WRIGHT STATE UNIVERSITY

Policy: P9
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Reportable Problems or Events

1.0 Purpose:

The purpose of this policy is to define the information that requires prompt reporting to the Wright State University Institutional Review Board (hereafter referred to as the WSU IRB).

2.0 Scope:

This policy applies to all human subject research for which the WSU IRB acts as the IRB of record.

3.0 Definitions:

3.1 **Unanticipated Problem Involving Risks to Participants or Others** means:

3.1.1 The problem/event is UNEXPECTED in terms of nature, severity, or frequency, given:

3.1.1.1 The research procedures described in the protocol, Investigator Brochure, informed consent document and/or other study related documents; and

3.1.1.2 The characteristics of the subject population being studied; and

3.1.2 The information indicates the research places subjects or others at SERIOUS risk (as defined below) **or** an increased risk of physical, psychological, economic, legal, or social harm than was previously known or recognized, and

3.1.3 The problem/event is RELATED or POSSIBLY RELATED to the procedures involved in the research.

3.2 **Serious** means a problem/event that:

3.2.1 Results in death;
3.2.2 Is life-threatening (places the subject at immediate risk of death from an event as it occurred);
3.2.3 Results in inpatient hospitalization or prolongation of existing hospitalization;
3.2.4 Results in persistent or significant disability/incapacity;
3.2.5 Results in congenital anomaly/birth defect; or
3.2.6 Based on appropriate medical judgement, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

3.3 **Unanticipated Adverse Device Effect** means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the

investigational plan or application. Any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

3.4 **Prompt Reporting means** reporting of problems or events that are defined in this policy should occur as soon as possible after the Principal Investigator (PI) learns of the event, but in all cases within 10 calendar days.

3.5 **WSU Subject** means as an individual enrolled in a research study either that is conducted at a WSU/affiliated hospital facility hospital or that is conducted off-site under the direct supervision of a WSU/affiliated hospital PI at a non-WSU/affiliated hospital site.

3.6 **Major Protocol Deviation** means any alteration/modification to the WSU-approved research that has the potential to negatively impact subject safety or integrity of study data (ability to draw conclusions from the study data), or affect the subject's willingness to participate in the study.

3.7 **Minor Protocol Deviation**: means any alteration/modification to the WSU-approved research that DOES NOT have the potential to negatively impact subject safety or integrity of study data (ability to draw conclusions from the study data), or affect the subject's willingness to participate in the study.

3.8 **Investigator** means the Project Director/Principal Investigator (PD/PI) and any other person, regardless of title or position, who is responsible for the design, conduct, or reporting of research, or proposing of research, including persons who are subcontractors, collaborators or consultants. At WSU this definition includes, but is not limited to, the following roles: Principal investigator, co-investigators, research coordinators, research associates, collaborators and consultants, and may include research assistants and students as identified by the PD/PI depending on their specific roles and responsibilities.

4.0 Policy

Wright State University requires that investigators comply with all applicable local, state, and federal laws and regulations in the conduct of research studies. As part of this requirement, investigators are required to submit to the WSU IRB written reports of certain problems or events listed below, including "unanticipated problems involving risks to participants and others."

This policy is established to ensure compliance with applicable regulatory requirements and to assist investigators in understanding when and what new information (reportable event or problem) must be reported to the WSU IRB.

5.0 Procedure

5.1 Reportable Events or Problems that Require Prompt Reporting

WSU requires PROMPT (i.e., ASAP and within 10 calendar days) reporting of the following problems or events:

5.1.1 Any INTERNAL or EXTERNAL Unanticipated Problem Involving Risks to Participants or Others (as defined above). *Note that the VA requires that all events meeting the definition of an Unanticipated Problem involving VA research or personnel be reported to the IRB within 5 business days.*

5.1.2 Information that indicates a change to the risk to benefit ratio of the research. For example:

- 5.1.2.1 An interim analysis indicates that participants have a lower rate of response to treatment than initially expected;
- 5.1.2.2 Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected; or
- 5.1.2.3 A paper is published from another study that shows that an arm of the research study is of no therapeutic value.

5.1.3 Change(s) in FDA labeling (e.g., black box warning), withdrawal from marketing, manufacturer alert from the sponsor, or recall of an FDA-approved device, or biologic used in the research

5.1.4 Change(s) to the research (without prior IRB approval) taken to eliminate an apparent immediate hazard to a research subject

5.1.5 Any major protocol deviation. Examples include, but are not limited to:

- 5.1.5.1 Failure to obtain informed consent (i.e., there is no documentation of informed consent)
- 5.1.5.2 Informed consent obtained after initiation of study procedures
- 5.1.5.3 Drug/study medication dispensing error
- 5.1.5.4 Performing a study procedure not approved by the IRB
- 5.1.5.5 Failure to perform a required lab test that, in the opinion of the PI, may affect subject safety or data integrity
- 5.1.5.6 Enrollment of a subject who did not meet all inclusion/exclusion criteria
- 5.1.5.7 Study visit conducted outside of required timeframe that, that in the opinion of the PI, may affect subject safety
- 5.1.5.8 Failure to follow safety monitoring plan

5.1.6 Incarceration of a WSU research subject

5.1.7 Complaint of or related to a WSU research subject when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team.

5.1.8 Any unanticipated adverse device effect (as defined above)

5.1.9 Any audit, inspection, inquiry by a governmental agency, or correspondence with a government agency

5.1.10 Any written report of a federal agency (e.g., FDA Form 483, Establishment Inspection Report (EIR), Warning Letter)

5.1.11 Any written audit report by a sponsor regardless of findings

5.1.12 Any internal subject death in a "greater than minimal risk" study, even if "anticipated," if it occurs within 30 days of a study-related procedure or the administration of a study drug

5.1.13 Any breach of confidentiality

5.1.14 Violations of Dayton VAMC Information Security Requirements

All problems/events listed above must be reviewed by the PI (or his/her designee) and submitted by the PI or delegated staff using the Reportable Problem/Event Form in the Human Subjects Module. Initial reports to the WSU IRB may be accepted by other means such as email or phone only if the report is of an urgent nature. However, a Reportable Problem/Event Report Form still must be submitted as soon as possible in InfoED in such instances.

When making problem/event reports, investigators should take into consideration whether substantive changes in the research or informed consent document may be warranted to protect the safety, welfare, or rights of subjects or others. Any proposed changes must be submitted via the Human Subjects Module as an Amendment. Examples of substantive changes include:

5.1.15 Changes to eligibility criteria

5.1.16 Changes to safety monitoring procedures

5.1.17 Changes to the informed consent document to describe newly identified risk

5.1.18 Suspension of enrollment of new subjects

5.1.19 Suspension or termination of the research

Note: The WSU IRB does not accept sponsor IND/IDE safety reports describing adverse events that have occurred at sites other than those subject to this policy unless the report is of an incident that is: (1) serious; (2) unexpected or unanticipated; (3) related to the investigational drug/device; and (4) suggests that subjects are at an increased risk of harm and as such warrants changes in the research, consent process, or informing subjects. IND/IDE safety reports that warrant changes must be submitted in via the Human Subjects Module as an Amendment, not a Reportable Problem/Event.

5.2 Reportable Events or Problems that Require Reporting at Continuing Review and Study Closure

5.2.1 Minor Protocol Deviations:

During the conduct of the study all minor protocol deviations must be recorded on the Study Deviation Summary Sheet or other IRB-approved form. Minor protocol deviations must be reported to the WSU IRB at the time of continuing review or study closure by attaching the form to the appropriate InfoED submission.

Examples of minor or administrative deviations could include: follow up visits that occurred outside the protocol required time frame because of the participant's schedule, or blood samples obtained at times close to but not precisely at the time points specified in the protocol.

Please note that FDA device regulations at 21 CFR 812.150(a)(4) require prior approval from the sponsor of all planned deviations, including minor deviations. Planned deviations requested of a sponsor must be submitted for IRB review and approved by the WSU IRB prior to instituting any IDE research planned deviations. The PI must submit an Amendment to the study via InfoED. For device research, the PI must keep on file a copy of the written approval document from the sponsor when a deviation is granted.

5.2.2 Internal Serious Events that Do Not Meet Definition of an Unanticipated Problem

Information regarding internal SERIOUS Problems/Events that occurred during the previous approval period, but did not meet the PROMPT reporting requirements above, must be submitted as part of the Continuing Review Application or Study Closure Form in InfoED.

5.2.3 Sponsor Monitoring Reports

Information as to whether monitoring by the sponsor was conducted during the previous approval period must be submitted as part of the Continuing Review Application or Study Closure Form in InfoED. Investigators are required to attach a copy of any monitoring report in which the monitor required corrective actions to the application being submitted.

5.3 IRB Review of Problem/Event Reports

Each reported problem or event will be assessed to determine if it meets the definition of an unanticipated problem involving risks to participants or others. Review of a problem or event may require use of a consultant, or assistance from the division or department chair to collect additional information before a determination is made. Action will be taken to address the problem. The actions may be taken by the Institutional Official (IO), other senior WSU/affiliated hospital officials charged with taking action, or the IRB. The range of actions includes items listed

below, but the list does not preclude taking additional actions as determined on a case-by-case basis:

5.3.1 Administrative hold on the study pending IRB receipt of further information from the PI in a time period not to exceed 90 days;

5.3.2 Modification of the protocol;

5.3.3 Modification of the information disclosed during the consent process;

5.3.4 Providing additional information to current subjects (this must be done whenever the information may relate to the participant's willingness to continue participation);

5.3.5 Making arrangements for clinical care outside the research or additional follow-up for subjects;

5.3.6 Providing additional information to past subjects;

5.3.7 Requiring current subjects to re-consent to participation;

5.3.8 Alteration of the frequency of continuing review;

5.3.9 Observation of the research or the consent process;

5.3.10 Requiring additional training of the PI, co-investigator and/or other study team members;

5.3.11 Notification of investigators at other sites;

5.3.12 Obtaining additional information;

5.3.13 Termination or suspension of the research.

The IO will be informed when a determination has been made that a problem or event meets the definition of an unanticipated problem involving risks to participants or others and/or when research is suspended or terminated. The IO will fulfill the requirements to report the action to federal departments or agencies as required by regulation in accord with WSU IRB policy.

If a determination is made that a problem or event does not meet the definition of an unanticipated problem involving risks to participants or others, IO notification is not required.

5.4 Dayton Veterans Affairs (VA) Medical Center Additional Reporting and IRB Review Requirements

VA investigators (aka personnel) must notify the IRB orally immediately upon becoming aware of any local research death that is both unanticipated and related to the research. The IRB must alert the VA Office of Research Oversight (ORO) by e-mail or telephone within two business days

after receiving such notification and provide relevant information as requested. The Dayton VA facility Director and the ACOS/R&D must receive concurrent notification. VA investigators must submit the reportable event form in InfoED to the IRB within five business days of becoming aware of the death.

Within five business days after receiving written notification of the death, the IRB Chair or a qualified IRB member-reviewer must determine and document whether any actions are warranted to eliminate apparent immediate hazards to subjects.

The IRB must review the death and the determination of the IRB Chair or qualified IRB member-reviewer at its next convened meeting and must determine and document that:

- The death was both unanticipated and related to the research; or
- There is insufficient information to determine whether the death was both
- unanticipated and related to the research; or
- The death was not unanticipated, and/or the death was not related to the
- research.

Regardless of the determination above, the convened IRB must also determine and document whether any protocol or informed consent modifications are warranted. If modifications are warranted, the convened IRB must determine and document whether investigators must notify or solicit renewed/revised consent from previously enrolled subjects; and if so, when such notification or consent must take place and how it must be documented.

The IRB must notify the Dayton VA facility Director and the ACOS/R&D of its determinations within five business days of the determinations. The Dayton VA facility Director must report the determinations to ORO within five business days after receiving the IRB's notification.

In cases of unauthorized use, loss or disclosure of VA 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.

6.0 Responsibilities and Authorities:

6.1 Investigators

All investigators must understand what constitutes reportable problems or events, and how and when to report them. However, the PI is ultimately responsible for prompt reporting. Before a study is initiated, the PI should review potential reportable problems/events based on the

protocol (e.g., events that requires prompt reporting to the sponsor) and this policy with all study investigators and have a clear process in place to ensure that potential problems/events identified by study investigators are reported to him/her as soon as possible. A written delegation plan should also be in place for limited situations in which the PI is unable to meet the reporting requirements of this policy (i.e., extended absence or illness).

It is important to understand that reporting an event to the WSU IRB does not relieve the PI of his/her obligation to report the event to other agencies such as the FDA or study sponsors when required. Sponsored research agreements may require the PI to notify the sponsor of other adverse events and all unplanned deviations or departures from IRB approved protocol procedures. Sponsor reporting requirements for deviations and/or adverse events may differ from WSU reporting requirements. It is the PI's responsibility to comply with the reporting requirements outlined in the signed contract. Before a PI signs a research agreement, the PI is strongly advised to read and understand the contract terms.

6.2 WSU IRB

The WSU IRB is responsible for reviewing all reportable problems or events via a process that is compliant with all applicable regulatory requirements. It is also responsible for providing any determinations and required actions in writing to the PI.

It has the authority to require changes to research and to suspend or terminate research to protect current and potential WSU research subjects.

7.0 Records

All records related to this process will be stored and maintained in accordance with any WSU policy, federal regulations and sponsor requirements associated with the human subject research protocol under review.

8.0 References:

8.1 45 CFR 46.103(b)(5)
8.2 45 CFR 46.103(a)
8.3 45 CFR 46.108
8.4 45 CFR 46.113
8.5 21 CFR 56.108(b)(1)
8.6 21 CFR 56.113
8.7 21 CFR 312.32
8.8 VA Handbook 1058.01
8.9 38 CFR 16