

Guidance for Assessing and Monitoring Adverse Events in Behavioral Clinical Trials

1. INTRODUCTION.

The Institute for Clinical and Translational Research Data Monitoring Committee (DMC) at the University of Wisconsin-Madison recommends the following guidance for monitoring, documentation and reporting of Adverse Events during behavioral focused clinical trials. Behavioral clinical trials may include, but are not limited to, interventions targeting health practice change (e.g., dietary, physical activity), psychological function or emotions (e.g., psychotherapy, mindfulness-based interventions); knowledge, attitudes, or beliefs; or cognition (e.g., memory, attention, problem-solving).

This plan is compliant with the International Conference on Harmonization-10 (ICH-10) and Good Clinical Practice Guidelines (GCP) to document the assessment of potential Adverse Events (AEs). Procedures require designated and competent staff to be trained in the source documentation of AEs observed during the conduct of the trial and documentation of the PI review and assessment of those events for patient safety monitoring purposes as well as reporting of AEs to IRBs and Data and Safety Monitoring Boards/Data Monitoring Committees (DSMBs/DMCs).

2. SCOPE.

This guidance document provides preparation and guidance for all research personnel to fulfill their role in the safety monitoring required by the UW-Madison Health Institutional Review Board (IRB). Procedures outlined include systematic assessment of participant health status and possible occurrence of Adverse Events (AEs), to include:

- personnel responsibilities
- definition of AEs
- timing of assessment
- identification, assessment, and documentation of AEs
- adjudication of AEs
- reporting of AEs to meet regulatory requirements

3. APPLICABLE REGULATIONS AND GUIDELINES.

- Code of Federal Regulations (CFR-Part 11)
- International Conference on Harmonization-10 (ICH-10)
- UW-IRB Guidelines
 - a. [Investigator Manual \(HRP-103\)](#)
 - b. [New Information \(HRP-024\)](#)
 - c. [Review of Information Items \(HRP-321, Worksheet\)](#)
 - d. [Unanticipated Problems/Adverse Event Reporting Decision Guide](#)

4. RESPONSIBILITY.

This guidance document applies to those members of the clinical research team involved in ensuring the appropriate management and reporting of adverse events. This includes the following:

- Principal Investigator
- Associate Investigator
- Study Coordinator
- Research Associate/Assistant
- Therapist/Clinical Provider
- Independent Evaluator
- Research Nurse
- Consortium Coordinator
- Regulatory Coordinator
- Research Operations Manager
- Research Compliance Manager
- Other Research Staff

5. DEFINITIONS.

- **Data Safety and Monitoring Plan (DSMP):** The formal plan for the safety monitoring of human subjects participating in studies. This plan specifies the regulatory processes, procedures, and authorities involved in clinical trials operations and the entities, roles, and responsibilities of clinical trial participants in the monitoring for safety and reporting of adverse events observed in various UW-Madison-based clinical trials.
- **Data Monitoring Committee (DMC):** An independent group of scientists and who oversee the interim (unblinded) findings of a research project to determine whether the research undertaken is proceeding without evidence of unexpected harms to the subjects enrolled in the study.
- **Adverse Events (AEs):** Any *clinically significant deterioration* in the physical, psychological, mental, cognitive, or psychosocial health status of the subject, observed during the time period of the study and representing a change from the baseline condition which existed prior to study.
 - **For behavioral-focused clinical trials:** While there is no standard definition of AEs for behavioral trials, study teams should monitor participants for known intervention side effects and clinically meaningful worsening of target symptoms regardless of attribution, as well as for unexpected AEs attributed to study participation (i.e., possibly, probably, or definitely related to participation).
 - Minor, transient, or clearly unrelated medical issues (e.g., common cold and minor injuries) typically do not require documentation unless they are reasonably believed to be related to study participation.
 - **EXAMPLES of AE DEFINITIONS**
 - Examples for a psychological intervention trial: clinically significant symptom worsening, defined as:
 - ≥ 5-point increase from baseline PHQ-9 (depression), and/or
 - ≥ 4-point increase from baseline GAD-7 (anxiety)
 - ≥4-point increase on the AUDIT-C (alcohol use), and/or
 - ≥3-point increase on the DAST-10 (substance use)
 - Suicidality not meeting SAE criteria, defined as suicidal ideation without life-threatening intent or requiring hospitalization

- Mental health conditions measured at study baseline are not considered AEs unless worsening meets the above criteria.
 - Examples for a physical activity trial:
 - Self-reported pain score $\geq 4/10$ on a numerical rating scale lasting >72 hours after a session
 - Any musculoskeletal complaint (tendinopathy, stress fracture, joint pain) requiring a reduction in training load or medical attention
 - Fall during exercise
 - Examples for a behavioral sleep intervention trial:
 - Total sleep time falling below 5 hours/night for ≥ 3 consecutive nights as recorded by sleep diary or actigraphy
 - Increase in Insomnia Severity Index (ISI) score of ≥ 6 points from baseline at any mid-treatment assessment
 - New-onset restless legs symptoms, sleepwalking, or REM sleep behavior disorder symptoms
 - Participant report of involuntary sleep episodes during activities requiring alertness (driving, meetings)
- **Serious Adverse Events (SAE's):** AEs which are considered “serious” because of the gravity of their effect upon the subject. AE's are SAE's if they meet any one of the following criteria:
 - i. life-threatening, including suicide attempt (i.e., life or limb was in danger)
 - ii. results in hospitalization, including psychiatric hospitalization (i.e., actual admission, not an ER visit);
 - iii. results in death (subject deceased).
 - iv. results in persistent or significant incapacity or substantial disruption of ability to conduct normal life function;
 - v. results in congenital anomaly or birth defect of offspring.
 - vi. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- **Unanticipated Problems:** AEs observed in the study that are “possibly” “probably” or “definitely” related to the study procedures, but represent an increased risk in that they were not previously anticipated and/or disclosed in the informed consent process. Basically, an AE is a UP if it meets all three criteria below:
 - i. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures described in the IRB-approved research protocol and informed consent document; or (b) the characteristics of the subject population being studied;
 - ii. at least “possibly related” to participation in the research; and
 - iii. the observation of a previously unanticipated but possibly related AE suggests that there is now known to be a greater risk of harm (including physical psychological economic, or social harm) than was previously known or recognized.

6. PROCEDURES:

1) AE ASSESSMENT AND DOCUMENTATION

AEs, SAEs, and UPs are being assessed by the DMC to fulfill the ethical requirement for safety monitoring in clinical trials. AE observations also may be useful for study publications to document the frequency and severity of problems observed in the study population undergoing these kinds of treatment. Standard UW IRB guidelines suggest AE assessment at each clinical visit or assessment time point, though allowances can be made depending on the frequency of visits and the manner of assessment. Regardless, every safety assessment for potential AEs must be documented on the AE Record Log.

- Each new visit or assessment occurrence must be recorded as a row on the AE form log to document that an assessment occurred on that visit. If no AE is observed, then note “none” and if more than one AE is observed, devote one row per event because each AE can have its own course and outcome.
- **RECORDING THE EVENT**
 - a) The AE assessor will provide a brief description of the possible AE and an actual or estimated start date.
 - The assessment process may identify a symptom or problem that pre-existed at the time of consent even though it had not been recorded at the baseline assessment. This newly recognized problem is not an AE if it does not represent a worsening of health status, but should be noted in the health record. The proper procedure for this is:
 1. Record the newly identified information on the baseline Health Questionnaire (or other baseline source document assessing health status), initial and date these edits per GCP.
 2. Delete previous data entry from the electronic database and re-enter the data with the newly added information.
 3. Ensure that a Note to File is written for the study file describing this alteration of documentation and database entry, and enter the corresponding information into the Progress Note section of the electronic database.
 - b) Action Taken should be indicated, whether referring to something the participant did (e.g. rest and medication), intervention provided by study personnel (e.g. continue in study treatment), or action taken by a third party (e.g. supervisor sent participant home from work).
 - If “Action Taken” involves an ER visit and/or hospital admission, this should be explicitly indicated by checking the appropriate box(es) on the log for that event.

- Note that an ER visit is not always an SAE but a hospital admission is always an SAE. An ER visit may lead to a hospital admission, which would require checking both boxes on the log.
 - c) The AE assessor is responsible to review the log form to check for previous AEs that may be unstopped, and then to query the patient as to whether that previously unstopped AE is continuing or had stopped since last assessment. Either record a stop date if the AE had stopped or check the box for “...*previous AEs are still ongoing*” if it has not stopped.
 - In some studies, accommodations must be made to ensure blinding by the Independent Evaluators (IE) is maintained at follow ups, and for that reason the full, original AE log should not be provided to the IE at a follow up assessment. In such cases, procedures may be implemented by which any ongoing AEs are identified on a clean AE log to be assessed by the IE, and these separate pages are incorporated into the study file and all pages documented appropriately according to GCP. Consultation with the study Regulatory Coordinator is recommended.
- **CLINICAL COURSE OF SYMPTOMS**
- a) “Single episode” refers to a problem or symptom that has a discrete start and stop date, is relatively short-lived and is not usually, by nature, anticipated to be recurrent. Injuries and illnesses are common examples of single episode events.
 - b) “Intermittent” refers to a problem or symptom that may have multiple start and stop dates and is usually, by nature, anticipated to be recurrent. Seasonal allergies, longstanding history of migraines, or psychological symptoms that worsen and improve in cycles over time are common examples of intermittent events.
 - c) “Continuous” refers to a problem or symptom that is present over time without complete remission. Chronic pain and serious disease are common examples of continuous events.
 - **SPECIAL CONSIDERATION:** If a previously recorded AE was initially determined to be a “single episode” with a stop date and then is reported again on a later study visit, the following issues must be considered for accurate documentation:
 - If the underlying nature, cause, or study-relatedness of the previously reported AE has changed significantly since the original report, this should be recorded as a new AE on the AE Record Log, with a new Start Date. This will likely be the case for symptoms associated with “single episode” events that are not expected to recur, or symptoms that may recur but for different reasons.
 - Example: If a participant reports that they had a flu virus during early participation in the treatment phase that fully remitted, then

- at a follow up assessment months later reports having had the flu virus again, these would be reported as separate AEs.
- Example: If a participant reports symptoms of depression related to memories of the traumatic event being discussed during study treatment, then later reports symptoms of depression related to the death of a loved one, these would be reported as separate AEs. Either or both events may be identified as a single episode, continuous, or intermittent as they have different trajectories.
 - If the nature of a previously recorded AE suggests the expectation of recurrence (e.g. seasonal allergies, migraine headaches, chronic pain in one specific area, psychological symptoms that have been present in the past and are expected to recur intermittently), and is reported the first time as a single episode with a stop date then re-emerges with the same determination of relatedness, the initial adjudication may be amended to indicate the symptom is ongoing and intermittent. The following steps should be taken for accurate documentation:
 - AE log: The originally reported AE should be located. Confirm or correct “Clinical course” to indicate “Intermittent” and cross out previous stop date. Per GCP guidelines, initial and date all corrections.
 - Adjudication: Study coordinator should bring this update to the next study call to provide updated information to ensure PI awareness that the AE status has changed.
 - REDCap database: Edit previously entered AE data in accordance with new information provided.
 - **SEVERITY:** Determined based on clinical judgment regarding the level of disruption of daily functioning. Initial determination by AE assessor can be discussed during adjudication process if in question.
 - a) Mild = Minimal or no disruption
 - b) Moderate = Some disruption of usual activity
 - c) Severe = Major disruption of usual activity
 - **RELATEDNESS:** Determined based on clinical judgment regarding causality of the problem or symptom. Initial determination by AE assessor can be discussed during adjudication process if in question.
 - a) Definitely related to Study – there is a clear and direct relationship between onset of symptoms and study procedures as experienced by the participant.
 - b) Probably related to Study – there is a reasonably clear relationship between onset of symptoms and some aspect of study procedures as experienced by the participant. There may be other factors contributing to the problem but study activity is clearly identified.
 - c) Possibly related to Study – there is reason to believe that some aspect of study procedures may have contributed to the onset of symptoms.

- d) Unlikely related to Study – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provide plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- e) Unrelated to Study – there is clearly some other factor that caused the problem or symptom or there is no identifiable factor that may have caused the problem or symptom, but there is no reason to believe that study procedures may have contributed to the onset of symptoms.
- **CONSIDERATIONS DURING ASSESSMENT OF RELATEDNESS:**
 - Relatedness could reasonably be determined solely by the participant's description of the problem or symptom without additional prompting by the AE assessor. For example, "I started having nightmares again. I hadn't had a nightmare in six months but the night after I did those interviews about my trauma I had nightmares so bad I couldn't sleep."
 - Relatedness could reasonably be inferred from the participant's description of the problem and the timing of onset. For example, "I've been really anxious lately, since I started talking to Dr. Smith about my trauma."
 - Some querying may be necessary to help determine relatedness, but any query should be open ended and should not suggest relatedness to the study if the participant does not spontaneously make such a reference.
 - Appropriate queries might be, "What do you think might be causing you to feel this way," or "Why do you think that symptom is worse now?"
 - INAPPROPRIATE queries might be, "Do you think those feelings might be worse since you started talking to your study therapist?" or "Sometimes the treatment we provide in the study can make these symptoms worse. Do you think that's the case for you?"
 - If a participant clearly gives a possible cause for their reported symptom that is NOT part of the study, no further query should be made. For example, do not query further if a participant says, "I've been feeling really anxious because my job might be changing and there's a lot going on at home that is stressing me out," or "I've been thinking a lot about my buddy who died because last week was the anniversary of his death."
 - If a participant is unable to name any possible cause for their reported symptom when asked an open-ended question, no further query should be made. For example, a participant reports sleep problems and the AE assessor asks, "What do you think might be causing these sleep difficulties?", and the participant responds, "I'm not sure, maybe

it's because of work stress or because of my allergies or something. I really don't know why I can't sleep." An INAPPROPRIATE query would be to continue probing by asking, "Are you sure your sleep problems aren't related to anything you've been doing for the study?"

- If no specific cause can be reasonably identified for the symptom or problem, but there is not sufficient reason to believe it is related to the study, the determination should be "Unrelated".
- The AE log review process has several checks and balances intended to promote liberality in possible reports, and an adjudication process to resolve the final regulatory reports.
- If the AE assessor ever has any doubts or questions about whether or not a particular event should be recorded as a possible AE, they should feel free to consult with the Study Coordinator, PI or member of the UW-IRB office. Generally, over-reporting is not a problem, because the subsequent adjudication process will determine what is finally reported as an AE.
- The adjudication process (described in section 2 below) involves a review by PIs with their Study Team to both document the monitoring of AEs and permit a decision of whether or not an event qualifies as an AE. PIs have a primary role in this decisional process.
- Clinically important changes in health status, or any AE needing to be addressed clinically, must be dealt with as clinically appropriate and must be brought to the attention of the primary clinician or Study Therapist, PI, or the Study Coordinator for possible intervention and resolution as necessary.
- It is also essential that AEs possibly meeting the definition of a UP be brought to the immediate attention of the study PI and UW IRB in order to satisfy the prompt reporting requirements of regulatory authorities.

2) AE Adjudication

- AE assessor (study therapist, independent evaluator, research nurse, coordinator, research assistant, or any study staff engaged in research with subjects) will log observations of all possible AEs onto the individual subject Adverse Events (AE) Log Record (hardcopy or electronic).
- Possible AEs that may also be Serious Adverse Events (SAEs) possibly related to the study or Unexpected Problems (UPs) will be communicated upon discovery to the PI (or PI designee) and the UW IRB for immediate adjudication and reporting if necessary.
- AE assessor will present all possible AEs, including SAEs/UPs, at the next scheduled study team conference for discussion and adjudication. If the assessor is not available to present during the teleconference, another study team member or the study coordinator will present on the assessor's behalf.
 - It is expected that the assessor will have completed reasonable follow up with the subject and documented the AE log appropriately with sufficient information for adjudication.

- To prevent unblinding and minimize potential bias during adjudication, the subject's randomization assignment and session number (as applicable) will not be disclosed when presenting the possible AE.
- Study PI (or PI designee) will consider all information and adjudicate the following:
 1. Does the event constitute an AE (meeting consortium definitions for an AE)?
 - If there is difficulty determining whether or not an event constitutes an AE, consultation with the UW IRB is advised.
 2. If it is an AE:
 - What is the relationship of the AE to study participation?
 - Is the AE unexpected?
 - Does the AE suggest the possibility of increased risk for the subject or potential risk for other subjects related to continued participation in the study?
- The adjudication results will be documented in the appropriate section on the source AE log, to include the date of adjudication and initials of the individual who presented the event for adjudication.
- For events determined to be AEs, the assessor of the AE may enter the AE into the study database OR the source AE log will be given to the Study Coordinator, who will enter the AE into the study database. In either instance, it is ultimately the Study Coordinator's responsibility to ensure that every adjudicated AE is entered into the study database in a timely manner.
- AEs to be reported to Regulatory entities will be downloaded from the study database and will be submitted to the PI for final review prior to submission of official reports as applicable.

3) AE Reporting

Various institutions and regulatory entities require annual or prompt reports of these events in various formats and manners. The UW ICTR DMC requires AE, SAE, and UP reporting in a timely and appropriate in the manner required to prepare reports to the DMC and UW IRB. For multisite trials, investigators at each of their institutions also will have to file reports as required by their own regulatory entities.

- *Roles and Responsibilities in Adverse Event (AE) reporting*
Generally, AEs do not require immediate or prompt reporting, but are regularly listed or summarized in annual or semi-annual reports to the IRB and DMC. Each of the study team members have a role and responsibility to insure that AEs are properly reported.
- *Reporting of Adverse Events (AEs)*
A member of the research team will record all AEs in the Adverse Events (AE) Log Record. AEs that do not meet the definition of an SAE that is possibly related to the study or UP will be reported to the IRB at the time of the study's next progress report/continuing review to include any AE that has occurred since the last IRB review.

A cumulative AE log will be provided to the DMC within each DMC report prior to a scheduled review meeting.

- *Reporting of Serious Adverse Events (SAEs)*

SAEs are AEs which are serious enough to threaten or cause loss of life, limb, or capacity or to result in hospitalization. The DMC requires only that SAEs that are at least possibly related to the study be promptly reported; however, each regulatory entity has its own requirement for SAE reporting. Please note that relatedness of the SAE to the study has nothing to do with the decision of whether an AE meets the criteria as an SAE – i.e., a serious traffic accident could result in the SAE even though there is no reason to believe the traffic accident was caused by any study procedure.

In order to help assure the prompt reporting requirements of the DMC, the AE assessor should always bring any occurrence of a possible SAE to the attention of the Study Coordinator and the study PI who can help to triage the report and decide whether or not this particular SAE is one requiring a prompt report to regulatory authorities. Following the procedures described in [UW-Madison HRPP Investigator Manual](#), please notify the UW IRB within 24 hours of the first observation that a possible SAE has occurred which may meet the prompt reporting criteria of being at least possibly related to the study.

In addition to any prompt report, SAEs will also be reported to the IRB at the time of the study's next progress report/continuing review to include any SAE that has occurred since the last IRB review.

- *Reporting of Unanticipated Problems (UPs)*

The ethical conduct of research requires the informed consent disclosure to subjects of risks that are known or possibly expected during their participation in the research. AEs become a UP when the PI or study staff realizes that an AE is at least possibly related to the study or study procedure and was not anticipated as a risk of the study or of the underlying condition of the subject population.

UPs REQUIRE PROMPT REPORTING: The UW IRB requires that UPs are promptly reported within 24 hours. **Thus, it is essential that study staff observing AEs bring any possible UP to the attention of the Study Coordinator and that the Study Coordinator or other designee follow the prompt reporting procedures in UW IRB [Investigator Manual \(HRP-103\)](#) to bring the possible to the attention of Regulatory Section within 24 hours.**

In addition to any prompt report, UPs will also be reported to the IRB at the time of the study's next progress report/continuing review to include any UP that has occurred since the last IRB review.

The Regulatory Manager on a study will also submit UPs to the DMC in concurrence with the IRB submission.

Any questions regarding the process for reporting AEs, SAEs, and/or UPs should be directed to the UW IRB.

UW-Madison Internal Document