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ADVERSE EVENTS OR UNANTICIPATED PROBLEMS

PURPOSE

The Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) recognize that any adverse event in a trial is a potentially important occurrence because it may reflect additional risks to subjects. In accordance with their requirements, these regulatory bodies have charged Institutional Review Boards with the responsibility of conducting continuing review of research. Included in this review is the monitoring of adverse reactions and unexpected events (21 CFR 56.108 and 45 CFR 46.103).

DEFINITIONS

Adverse events: Any unfavorable diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease shown by the participant which either occurs during the study, having been absent at baseline, or, if present at baseline, appears to worsen. The event may have been anticipated by the protocol and listed as a side effect in the consent form. It is an adverse event even if the event is not associated with the study or caused by the investigational agent. In addition, occasions may occur where an adverse event has not yet occurred, but is likely to occur, as determined by an IRB, research, or clinical team member, unless preventative measures are taken. This is defined as an imminent threat of an adverse event in research and must also be reported as if an actual adverse event had occurred.

Serious adverse events - Any untoward medical occurrences that: (1) result in death, (2) are life threatening, (3) requires inpatient hospitalization or prolongation of existing hospitalization, (4) cause serious, persistent or significant disability or incapacity, (5) result in a congenital anomaly or birth defect, or (6) causes cancer, or (7) results in an overdose of the investigational drug or (8) is any medical event that requires treatment to prevent one of the medical outcomes listed above.

Non-Serious Adverse Event: An adverse event which appears not to have harmed or have the potential to harm participants. The Adverse Event may or may not have been contemplated and listed as side effect in the Informed Consent document.

Expected Adverse Events - Adverse events described in the Package Insert on FDA approved drugs, biologics or devices; adverse events described in the FDA Investigator's Brochure/Device Description for investigational drugs, biologics or devices.

Unexpected Adverse Events - An event is unexpected when the event or its severity are not accurately reflected in the informed consent document, current investigator brochure or product labeling. Further, it is not consistent with the risk information described in the general investigational plan or proposal.

Relationship of Adverse Event to Study Drug or Procedure

Adverse events may be related (are or may have been caused by the study drug or procedure) or unrelated (clearly due to extraneous causes (e.g., underlying disease, environment) to the study drug or procedure.

The following criteria may be used to determine the likelihood that an adverse event is related to the study drug or procedure:

Unlikely (must have 2):

- 1) does not have temporal relationship to intervention,
- 2) could readily have been produced by the subject's clinical state,
- 3) could have been due to environmental or other interventions,
- 4) does not follow known pattern of response to intervention,
- 5) does not reappear or worsen with reintroduction of intervention

Possibly Related (must have 2):

- 1) has a reasonable temporal relationship to intervention,
- 2) could not readily have been produced by the subject's clinical state,
- 3) could not readily have been due to environmental or other interventions,
- 4) follows a known pattern of response to intervention

Probably Related (must have 3):

- (1) has a reasonable temporal relationship to intervention,
- (2) could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions,
- (3) follows a known pattern of response to intervention,
- (4) disappears or decreases with reduction in dose or cessation of intervention

Definitely Related (must have all 4):

- (1) has a reasonable temporal relationship to intervention;
- (2) could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions;
- (3) follows a known pattern of response to intervention;
- (4) disappears or decreases with reduction in dose or cessation of intervention and recurs with re-exposure.

Unanticipated Problem – Any problems that were not contemplated when the research was approved (i.e. are unexpected) and which present risk of serious harm to subjects or to others, including the research team, the university community, or the broader community. Unanticipated problems are always related to an approved study, either ongoing or closed. Adverse events

may meet the criteria for unanticipated problems when they are unexpected, related or possibly related to participation in research, and serious in nature.

Examples of Unanticipated Problems (other than adverse events) that present the risk of serious harm to participants and must be reported to the IRB are:

- subpoena to the PI for sensitive participant data;
- the arrest of a PI on a felony charge;
- the pregnancy of a participant in a study of an unapproved drug;
- the incarceration of a participant
- the loss of copies of participant data carelessly left somewhere outside the study site (or other breaches of confidentiality);
- the results of data safety monitoring of the investigational agent showing an unexpected toxicity that puts other participants at risk.
- complaints
- protocol deviations (e.g. unapproved modification to a research protocol)
- sponsor-imposed suspension for risk.

Protocol deviation – Any unapproved deviation from the protocol, including deviations from eligibility criteria or patient visits outside the time specified in the protocol.

Significant protocol deviation - Any unapproved deviation from the protocol that significantly affects the safety of the subject, the scientific quality of the study, or the safety of researchers. Protocol deviations can include deviations from eligibility criteria, from the manner of completing pretreatment procedures, in using an incorrect form obtaining informed consent or failing to re-consent a participant when required by the IRB, in administering study treatments, complications from study procedures, or failures of safety monitoring.

Complaints - an expression of dissatisfaction or concern about safety, privacy or protection of a subject regarding human subject research.

- Minor complaint – a complaint that alleges an inconvenience to human participants but does not result in an unanticipated problem or serious adverse event or increase in risk. Examples are questions about the amount of participant payment; no close parking available; study personnel were rude; incorrect form was used.
- Major complaint – a complaint that alleges that human participants are being put at risk or increased risk compared with what is described in the consent form. Examples are PI not allowing enough time for the consent process; PI not following inclusion/exclusion criteria; failure to follow protocol; failure to report unanticipated problems or SAEs; participant feels like their rights have been violated; PI not complying with HRC policies or federal regulations; a series of minor complaints.

REPORTING REQUIREMENTS

A. FOR ADVERSE EVENTS INVOLVING PARTICIPANTS FROM WSU SITES

All events that are unexpected, related or possibly related to the study, or suggest that participants are at greater risk than was previously known or recognized, must be reported. All reported adverse events related to the study will be reviewed to determine if they are unexpected and serious, and if they warrant a re-evaluation of the risk level of the study. If subject complaints arise from an observational study, the IRB should be notified in writing of the subject's concern and how the concern was addressed.

For adverse events that are unexpected, related or possibly related to the study, the principal investigator must complete the WSU-IRB Adverse Event/Unanticipated problem form and submit to the IRB within the required time frame for reporting as described in the chart below. Investigators are encouraged to report events as soon as possible within the required time frame shown in the table below.

SEVERITY OF THE EVENT	NATURE OF THE EVENT	RELATIONSHIP OF THE EVENT	REPORTING TO THE WSU IRB
Serious ¹	Expected ² Unexpected	Definite Probably Possible Unlikely Unrelated	Report immediately (within 24 hours of the event) by telephone, fax or e-mail followed by a full written report using the WSU Adverse Event Form within 10 working days. VA personnel, must ensure written notification of the IRB within 5 business days after becoming aware of any local SAE that is both unanticipated and related to the research.
Moderate Minor	Unexpected	Definite Probably Possible	Report in writing using the WSU Adverse Event Form within 20 working days
Moderate Minor	Unexpected	Unlikely Unrelated	Summarize events in progress report at continuing review unless the study is being monitored by the sponsor and the FDA under an IND or IDE, in which case FDA regulations do not require reporting to the IRB
Moderate Minor	Expected	Definite Probably Possible Unlikely	Summarize events in progress report at continuing review
Non-Serious	Unexpected Expected	Definite Probable Possible Unlikely Unrelated	Summarize events in progress report at continuing review

¹ Report all serious adverse events that occur after active study participation for a minimum of 30 days post-study discontinuation or as specified in the protocol, whichever time period is greater

² Reporting of expected serious adverse events to the IRB is not required prior to continuing review for NIH-sponsored cooperative Group trials, such as NCSI-sponsored

oncology trials or certain AIDS trials. Refer to the sponsor's protocol for specific reporting requirements

B. FOR ADVERSE EVENTS FROM SPONSOR REGARDING ADVERSE EVENTS AT SITES EXTERNAL TO WSU

When adverse events are reported in a study that is not being conducted at Wright State or one of its affiliated institutions, the investigator should review the event and answer the following questions:

1. Is the adverse event Serious and Unexpected?
2. Is the adverse event related to the study drug/device/procedures (based upon the assessment of the WSU investigator)?

If the answer to **both** of the above questions is "Yes" then the event should be reported to the IRB. In addition, if a change to the protocol or consent form is necessary, the standard process for submitting these modifications to the IRB should be followed. If the answer to **either** of the questions is "No" then the Adverse Event does not need to be submitted to the IRB but should be **filed** with the investigators research documents as required by the protocol.

C. FOR UNANTICIPATED PROBLEMS (OTHER THAN ADVERSE EVENTS)

1. If reporting is required, the investigator should complete and submit the Adverse Event/Unanticipated Problems Report.
2. When an Unanticipated Problem occurs, the principal investigator (PI) must do the following:
 - a. Report in writing within ten (10) working days of the date the researcher becomes aware of the problem. The VA must report in writing within five (5) working days of the date the researcher becomes aware of the problem. If the unanticipated problem poses an immediate threat to the participant or others, report to the IRB within (1) business day by telephone or e-mail with a follow-up in writing.
 - b. Complete and submit the Adverse Events/Unanticipated Problems Report Form and submit any corroborating reports to the IRB.
 - d. Inform, in writing the appropriate research team members, pharmacist, support staff, administrative officials, and funding or sponsoring agencies if applicable of the unanticipated problem.
3. Specific guidance for situations involving noncompliance is provided in WSU IRB policy 13 (Non-compliance with the Requirements of the Human Research Protection Program).

IRB REVIEW PROCESS

A. ADVERSE EVENTS

1. Principal Investigators will submit required reports of adverse events as defined in the previous sections. The IRB Coordinator will review all adverse event reports submitted to determine whether they are serious adverse events involving risks to participants or others that may require action prior to the next IRB meeting. When uncertain, the IRB Coordinator will refer the report to the IRB Chair. The IRB Chair may choose to refer the report to another IRB member or to the full committee for review. All reported adverse events that occur locally will be reviewed by the IRB board at its next meeting.
2. The IRB will individually review all reported local adverse events and determine if they are unanticipated problems involving risks to participants and others. This finding will be entered into the minutes of the meeting.
3. If the event is determined to be an unanticipated problem involving risk to participants or others, it will be handled as described in (B) below.
4. Questions to be considered when reviewing an adverse event:
 - a. Date and time of onset of adverse event.
 - b. Was the event/problem from this institution, or another participating site if a multi-center sponsor or study?
 - c. Was the event/problem deemed mild, moderate, severe, or fatal? If fatal, date of death, including copy of the death certificate and autopsy report should be obtained.
 - d. Was the event/problem expected or unexpected?
 - e. Was the event/problem related to the research intervention (study related)?
 - f. What was the outcome? Is it resolved, ongoing or did the subject die?
 - g. Based on this event, will additional monitoring of other patients be performed in the study to detect similar problems early?
 - h. Are the possibility, severity and specificity of this event described in the consent form, protocol, and investigator brochure for this study?
 - i. Will the consent procedures be revised as a result of this event? Has the revised consent been submitted to the IRB?

- j. Will patients already enrolled in the study be informed about the possibility of this adverse event? If yes, how?
5. The reviewer(s) shall report on the following to the IRB at a convened meeting:
 - a. Additional risks that may need to be included in the risk section of the consent form.
 - b. An increase in risks that may indicate the need to halt study enrollment; close the study entirely; or modify the study design.
 - c. If the reviewers (or the Committee) feel it necessary to supplement their review, they may request an outside "expert" to review and comment
 - d. Approval of the description and reporting of the adverse event.
6. The IRB may suspend or terminate research if the information gained during its review of the adverse events indicates that human subjects in a research project are exposed to unexpected serious harm. [21CFR 56 108(b)(1); 45 CFR 46 103(b)(5)] When such action occurs, the IRB will provide a written statement of action to the investigator, and the Institutional Official or designee will notify the sponsor and governing regulatory authority in writing of all protocols suspended for cause (see below for specific VA reporting mechanism). This notification will include the reason for suspension and the action taken to resolve the issue. All notification will occur within 10 days.
7. The IRB may accept the findings of the PI and designated reviewers. The AE report will be placed in the protocol file and reported during continuing review.

B. UNANTICIPATED PROBLEMS

The IRB Coordinator will initially review reports to determine whether the reported event is an unanticipated problem involving noncompliance (see Policy 13), involving risks to participants or others, is serious, or is continuing in nature. If uncertain, the coordinator will immediately refer the report to the IRB Chair or designee. The Chair or designee will review and assess the facts of all reported events, including review of the related IRB records and the IRB approved protocol. The IRB Chair may consult with others to achieve a more thorough or faster assessment.

If the IRB Chair decides that the reported incident is an unanticipated problem involving noncompliance, involving risks to participants or others, is serious, or is continuing in nature, he/she will bring the problem to the attention of the IRB at its next convened meeting. The IRB members will be provided with a copy of the report, documents from the IRB records concerning the report, and have available the approved protocol for necessary and appropriate deliberations. The IRB may interview the researcher who

reported the problem or the principal investigator of the research study.

1. If the IRB determines that the event was **not** an unanticipated problem involving noncompliance, does not involve risks to participants or others, is not serious, and is not continuing in nature, no further action will be taken.
2. If the convened IRB determines that the event was an unanticipated problem involving risks to participants or others, the IRB will take action as described in Policy 13 (Non-compliance with the Requirements of the Human Research Protection Program)

IRB REPORTING OF ADVERSE EVENTS OR UNANTICIPATED PROBLEMS

Any adverse event or unanticipated problem reviewed by the IRB will be recorded in the minutes of the meeting at which it was reviewed. The minutes will reflect whether the problem involved noncompliance, risks to participants, is serious in nature, and/or is ongoing in nature.

Any substantive action taken by the IRB (defined as an action that materially alters the substance and meaning of a protocol, informed consent form or process, or investigator status, including, but not limited to, restriction, suspension or termination of a study or investigator participation, and actions taken to prevent future occurrence(s) of the AE in research) must be reported in writing to the WSU Institutional Officer, the investigator's department head, and the Dean of the Investigator's school.

Within 10 days the Institutional Official will inform OHRP, for federally funded studies, the FDA for studies involving drugs, devices, and biologics, the sponsor of the study and any other regulatory of the action taken.

VA REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

For VAMC research (see VHA Handbook 1058.01), reportable events will be reported to the IRB Coordinator by the investigator (through the VA Research Office) within the time frames specified earlier in this procedure. If the convened IRB indicates that the event is further reportable (see bulleted statements below), the VA Designated Institutional Official will then report to the appropriate bodies and will send a copy of all correspondence will be provided to the IRB.

- All adverse events or unexpected problems in research, and imminent threats of AEs in research that result in either:
 - The IRB taking substantive action or
 - An unexpected death of a research subject, regardless of IRB action. Such deaths must be reported to the Dayton VAMC within 24 hours after the IRB determination that the death was unexpected. If the IRB is unable to determine whether a research subject's death was unexpected after 10 working days of being informed of the

death, the death must then be reported to the ORO. When a final determination is made as to whether or not the death was unexpected, a follow-up report must be made to the ORO.

- Any unexpected death of a subject

Note: Such deaths must be reported to the ORO by the Dayton VAMC within 24 hours after the IRB determines that the death was unexpected, as defined below. If the IRB is unable to determine whether a research subject's death was unexpected after 10 working days of being informed of the death, the death must then be reported to the ORO. When a final determination is made as to whether or not the death was unexpected, a follow-up report must be made to the ORO.

Unexpected Death. The death of a research subject in which a high risk of death is not projected, as indicated by the written protocol, informed consent form, or sponsor brochure. This definition does not include deaths associated with a terminal condition unless the research intervention clearly hastened the subject's death. A subject's death that is determined to be clearly not associated with the research is also not an "unexpected death" for purposes of the reporting requirements of this Charter and Standard Operating Procedures.

- Any noncompliance which is serious or ongoing in nature
- Unauthorized use, loss or disclosure of individually identifiable patient information
- Information that indicates a change to the risks or potential benefits of the research.

For example:

- An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB
- A paper is published from another study that shows that the risks or potential benefits of your research may be different than initially presented to the IRB.
- A breach of confidentiality.
- Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant Incarceration of a participant in a protocol not approved to enroll prisoners.
- Event that requires prompt reporting to the sponsor.
- Sponsor imposed suspension for risk.
- Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional change to the IRB approved protocol) that harmed participants or others or that indicates participants or others may be at increased risk of harm.

- Violations of VAMC information security requirements .

In cases of unauthorized use, loss or disclosure of individually identifiable patient information the Associate Chief of Staff (or equivalent) for Research must immediately notify the VA Facility Director, the R&D Committee, and any relevant research review committee upon discovering, receiving, or otherwise becoming aware of a credible report of an incident regarding any unauthorized use, disclosure, transmission, removal, theft, loss, or destruction of VA research-related protected health information (PHI), individually identifiable private information, or confidential information, as defined by the HIPAA Privacy Rule, the Common Rule, the Privacy Act, or 38 U.S.C. §§5701, 5705, and 7332..

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