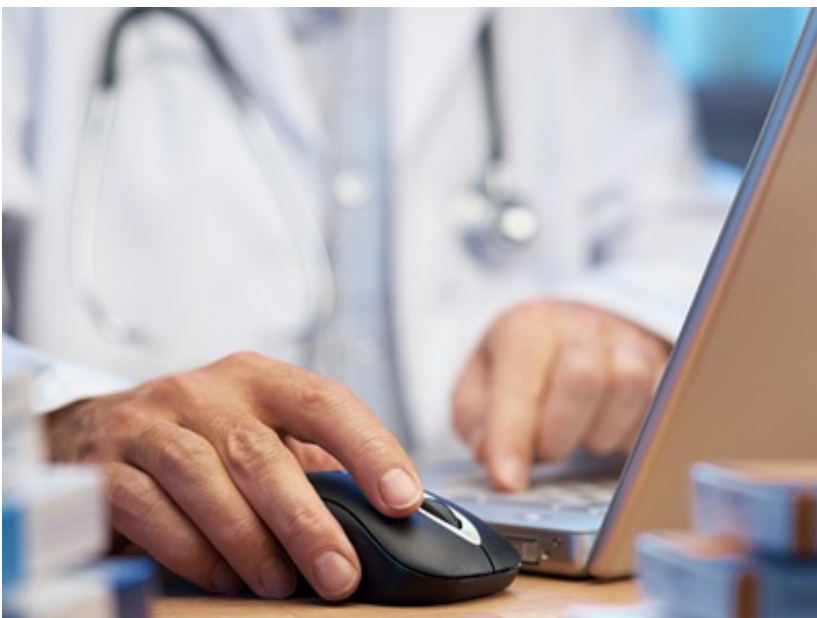
For studies conducted under an IND, it is then NIDA's responsibility (as sponsor of most investigational new drug studies conducted within the CTN) to send an IND (Investigational New Drug) Safety Report to the FDA within the required timeframe.

SAEs that are exempt from expedited reporting must be documented and reported in a timely fashion (e.g., monthly, quarterly) in accordance with local IRB requirements. For all CTN studies, any serious adverse event (SAE) must be reported to NIDA within 24 hours after CTN protocol staff learn of the event. This deadline applies:

- Whether or not the investigator considers the SAE to be related to the study intervention.
- Regardless of the severity or outcome of the SAE.
- For SAEs that occur in both drug studies and behavioral studies.
- For studies conducted under the Investigational New Drug regulations and those that are not.
- For all SAEs that occur during a study, including those that occur during a post-treatment observation period as defined by the study protocol.

The National Institutes of Health (NIH) has issued guidance to NIH-supported investigators on reporting to IRBs about AEs that occur in multi-center clinical trials. Investigators must know the policies of the local IRB, adhere to them, and keep a copy of them in the study file. Investigators are also responsible for accurately documenting, investigating, and following up all possible study-related adverse events.

Site PIs should follow the policies of their Institutional Review Board on timeframes for reporting AEs. Additionally, investigators must ensure that NIDA is informed of any actions taken by the IRB as a result of its continuing review of participant safety.



# Adverse Event Reporting in CTN Studies

Multiple parties need to be notified of AEs that occur in CTN studies. This can lead to confusion.

Study investigators must report AEs to:

- The study sponsor (NIDA for most CTN trials).
- Relevant [IRBs](#).

If NIDA is the study sponsor, and the study is conducted under an IND, NIDA must inform FDA and any other relevant regulatory agencies of findings that could adversely affect participant safety, affect the conduct of the trial, or alter IRB approval to continue the trial.

The [research protocol](#) may, if appropriate, establish additional reporting requirements based on the severity of an AE. For example, the protocol and consent forms could state that trial-related hospitalizations will be reported to the participant's treating physician.

In CTN trials, any AE that occurs between the times a participant signs the informed consent form and the time he or she leaves the study after the final follow-up visit must be captured and recorded, unless the protocol states differently. The investigators and NIDA (as the study sponsor) may jointly determine an alternative period (e.g., beginning with the first trial-related procedure or the first time a participant takes the study drug) during which AEs must be reported.

How quickly an AE must be reported and to whom depends, in part, on the nature of the event. Reporting requirements encompass both routine reporting and expedited (rapid) reporting.

For studies conducted under an IND, FDA regulations require investigators to “promptly” report to the study sponsor any AE that is reasonably likely to have been caused by the study drug. If the AE is “alarming”, the investigator must report it immediately. The sponsor, in turn, is responsible for expedited (rapid) reporting to the FDA of certain serious adverse events (SAEs) that are both reasonably related and unexpected. All other AEs must be reported to the FDA in protocol amendments or in annual reports ([21 CFR 312.32](#)).



## Adverse Event Reporting in CTN Behavioral Studies

For NIH-funded studies that do not involve the use of investigational new drugs, requirements for AE reporting vary depending on the nature of the study. Federal regulations (45 CFR Part 46, Subpart A)

require written procedures and policies for ensuring that “unanticipated problems” involving risks to participants are reported to the IRB, appropriate institutional officials, and the relevant department or agency head.

Most AEs that occur in CTN behavioral studies are found to be unrelated to the study treatments received. For this reason, unlike FDA requirements for drug trials, non-serious AEs are sometimes not tracked in CTN studies. The [Lead Investigator](#) should specify in the [protocol](#) of a behavioral study which untoward occurrences should be captured and reported as adverse events, and which should not. Furthermore, the protocol should specify the types of events that will or will not qualify as SAEs and be reported as such.

For NIH-funded studies in which investigational drugs or devices are used, i.e. studies conducted under IND or IDE, investigators must comply with both NIH and FDA requirements for the reporting of AEs.

Additionally, OHRP provides the definition of unanticipated problems that affect the safety risks to study participants and others. As NIH-funded studies are regulated by 45 CFR 46, OHRP provides the criteria for determining unanticipated problems and the review and reporting of these incidents and AEs (follow this [link](#) for guidance).

## **Expedited Reporting of Adverse Events**

Participants in clinical studies may experience AEs which, if they are thought to be probably or possibly caused by an experimental intervention, might be significant enough to lead to important changes in the way a drug or other intervention is developed or used (e.g., changes in dose, treatment population, required monitoring, consent forms). This is particularly true for AEs that, in their most severe forms, threaten life or function.

Such AEs must be reported promptly to investigators, sponsors, regulators, and IRBs. This is referred to as expedited or rapid reporting. The purpose of expedited reporting is to ensure that the appropriate parties are quickly made aware of important new information about the potential adverse effects of a drug or other experimental intervention.



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## Part 5: Adverse Event Follow-Up



### Medical Follow-Up of Participants with an Adverse Event

Unless otherwise specified in the protocol, in some networks it is common practice that all AEs and non-study-related SAEs should be followed-up until they have resolved or stabilized or until 30 days after the participant's involvement in the study has ended, whichever occurs sooner.

All SAEs should be followed until resolution, or until the condition has stabilized with no further change expected. According to FDA guidance, participants should receive appropriate medical evaluation and treatment until resolution of any emergent condition related to the study intervention that develops during or after the course of their participation in a study, even if the follow-up period extends beyond the end of the study.

When a participant discontinues participation in a study because of an SAE, investigators should:

- Continue to follow up the SAE as noted above.
- Document the SAE and its follow-up in the participant's record.
- Attempt to complete any final evaluations required by the study [protocol](#).
- Attempt to perform other medical evaluations to try to determine the cause of the SAE and its possible relationship to the study intervention. These evaluations would include obtaining an autopsy report, if available, in the event of a participant's death.

For a woman who is discontinued from a study because of pregnancy, attempt to follow up the outcome of the pregnancy to term. If the woman was enrolled in a trial of an investigational drug that is known to present a risk of birth defects, any information regarding birth or congenital abnormality should be obtained.

Loss to follow-up of participants with ongoing SAEs is a serious problem that can affect the validity of a study's results. For this reason, every effort should be made to contact participants who leave a study after experiencing an SAE. Documentation of that effort should be maintained by the PI.



## Part 5: Adverse Event Follow-Up



### Data and Safety Monitoring

Data and safety monitoring plays an essential role in protecting participant safety and ensuring the integrity of a research study. The objectives of data and safety monitoring are to:

- Ensure that risks of participation in a clinical study are minimized as far as is reasonably possible.
- Avoid exposing participants to excessive risk.
- Ensure the integrity of the data collected in a clinical study.
- Stop a study
  - If safety concerns arise, or
  - As soon as the study objectives have been overwhelmingly met, criteria usually spelled out before the study begins.

The following are key points to remember about data and safety monitoring:

- Data and safety monitoring must occur periodically throughout every study. The frequency of monitoring is commensurate with the risks involved in the study, as well as the size and complexity of the study (i.e. a small, single-site Phase I trial versus a large, blinded, multi-site Phase III trial).
- Periodic data summary reports are prepared to determine if the study should change in any way or stop. Any significant changes in the study are implemented with the approval of the local IRB and reported to appropriate institutional officials, the study sponsor, and the FDA (if the study involves an investigational new drug or device).
- The risks and benefits of the study must be reassessed whenever any new study data become available.

## Part 5: Adverse Event Follow-Up

### Interactive: Participant Safety and Adverse Events - Part I

**Scenario:** Based on the research protocol for a behavioral non-drug study, research staff report all serious adverse events (SAEs) and report adverse events (AEs) only when an increase in the severity or frequency of a pre-existing symptom or condition occurs.

**Question:** For participants that were screened, enrolled, and randomized sometime prior to experiencing the medical events described below, which are considered SAEs?

- A. Participant reports severe neck pain after a whiplash injury in a car accident that occurred in the previous week.
- B. Participant reports an ER visit due to pneumonia and was hospitalized subsequently for treatment with intravenous antibiotics.
- C. Participant with a history of mild asthma reports a 2-day hospital stay for severe asthma attack treatment in the study's final week.
- D. Participant (A) and (B) only
- E. Participant (B) and (C) only
- F. Participant (A) and (C) only

*Feedback:* Which is the best response: A, B, C, D, E, or F? For Scenario B, the participant experienced a medical occurrence that led to hospitalization. For Scenario C, the participant's pre-existing condition worsened to require intensive treatment and a hospital stay. Both cases are considered SAEs. Therefore, the correct response is E.

## Part 5: Adverse Event Follow-Up

### Interactive: Participant Safety and Adverse Events - Part II

**Question:** A 15 year old male has come in for a site visit. The participant was randomized to product Z for treatment of severe cystic acne. The participant's parents report that after several weeks on the treatment the participant had mood swings, was crying, said he was "feeling blue" and attempted suicide. The participant discontinued the drug.

**Is this a reportable event(s)?**

- A. Yes
- B. No

*Feedback:* Which is the best response: A or B? Suicide attempt is a reportable event. Therefore, the correct response is A.

## Part 6: Summary of Key Points

- The safety and well-being of study participants must be safeguarded at all times during the conduct of a clinical research study.
- An adverse event (AE) is defined in the Good Clinical Practice guidelines as any “untoward medical occurrence” in a person who receives a drug while participating in a clinical study. The occurrence need not be causally related to the drug treatment.
- For behavioral studies, an AE may be defined as “any unfavorable, unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome, or disease that occurs during the study, having been absent at baseline, or—if present at baseline—appears to worsen.”
- An AE is considered serious if it poses a threat to the patient’s life or functioning. The U.S. Food and Drug Administration (FDA) defines a serious adverse event (SAE) as any untoward medical occurrence that:
  - Results in death, or
  - Life threatening (places the patient at risk of death), or
  - Requires hospitalization or prolongs an existing hospitalization, or
  - Causes persistent or significant disability or incapacity, or
  - Is a congenital anomaly/birth defect, or
  - Requires medical intervention to prevent one of the above outcomes.
- The Investigator in a behavioral trial may modify or expand the FDA criteria for an SAE to reflect the specific risks of the intervention and the characteristics of the study population.
- The severity of an AE is not the same as its seriousness. An adverse event may be severe (e.g., severe pain from a toothache) without being serious (threatening the patient’s life or functioning).
- SAEs must be reported by phone or fax immediately to all parties notified as specified in the protocol.
- The purpose of expedited reporting to the FDA or other regulatory authority is to ensure that the appropriate parties—including investigators, sponsors, regulators, and IRBs—are quickly made aware of new, important information about the potential adverse effects of a drug or other experimental intervention.
- In addition to reporting AEs and SAEs, NIH-funded studies are required to report unanticipated problems that affect the safety of study participants and others. While unanticipated problems are found in and regulated by 45 CFR 46, OHRP provides the criteria for determining unanticipated problems and the reporting and review of these incidents (see OHRP, 2007).
- Generally, all AEs and SAEs should be followed up until they have resolved or stabilized.
- Data and safety monitoring must occur periodically throughout every study to protect participant safety and ensure the integrity of study data, for example, by the Data and Safety Monitoring Board for a clinical trial.