HRPP STANDARD OPERATING PROCEDURE/POLICY APPROVAL & IMPLEMENTATION

OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

SOP Number: 16

SOP Title: Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations

Distribution: Scientific Directors; Clinical Directors; Clinical Investigators, IRB Chairs, IRB Administrators, Protocol Navigators

Revision Approval: Michael Gottesman 10/1/13
Deputy Director for Intramural Research — Date

Revision Implementation date: 10-1-2013

Materials Superseded: SOP 16 rev. 1 dated 9/27/2013

DHHS/NIH/OD/OIR/OHSRP — Implementation Approval

SOP 16. REPORTING REQUIREMENTS FOR UNANTICIPATED PROBLEMS, ADVERSE EVENTS AND PROTOCOL DEVIATIONS

TABLE OF CONTENTS

16.1 PURPOSE 1
16.2 POLICY 1
16.3 DEFINITIONS 1
16.4 BACKGROUND 5
16.5 POLICY ON REPORTING TO THE IRB 6
16.5.1 REGULATORY REQUIREMENTS 6
16.5.2 ADDITIONAL NIH REQUIREMENTS 7
16.6 POLICY ON REPORTING TO THE CLINICAL DIRECTOR (CD) 7
16.7 POLICY ON REPORTING TO THE SPONSOR OF FDA-REGULATED RESEARCH 7
16.7.1 REGULATORY REQUIREMENTS 7
16.8 PI MONITORING AND REPORTING RESPONSIBILITIES 8
16.8.1 MONITOR EVENTS AND DETERMINE THE NATURE OF THE EVENT 8
16.8.2 OBTAINING A WAIVER FROM IRB REPORTING: ANTICIPATED PDS, EXPECTED NON-UP AES, AND DEATHS 8
16.8.3 REQUIRED METHODS AND TIME FRAMES FOR PI REPORTING TO THE IRB, THE INSTITUTE CLINICAL DIRECTOR (CD), AND SPONSOR (IF APPLICABLE) 8
16.8.4 NIH PROTOCOLS THAT ARE OVERSEEN BY A NON-NIH IRB 11
16.8.5 REPORTING UPS AND AES OCCURRING AT OUTSIDE ENTITIES 11
16.8.6 MONITORING REPORTS FROM A SPONSOR 11
16.9 REPORTING RESPONSIBILITIES OF INVESTIGATORS WHO ARE ALSO SPONSORS 11
16.10 IRB RESPONSIBILITIES 12
16.10.1. IRB WAIVER OF CERTAIN IRB REPORTING REQUIREMENTS FOR EXPECTED EVENTS 12
16.10.2 INITIAL IRB RECEIPT, REVIEW, DETERMINATIONS, AND ACTIONS REGARDING REPORTS OF UPS AND PDS 12
16.10.3 IRB REVIEW AND DETERMINATION REGARDING UPS AND PDS 12
16.10.4 IRB REPORTING OF UPS TO THE NIH OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS (OHSRP) 13

DHHS/NIH/OD/OIR/OHSRP

16.11 NIH REQUIREMENTS FOR REPORTING UPS TO THE OFFICE FOR HUMAN RESEARCH PROTECTIONS (OHRP) AND THE FOOD AND DRUG ADMINISTRATION (FDA) 14

REFERENCES 15

A. REGULATIONS AND POLICIES 15

B. GUIDANCE 15

LIST OF APPENDICES 16

LIST OF ATTACHMENTS 16

APPENDIX A: DECISION TREE FOR PROMPT REPORTING OF EVENTS OCCURRING DURING HHS- AND FDA-REGULATED RESEARCH 17

APPENDIX B: HOW TO DETERMINE WHETHER AN ADVERSE EVENT IS ALSO AN UNANTICIPATED PROBLEM 18

APPENDIX C: EXAMPLES OF UNANTICIPATED PROBLEMS (UPS) 19

APPENDIX D: FDA GUIDANCE ON TYPES OF AES THAT SHOULD BE CONSIDERED UPS AND MUST BE REPORTED TO THE IRB 24

APPENDIX E: EXAMPLES OF PROTOCOL DEVIATIONS 27

ATTACHMENT A: NIH PROBLEM REPORT FORM 30

SOP 16. REPORTING REQUIREMENTS FOR UNANTICIPATED PROBLEMS, ADVERSE EVENTS AND PROTOCOL DEVIATIONS

16.1 PURPOSE

This Standard Operating Procedure (SOP) describes requirements and time frames for NIH Principal Investigators (PIs) to report events that may indicate increased risks to human subjects. These events are known as Unanticipated Problems (UPs), Protocol Deviations (PDs), Adverse Events (AEs), and deaths. Reports will be made, as described below, to the Institutional Review Board (IRB), NIH Institute Clinical Director (CD), and/or, if applicable, to the Sponsors of FDA-regulated research. This SOP also describes the roles and responsibilities of IRBs regarding these events.

16.2 POLICY

PIs must track and/or report UPs, PDs, AEs, and deaths. PIs report these events to their NIH IRBs, NIH Institute CD, and/or, if applicable, to the Sponsors of FDA-regulated research. The type and severity of the event dictates how quickly it must be reported and to whom.

The PI and IRB must determine whether the reportable event requires changes in the protocol or consent and whether other actions are needed to protect the safety, welfare, or rights of study participants or others. This SOP also describes requirements and time frames for NIH IRBs to review and report these events to the NIH Office of Human Subjects Research Protections (OHSRP), see section 16.10.3 below.

PIs and Sponsor-investigators who are conducting protocols involving FDA-regulated research have additional Sponsor reporting requirements, some of which are described in Section 16.7 below. Other PI responsibilities related to FDA requirements are set forth in SOP 15, “Research Regulated by the Food and Drug Administration: General Procedures for both IND and IDE Applications”; SOP 15A “Research Regulated by the Food and Drug Administration (FDA): Information and Policies Specific to Research Involving Investigational New Drugs (Including Biological Products)” and SOP 15B “Research Regulated by the Food and Drug Administration (FDA): Information and Policies for IDE Applications.”

16.3 DEFINITIONS

Events covered by this policy may sometimes satisfy more than one of the definitions below.

A. **Adverse Event (AE):** Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research. In the context of FDA-required reporting, an AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

B. **Serious Adverse Event* (SAE):** is any Adverse Event that:

   1. Results in death

   2. Is life-threatening (places the subject at immediate risk of death from the event as it occurred)

   3. Results in inpatient hospitalization or prolongation of existing hospitalization

   4. Results in a persistent or significant disability/incapacity

   5. Results in a congenital anomaly/birth defect, **OR**

   6. Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

   *In IND-regulated research, this term is used synonymously with "serious suspected adverse reaction." (See 21 CFR 312.32(a) for the FDA definition.)

C. **Non-compliance:** The failure to comply with applicable NIH HRPP policies, IRB requirements, or regulatory requirements for the protection of human research subjects (see SOP 16A, "Allegations and Incidents of Non-compliance"). Non-compliance may be further characterized as:

1. **Serious non-compliance:** Non-compliance that:

    a. Increases risks, or causes harm, to participants.

    b. Decreases potential benefits to participants.

    c. Compromises the integrity of the NIH HRPP.

    d. Invalidates the study data.

2. **Continuing non-compliance:** Non-compliance that is recurring. An example may be a pattern of non-compliance that suggests a likelihood that, absent an intervention, non-compliance will continue. Continuing non-compliance could also include a failure to respond to IRB requests to resolve previous allegations of non-compliance.

3. **Minor (non-serious) non-compliance:** Non-compliance that, is neither serious nor continuing.

D. Protocol Deviation (PD): Any change, divergence, or departure from the IRB-approved research protocol.

The impact of a PD is characterized by designation as serious or not serious (see Appendix E- Examples of Protocol Deviations.) This SOP addresses three types of protocol deviations: 1) Those that occur because a member of the research team deviates from the protocol; 2) Those that are identified before they occur, but cannot be prevented (e.g., when a subject alerts the research team that inclement weather will prevent the subject from attending a scheduled protocol visit); and 3) Those that are discovered after they occur. This SOP addresses the reporting of deviations from an investigational plan performed to eliminate immediate apparent hazards to the subject as required in device research (See 16.8.3). This SOP does not address other aspects related to deviations from the protocol performed to eliminate immediate apparent hazards to the subject in compliance with 45 CFR 46.103(b)(4) and, when applicable, 21 CFR 56.108(a)(4) or changes in research made with IRB review and approval in compliance with 45 CFR 46.103(b)(4) and, when applicable, 21 CFR 56.108(a)(3) and (a)(4) (see SOP 10, “Amendments to IRB Approved Research”).

E. Protocol Violation: This term was used previously at NIH to denote a Protocol Deviation having a major impact on the subject’s rights, safety, or well-being and/or

the completeness, accuracy and reliability of the study data. With this SOP, the term Protocol Violation has been superseded by the broader term "Protocol Deviation".

F. **Serious:** A UP or PD is serious if it meets the definition of a Serious Adverse Event (see above) or if it compromises the safety, welfare or rights of subjects or others**.**

G. **Sponsor:** A person or other entity who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the Test Article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct a clinical investigation that it has initiated is considered to be a Sponsor (not a Sponsor-investigator), and the employees are considered to be investigators, (21 CFR 56.102(j); see also 21 CFR 50.3(e)).

H. **Sponsor-investigator:** An individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency, (21 CFR 50.3(f); see also 21 CFR 56.102(k) and 21 CFR 312.3.)

I. **Test article:** Means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act [FDCA] or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n). (21 CFR 50.3(j); see also 21 CFR 56.102(l)). For more information see SOP 15 - "Research Regulated by the Food and Drug Administration (FDA): General Procedures for Both IND and IDE Applications."

J. **Unanticipated Problem (UP):** Any incident, experience, or outcome 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 (**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

3. Suggests that the research places subjects or others at a **greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized.

Expected Adverse Events may become Unanticipated Problems if they occur at a greater frequency or severity than was previously expected.

1. Appendix C provides the OHRP guidance on examples of Unanticipated Problems.

2. Appendix D provides the FDA guidance on types of Adverse Events that should be considered Unanticipated Problems and must be reported to the IRB

K. Unanticipated Problems that are not also Adverse Events (AEs): Unanticipated Problems that are not also AEs may involve a greater risk of social or economic harm (to subjects or others) rather than physical/psychological harm.

L. Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

16.4 BACKGROUND

It is important to understand that an event may qualify as more than one type of reportable event. For instance, a PD that suggests that the research places subjects or others at greater risk of harm than was previously recognized also qualifies as an Unanticipated Problem (UP). In that case, the PI would need to report the event as a PD and a UP as directed by this policy; both the PD and UP can be reported simultaneously.

Another example of overlapping reportable events are AEs and UPs. UPs include events that may be AEs, but also, as explained in this SOP, include other events that are not AEs. (See Appendix B – How to Determine Whether an Adverse Event is also an Unanticipated Problem.) The DHHS Office of Human Research Protections (OHRP)

diagram below summarizes the relationships between Unanticipated Problems and Adverse Events:

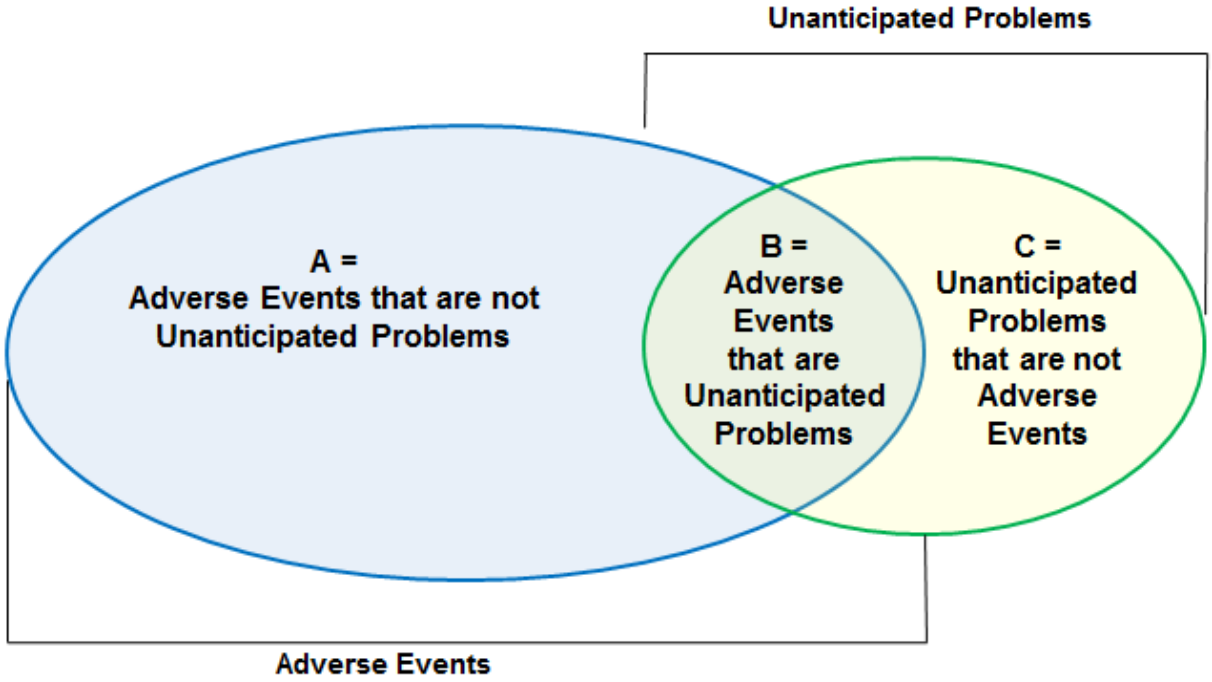

Image 1. OHRP Venn Diagram of Unanticipated Problems
A: The vast majority of AEs occurring in human subjects are not UPs
B: A small proportion of AEs are also UPs
C: UPs include other incidents, experiences or outcomes that are not AEs

NIH no longer requires PIs to immediately report all AEs to the IRBs. AEs that are UPs are reportable to the IRB individually according to UP reporting requirements, but AEs that are not UPs are reported only as aggregated summaries at Continuing Review (CR). Further, a PI must assess whether expected AEs are occurring at greater frequency or severity than previously expected. If this occurs, the aggregate information may also qualify as a UP and must be reported as such.

16.5 POLICY ON REPORTING TO THE IRB

16.5.1 REGULATORY REQUIREMENTS

NIH PIs are required to report promptly all UPs to the IRB in accordance with Office of Human Research Protections (OHRP) and applicable FDA regulations and

guidance as well as with reporting requirements specified in this SOP (see 16.8 below). Additionally, for FDA-regulated research, all Unanticipated Adverse Device Effects (UADEs) and deviations from a device study's investigational plan to protect the life or physical well-being of a subject in an emergency must be reported to the IRB within this SOP's specified time frames (see 16.8.3 below).

16.5.2 ADDITIONAL NIH REQUIREMENTS

All Protocol Deviations must be reported to the IRB within this SOP's specified time frames (see 16.8.3 below) unless the IRB has approved a waiver from reporting (see 16.8.2 below). AEs that are not UPs will be reported to the IRB in aggregate at the time of CR (see 16.8.3 below).

IRBs may impose additional reporting on a protocol-by-protocol basis if the additional requirements are no less strict than the policies set forth in this SOP.

16.6 POLICY ON REPORTING TO THE CLINICAL DIRECTOR (CD)

NIH PIs must report all UPs, Serious PDs, deaths, and UADES to the CD, unless otherwise specified by the CD and documented in the protocol. Reporting to the CD must occur within this SOP's specified time frames (see 16.8.3 below). Note that AEs that are not UPs and PDs that are not Serious do not need to be reported to the CD under this policy.

16.7 POLICY ON REPORTING TO THE SPONSOR OF FDA-REGULATED RESEARCH

16.7.1 REGULATORY REQUIREMENTS

FDA regulations require investigators to immediately report to the Sponsor any Serious Adverse Event (SAE), whether or not considered drug related, including those listed in the protocol or investigator brochure. For more information on the content of these reports, see 21 CFR 312.64(b). The investigator must record non-serious AEs and report them to the Sponsor according to the timetable for reporting specified in the protocol (see 21 CFR 312.64(b)). For more information on other investigator reports to a Sponsor, see 21 CFR 312.64 and SOP 15A – "Research Regulated by the Food and Drug Administration (FDA): Information and Policies Specific to Research Involving Investigational New Drugs (Including Biological Products". For device studies, investigators must also report UADEs and deviations from the investigational plan to protect the life or physical well-being of a subject in an

emergency to Sponsors (21 CFR 812.150(a)(1) and (a)(4)). For more information on these requirements, see SOP 15B- "Research Regulated by the Food and Drug Administration (FDA): Information and Policies for IDE Applications." See 16.8.3 for more details on this SOP's specified time frames for reporting to the Sponsor.

16.8 PI MONITORING AND REPORTING RESPONSIBILITIES

(See, in addition, SOP 19 – "Investigator Responsibilities")

16.8.1 MONITOR EVENTS AND DETERMINE THE NATURE OF THE EVENT

NIH PIs are responsible for collecting, tracking, evaluating and documenting all events (both expected/unexpected and related/not related to the research). The PI must assess and determine if an event fulfills the criteria for reporting to the IRB, CD, or applicable Sponsor per this SOP. The PI also must assess the seriousness of the event to decide on the timing of the report, if any, to the IRB, CD, and/or Sponsor, if applicable. Any changes to a protocol in response to a UP, PD, or AE must be reviewed and approved by the IRB (and Sponsor, if applicable) before being implemented, except when necessary to eliminate apparent immediate hazard to the subjects (see SOP 10, "Amendments to IRB Approved Research").

16.8.2 OBTAINING A WAIVER FROM IRB REPORTING: ANTICIPATED PDS, EXPECTED NON-UP AES, AND DEATHS

In response to a PI's sufficient justification in the protocol, an IRB may agree to waive individual events and aggregate IRB reporting requirements for anticipated PDs, expected non-UP AEs, or deaths based on the natural history of the disorder or population. The specific waiver sought and the expected frequency of the waived reportable event must be stated in the protocol. If the rate of these events exceeds the rate anticipated in the protocol or investigators' brochure (if applicable), the events should be classified and reported as though they are Unanticipated Problems – and this should be stated in the protocol. Such a waiver applies to NIH IRB reporting only and does not apply to other reporting requirements. (See Appendix E for examples of items that an IRB may waive from reporting requirements.)

16.8.3 REQUIRED METHODS AND TIME FRAMES FOR PI REPORTING TO THE IRB, THE INSTITUTE CLINICAL DIRECTOR (CD), AND SPONSOR (IF APPLICABLE)

NIH PIs are required to report UPs, PDs, deaths, and AEs to the IRB, CD, and/or Sponsor (when applicable) as follows (also shown graphically in Appendix A-Decision Tree for Prompt Reporting of Events Occurring During HHS- and FDA-regulated Research):

A. Method of Reporting: The PI must report to the IRB using the appropriate electronic IRB reporting system. If the PI is unable to access the appropriate IRB reporting system, the PI may use the NIH Problem Report Form in Attachment A. This form will be automatically routed to the CD and IRB. PIs should report to the Sponsor as mutually agreed upon. The PI may elect also to report events (especially if serious) to the IRB Chair/designee and/or the CD in person or by phone or e-mail. However, such reporting is in addition to reporting using the appropriate electronic IRB reporting system or NIH Problem Report Form.

B. Timing of Reporting:

1. Serious Events

a. Reports to the IRB and CD:

The PI must report Serious UPs, Serious PDs, and UADEs to the IRB and CD as soon as possible but not more than 7 days after the PI first learns of the event.

For device research, the PI must report to the IRB any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency as soon as possible, but no later than 5 working days after the emergency occurred.

b. (b) Reports to the Sponsor of FDA-regulated research (as applicable):

i. For drugs and biologics, the PI must immediately report SAEs to the Sponsor according to the requirements of 21 CFR 312.64(b) and as agreed upon with the Sponsor.

ii. For devices, the PI must report UADEs to the Sponsor as soon as possible, but no more than 10 working days after the PI first learns of the event. The PI must also report to the Sponsor any deviation from the investigational plan to protect the life or physical well-being of a

subject in an emergency as soon as possible, but no later than 5 working days after the emergency occurred.

2. Not Serious Events

a. Reports to the IRB and CD:

The PI must report all UPs that are not Serious to the IRB and CD, and PDs that are not Serious to the IRB, not more than 14 days after the PI first learns of the event.

b. (b) Reports to the Sponsor of FDA-regulated research (as applicable):

i. For drugs and biologics, the PI must record nonserious AEs and report them to the Sponsor according to the timetable for reporting specified in the protocol (21 CFR 312.64(b)).

ii. For devices, there is no regulatory requirement for PIs to report to the Sponsor anticipated adverse device effects or other nonserious events.

3. Deaths

The PI must report all deaths (that are not UPs) to the CD as soon as possible, but not more than 7 days after the PI first learns of the event, unless otherwise specified by the CD and documented in the protocol.

4. Event Reports at the time of continuing IRB review

At CR, the PI will provide the IRB with an aggregated summary of:

a. All UPs

b. All PDs (except anticipated PDs granted a waiver of reporting by the IRB, see Section 16.8.2 above)

c. All UADEs

d. All AEs (except expected AEs and deaths granted a waiver of reporting by the IRB, see Section 16.8.2 above)

e. If, while preparing the CR report, the PI identifies a greater frequency or level of severity of expected AEs than was previously expected and the aggregate information qualifies as a UP, the PI must also report these AEs as UPs.

See SOP 9, "Continuing Review by the Convened IRB" for additional PI duties regarding CR. Additional reporting requirements may also apply as required by other NIH offices, e.g., the NIH Office of Biotechnology Activities (OBA).

16.8.4 NIH PROTOCOLS THAT ARE OVERSEEN BY A NON-NIH IRB

For NIH protocols that are overseen by a non-NIH IRB, the PI should follow the reporting policies set forth in this SOP, unless more restrictive provisions are contained in the reliance (authorization) agreement between the NIH and the non-NIH IRB's institution. If so, the more restrictive provision must be followed. For more information on reliance agreements see SOP 20, "Obtaining a Reliance (Authorization) Agreement at the NIH".

16.8.5 REPORTING UPS AND AES OCCURRING AT OUTSIDE ENTITIES

It is no longer necessary to submit all reports from outside entities to an NIH IRB. These reports may come from a DSMB, a multicenter trial coordinating center, Sponsor, or Sponsor's monitor. When the NIH PI receives reports of UPs or PDs from an outside entity, these reports should be reported to the NIH IRB or non-NIH IRB of record and CD in accordance with this policy. PIs receiving reports of AEs not determined to be UPs or PDs (including, e.g., an Individual Notification, IND/IDE Safety or MedWatch report) should assess whether the event represents a UP. If the PI determines that an AE or series of AEs meets the definition of a UP, the PI must report the UP to the IRB and CD following the time frames set forth in this policy**.**

16.8.6 MONITORING REPORTS FROM A SPONSOR

Any UPs or PDs identified by a Sponsor's Monitor and reported to the NIH PI must be reported to the NIH IRB or non-NIH IRB of record following the time frames set forth in 16.8.3.

16.9 REPORTING RESPONSIBILITIES OF INVESTIGATORS WHO ARE ALSO SPONSORS

A Sponsor-investigator has the same requirements to report to the IRB and CD as those enumerated in this SOP for PIs. See SOP 15, "Research Regulated by the Food and Drug Administration: General Procedures for both IND and IDE Applications"; for more information on the responsibilities of Sponsors and Sponsor-investigators, such as Safety Reports.

16.10 IRB RESPONSIBILITIES

16.10.1. IRB WAIVER OF CERTAIN IRB REPORTING REQUIREMENTS FOR EXPECTED EVENTS

In response to a PI's sufficient justification in the protocol, an IRB may agree to waive immediate and aggregate reporting requirements for a predetermined rate of anticipated PDs, expected non-UP AEs, or deaths based on the natural history of the disorder or population. See 16.8.2 for additional details.

16.10.2 INITIAL IRB RECEIPT, REVIEW, DETERMINATIONS, AND ACTIONS REGARDING REPORTS OF UPS AND PDS

The review of UPs is the same for all studies; those involving no more than minimal risk are not treated differently from others. The IRB Chair/designee will review UP and PDs reports as soon as possible after receipt. He/she will determine whether the event should be submitted for review by the convened IRB at the next IRB meeting or at the protocol's next CR. Possible UPs and serious PDs must be discussed by the convened IRB at the next IRB meeting or sooner if necessary. The Chair/designee may act, as appropriate and consistent with law and NIH policy, to protect human subjects until the UP and/or PD is reviewed by the convened IRB.

If, in the IRB Chair/designee's judgment, immediate action is required to protect subjects--- such as suspension of the protocol, communication with enrolled subjects --- he/she shall inform the Institute CD, the Director CC (for protocols conducted at the NIH Clinical Center), and the NIH Office of Human Subjects Research Protections (OHSRP). The PI will also be informed in a timely manner.

16.10.3 IRB REVIEW AND DETERMINATION REGARDING UPS AND PDS

A. UP documents and serious protocol deviation reports will be distributed for review by the entire IRB. At the discretion of the chair, either a primary reviewer or the entire IRB may review not serious PDs. Convened NIH IRBs will review PI

reports of UPs and PDs forwarded by the IRB Chair/designee and make an independent determination, documented in the minutes, about whether the event is a UP and/or a PD. The minutes should include whether the event affects the IRB's assessment of the risks and benefits of the protocol under 45 CFR 46.111. The IRB may determine it needs more information from the investigator, the Sponsor, the study coordinating center, or DSMB about the event(s).

B. In addition to its determination about whether an event is a UP or PD, IRB actions may include, but are not limited to, the following:

1. No change is necessary to the protocol and/or consent document(s).

2. Revision of the protocol and/or consent document(s): The IRB will stipulate the required changes, which will be submitted by the PI as an amendment for future IRB review. The IRB will decide whether current subjects should be re-consented or informed by other means depending on the nature of the study.

3. Suspension of enrollment: Enrollment of new subjects on the study may be suspended by the IRB. The IRB will determine if, depending on the nature of the study, any current subjects may continue on the study or if subjects will be followed for safety purposes only. See SOP 11, "Suspensions & Terminations of IRB-approved Research and Administrative Holds."

4. Termination of the study: Subjects currently enrolled may be informed of the event and a plan will be submitted by the PI to the IRB for the safe withdrawal of remaining subjects.

5. Increased frequency/type of safety or other monitoring.

6. More frequent CR.

7. Recommendation for further evaluation and/or determination of possible Non-compliance, see SOP 16A, **"**Allegations and Incidents of Non-compliance."

16.10.4 IRB REPORTING OF UPS TO THE NIH OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS (OHSRP)

A. The IRB's UP reporting to OHSRP shall include:

1. The NIH Problem Report Form submitted by the PI to the IRB,

DHHS/NIH/OD/OIR/OHSRP

2. The IRB's determinations and/or actions, which may be addressed in the IRB section of the NIH Problem Report Form,

3. The IRB minutes (once available) containing its determinations and actions, and

4. Any other relevant documents, such as the IRB Chair/designee's initial evaluation, determination, and action (if applicable).

B. Once the IRB Chair or designee has determined that the PI's UP report should go to the convened IRB, that decision and a copy of the PI-submitted NIH Problem Report Form will be forwarded to OHSRP. Once the convened IRB has reviewed the UP, NIH IRBs are required to send any relevant documents, including the Problem Report Form with the IRB's determinations and actions, to OHSRP promptly. The IRB will also provide the minutes containing its determinations and actions to OHSRP within 7 days of approval of the minutes.

16.11 NIH REQUIREMENTS FOR REPORTING UPs TO THE OFFICE FOR HUMAN RESEARCH PROTECTIONS (OHRP) AND THE FOOD AND DRUG ADMINISTRATION (FDA)

These procedures are set forth in SOP 24, "NIH Reporting to the OHRP and the FDA Regarding Unanticipated Problems, Serious or Continuing Non-compliance or Terminations or Suspensions."

REFERENCES

A. REGULATIONS AND POLICIES

1. DHHS regulations at 45 CFR 46.

2. FDA regulations at 21 CFR 50, 56, 312, and 812.

B. GUIDANCE

1. Office for Human Research Protections (OHRP) Guidance on Reviewing and Reporting Unanticipated Problems involving Risk to Subjects or Others and Adverse Events, January 15, 2007 (see http://www.hhs.gov/ohrp/policy/advevntguid.html)

2. Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs — Improving Human Subject Protection, January 2009 see http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf) (Note that some Adverse Event reporting requirements listed in this guidance have been superseded by current regulations (see 21 CFR 312.64))

3. Guidance for Industry and Investigators: Safety reporting requirements of INDs and BA/BE studies, September 2010. See http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf.

4. Information Sheet Guidance for IRBs, Clinical Investigators and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies, January 2006.
5. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf

6. SACHRP Minutes, February 28-29, 2012_Attachment C: Recommendations on Protocol Deviations http://www.hhs.gov/ohrp/sachrp/mtgings/2012%20Feb%20Mtg/sachrpfebruary2012.html

DHHS/NIH/OD/OIR/OHSRP

LIST OF APPENDICES

Appendix A – Decision Tree for Prompt Reporting of Events Occurring During HHS- and FDA-regulated Research

Appendix B - How to Determine Whether an Adverse Event is also an Unanticipated Problem and/or Protocol Deviation

Appendix C - Examples of Unanticipated Problems (UPs)

Appendix D- FDA Guidance on Types of AEs that Should be Considered UPs and Must be Reported to the IRB

Appendix E - Examples of Protocol Deviations

LIST OF ATTACHMENTS

Attachment A - NIH Problem Report Form

APPENDIX A: DECISION TREE FOR PROMPT REPORTING OF EVENTS OCCURRING DURING HHS- AND FDA-REGULATED RESEARCH

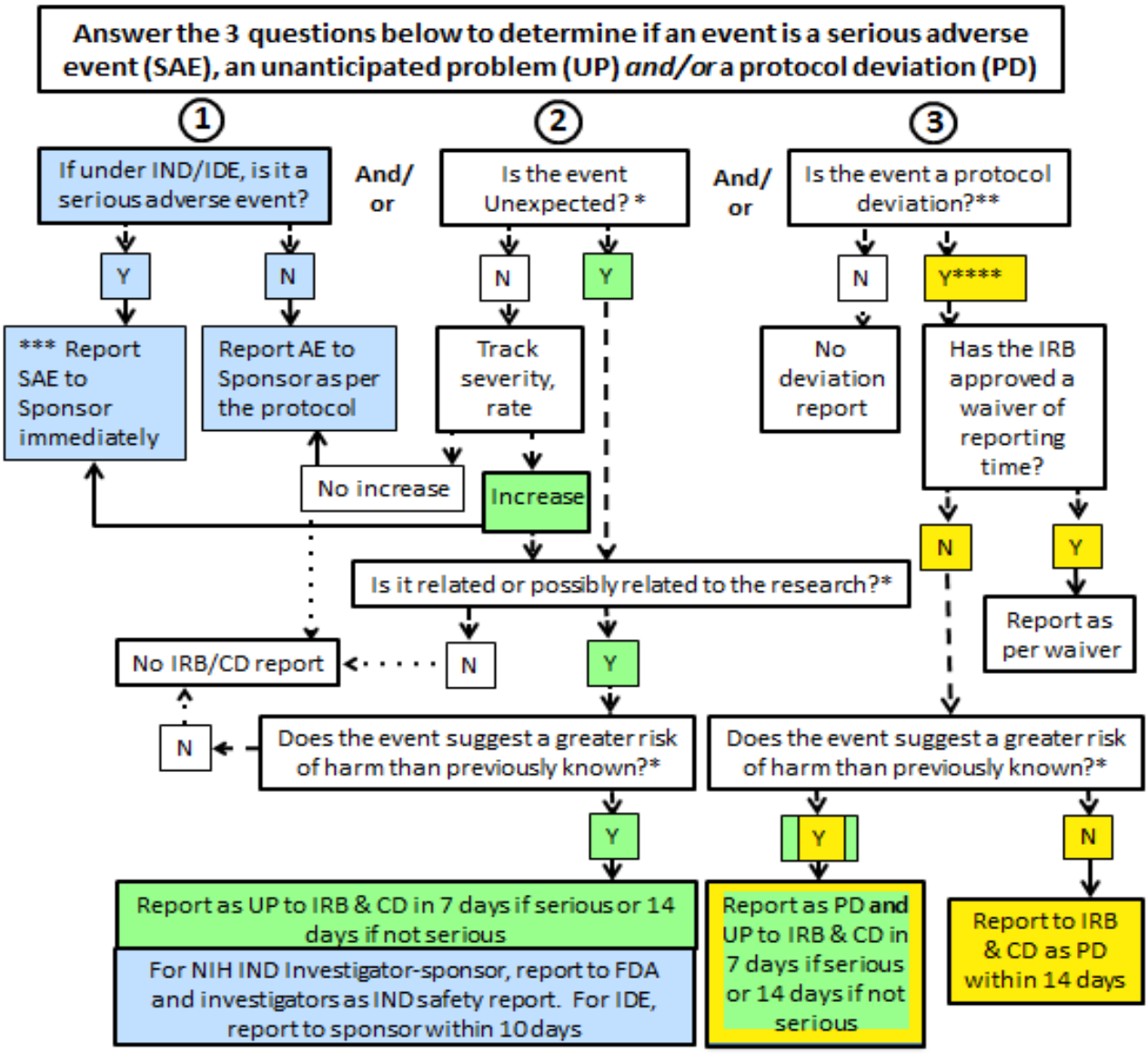

Image 2. Decision tree for prompt reporting of events occurring during HHS- and FDA-regulated research

* Refer to SOP 16 text for full definitions of UP questions and for requirements for reporting deaths to the CD
** See SOP 16A for requirements for reporting deviations that represent non-compliance
*** Serious adverse events (SAEs) of drugs and biologics must be reported immediately to the Sponsor, or as agreed upon with the Sponsor. Unanticipated Adverse Device Effects (UADEs) for IDE must be reported to Sponsor within 10 days.
**** For IDE research, report deviations from the investigational plan that were intended to protect life or physical well-being of a subject in an emergency to the Sponsor and IRB within 5 days

KEY: At No (N) and Yes (Y) answers follow the dashed line (**---**) to the next question; solid line (-) to reporting requirements or dotted line (….) when reporting is not required. This decision tree refers to matters that must be reported immediately**.** See SOP 9 for reporting requirements at Continuing Review. Green shading indicates likelihood of UP; Blue shading represents FDA requirements; Yellow shading corresponds to protocol deviation reporting.

APPENDIX B: HOW TO DETERMINE WHETHER AN ADVERSE EVENT IS ALSO AN UNANTICIPATED PROBLEM

A. The first step is to assess whether an Adverse Event is **unexpected**: An Adverse Event is unexpected if its nature, severity, or frequency is **not** consistent with either:

   2. The known or foreseeable risk of Adverse Events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure (IB), and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or

   3. The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the Adverse Event and the subject's predisposing risk factor profile for the Adverse Event.

B. The second step is to assess whether an Adverse Event is **related or possibly related** to participation in the research. If the event is either unrelated to the research, or *solely* caused by an underlying disease, disorder or condition of the subject's circumstances, then it *is not* considered related or possibly related to the research. However, Adverse Events that are determined to be at least *partially* caused by research or research interventions would be considered related or possibly related to participation in the research.

C. The third step is to assess whether an Adverse Event places subjects or others at a **greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized.

Note that OHRP considers Unanticipated Problems that are also Serious Adverse Events the most important subset of Unanticipated Problems. Other Adverse Events that are unexpected and related or possibly related to participation in the research, but not serious, would also be an Unanticipated Problem if they suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

APPENDIX C: EXAMPLES OF UNANTICIPATED PROBLEMS (UPs)

DEFINITION OF UNANTICIPATED PROBLEM

An **UP** is any incident, experience, or outcome that meets **all** of the following criteria:

A. **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;

B. **Related or possibly related** to participation in the research (**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

C. Suggests that the research places subjects or others at a **greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized.

The following examples are taken from the OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/2007, Appendix D)

Examples of Adverse Events that Represent Unanticipated Problems and Need to be Reported Under the HHS Regulations at 45 CFR Part 46

A. A subject with chronic gastroesophageal reflux disease enrolls in a randomized, placebo- controlled, double-blind, phase 3 clinical trial evaluating a new investigational agent that blocks acid release in the stomach. Two weeks after being randomized and started on the study intervention the subject develops acute kidney failure as evidenced by an increase in serum creatinine from 1.0 mg/dl pre-randomization to 5.0 mg/dl. The known risk profile of the investigational agent does not include renal toxicity, and the IRB-approved protocol and informed consent document for the study does not identify kidney damage as a risk of the research. Evaluation of the subject reveals no other obvious cause for acute renal failure. The investigator concludes that the episode of acute renal failure probably was due to the investigational agent. This is an example of an Unanticipated Problem that must be reported because the subject's acute renal failure was (a) unexpected in nature, (b) related to participation in the research, and (c) serious.

B. A subject with seizures enrolls in a randomized, phase 3 clinical trial comparing a new investigational anti-seizure agent to a standard, FDA-approved anti-seizure

medication. The subject is randomized to the group receiving the investigational agent. One month after enrollment, the subject is hospitalized with severe fatigue and on further evaluation is noted to have severe anemia (hematocrit decreased from 45% pre-randomization to 20%). Further hematologic evaluation suggests an immune-mediated hemolytic anemia. The known risk profile of the investigational agent does not include anemia, and the IRB-approved protocol and informed consent document for the study do not identify anemia as a risk of the research. The investigators determine that the hemolytic anemia is possibly due to the investigational agent. This is an example of an Unanticipated Problem that must be reported because the hematologic toxicity was (a) unexpected in nature; (b) possibly related to participation in the research; and (c) serious.

C. The fifth subject enrolled in a phase 2, open-label, uncontrolled clinical study evaluating the safety and efficacy of a new oral agent administered daily for treatment of severe psoriasis unresponsive to FDA-approved treatments, develops severe hepatic failure complicated by encephalopathy one month after starting the oral agent. The known risk profile of the new oral agent prior to this event included mild elevation of serum liver enzymes in 10% of subjects receiving the agent during previous clinical studies, but there was no other history of subjects developing clinically significant liver disease. The IRB-approved protocol and informed consent document for the study identifies mild liver injury as a risk of the research. The investigators identify no other etiology for the liver failure in this subject and attribute it to the study agent. This is an example of an Unanticipated Problem that must be reported because although the risk of mild liver injury was foreseen, severe liver injury resulting in hepatic failure was (a) unexpected in severity; (b) possibly related to participation in the research; and (c) serious.

D. Subjects with coronary artery disease presenting with unstable angina are enrolled in a multicenter clinical trial evaluating the safety and efficacy of an investigational vascular stent. Based on prior studies in animals and humans, the investigators anticipate that up to 5% of subjects receiving the investigational stent will require emergency coronary artery bypass graft (CABG) surgery because of acute blockage of the stent that is unresponsive to non-surgical interventions. The risk of needing emergency CABG surgery is described in the IRB-approved protocol and informed consent document. After the first 20 subjects are enrolled in the study, a DSMB conducts an interim analysis, as required by the IRB-approved protocol, and notes that 10 subjects have needed to undergo emergency CABG surgery soon after placement of the investigational stent. The DSMB monitoring the clinical trial concludes that the rate at which subjects have needed to undergo CABG greatly exceeds the expected rate and communicates this information to the investigators. This is an example of an Unanticipated Problem that must be

reported because (a) the frequency at which subjects have needed to undergo emergency CABG surgery was significantly higher than the expected frequency; (b) these events were related to participation in the research; and (c) these events were serious.

E. Subjects with essential hypertension are enrolled in a phase 2, non-randomized clinical trial testing a new investigational antihypertensive drug. At the time the clinical trial is initiated, there is no documented evidence of gastroesophageal reflux disease (GERD) associated with the investigational drug, and the IRB-approved protocol and informed consent document do not describe GERD as a risk of the research. Three of the first ten subjects are noted by the investigator to have severe GERD symptoms that began within one week of starting the investigational drug and resolved a few days after the drug was discontinued. The investigator determines that the GERD symptoms were most likely caused by the investigational drug and warrant modification of the informed consent document to include a description of GERD as a risk of the research. This is an example of an Adverse Event that, although not serious, represents an Unanticipated Problem that must be reported because it was (a) unexpected in nature; (b) possibly related to participation in the research; and (c) suggested that the research placed subjects at a greater risk of physical harm than was previously known or recognized.

F. A behavioral researcher conducts a study in college students that involves completion of a detailed survey asking questions about early childhood experiences. The research was judged to involve no more than minimal risk and was approved by the IRB chairperson under an expedited review procedure. During the completion of the survey, one student subject has a transient psychological reaction manifested by intense sadness and depressed mood that resolved without intervention after a few hours. The protocol and informed consent document for the research did not describe any risk of such negative psychological reactions. Upon further evaluation, the investigator determines that the subject's negative psychological reaction resulted from certain survey questions that triggered repressed memories of physical abuse as a child. The investigator had not expected that such reactions would be triggered by the survey questions. This is an example of an Unanticipated Problem that must be reported in the context of social and behavioral research because, although not serious, the Adverse Event was (a) unexpected; (b) related to participation in the research; and (c) suggested that the research places subjects at a greater risk of psychological harm than was previously known or recognized.

DHHS/NIH/OD/OIR/OHSRP

In all of these examples, the Adverse Events warranted consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects.

NOTE: For purposes of illustration, the case examples provided above represent generally unambiguous examples of Adverse Events that are Unanticipated Problems. OHRP recognizes that it may be difficult to determine whether a particular Adverse Event is unexpected and whether it is related or possibly related to participation in the research.

The following examples are taken from the OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/2007, Appendix B)

Examples of Unanticipated Problems that Do Not Involve Adverse Events and Need to be Reported Under the HHS Regulations at 45 CFR Part 46

A. An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator's car on the way home from work. This is an Unanticipated Problem that must be reported because the incident was (a) unexpected (i.e., the investigators did not anticipate the theft); (b) related to participation in the research; and (c) placed the subjects at a greater risk of psychological and social harm from the breach in confidentiality of the study data than was previously known or recognized.

B. As a result of a processing error by a pharmacy technician, a subject enrolled in a multicenter clinical trial receives a dose of an experimental agent that is 10-times higher than the dose dictated by the IRB-approved protocol. While the dosing error increased the risk of toxic manifestations of the experimental agent, the subject experienced no detectable harm or adverse effect after an appropriate period of careful observation. Nevertheless, this constitutes an Unanticipated Problem for the institution where the dosing error occurred that must be reported to the IRB, appropriate institutional officials, and OHRP because the incident was (a) unexpected; (b) related to participation in the research; and (c) placed subject at a greater risk of physical harm than was previously known or recognized.

C. Subjects with cancer are enrolled in a phase 2 clinical trial evaluating an investigational biologic product derived from human sera. After several subjects are enrolled and receive the investigational product, a study audit reveals that the

investigational product administered to subjects was obtained from donors who were not appropriately screened and tested for several potential viral contaminants, including the human immunodeficiency virus and the hepatitis B virus. This constitutes an Unanticipated Problem that must be reported because the incident was (a) unexpected; (b) related to participation in the research; and (c) placed subjects and others at a greater risk of physical harm than was previously known or recognized.

The events described in the above examples were unexpected in nature, related to participation in the research, and resulted in new circumstances that increased the risk of harm to subjects. In all of these examples, the Unanticipated Problems warranted consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects. In addition, the third example may have presented unanticipated risks to others (e.g., the sexual partners of the subjects) in addition to the subjects. In each of these examples, while these events may not have caused any detectable harm or adverse effect to subjects or others, they nevertheless represent Unanticipated Problems and should be promptly reported to the IRB, appropriate institutional officials, the supporting agency head and OHRP in accordance with HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

APPENDIX D: FDA GUIDANCE ON TYPES OF AEs THAT SHOULD BE CONSIDERED UPs AND MUST BE REPORTED TO THE IRB

"Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs – Improving Human Subject Protection," January 2009, Section III A

In general, an AE observed during the conduct of a study should be considered an unanticipated problem involving risk to human subjects, and reported to the IRB, ***only*** if it were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure). An individual AE occurrence ***ordinarily*** does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.

Many types of AEs generally require an evaluation of their relevance and significance to the study, including an aggregate analysis of other occurrences of the same (or similar) event, before they can be determined to be an unanticipated problem involving risk to human subjects. For example, an aggregate analysis of a series of AEs that are commonly associated with the underlying disease process that the study intervention is intended to treat (e.g., deaths in a cancer trial), or that are otherwise common in the study population independent of drug exposure (e.g., cardiovascular events in an elderly population) may reveal that the event rate is higher in the drug treatment group compared to the control arm. In this case, the AE would be considered an unanticipated problem. In the absence of such a finding, the event is uninterpretable.

The major exceptions to the general rule that an isolated event is not informative are serious AEs that are uncommon and strongly associated with drug exposure, such as angioedema, agranulocytosis, anaphylaxis, hepatic injury, or Stevens Johnson syndrome. In most cases, a single, unexpected occurrence of this type of event would be considered an unanticipated problem involving risk to human subjects and, thus, must be reported to the IRB. Similarly, one or a small number of serious events that are not commonly associated with drug exposure, but are otherwise uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy) should be considered an unanticipated problem involving risk to human subjects.

Because they have been previously observed with a drug, the AEs listed in the investigator's brochure would, by definition, not be considered unexpected and thus would not be unanticipated problems. Possible exceptions would include situations in

DHHS/NIH/OD/OIR/OHSRP

which the specificity or severity of the event is not consistent with the description in the investigator's brochure, or it can be determined that the observed rate of occurrence for a serious, expected AE in the clinical trial represents a clinically important increase in the expected rate of occurrence.

Therefore, FDA recommends that there be careful consideration of whether an AE is an unanticipated problem that must be reported to IRBs. In summary, FDA believes that only the following AEs should be considered as *unanticipated problems* that must be reported to the IRB.

A. A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angiodema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).

B. A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy).

C. Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an Unanticipated Problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). We recommend that a summary and analyses supporting the determination accompany the report.

D. An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an Unanticipated Problem involving risk to human subjects. We recommend that a discussion of the divergence from the expected specificity or severity accompany the report.

E. A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison). We recommend that a discussion of the divergence from the expected rate accompany the report.

F. Any other AE or safety finding (e.g., based on animal or epidemiologic data) that would cause the Sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects. We recommend that an explanation of the conclusion accompany the report.

APPENDIX E: EXAMPLES OF PROTOCOL DEVIATIONS

Definition of a Protocol Deviation (PD): Any change, divergence, or departure from the IRB approved study procedures in a research protocol. Some, but not all, Protocol Deviations also may be Unanticipated Problems, while others may be instances of Non-compliance (for more information on Non-compliance, see SOP 16A.)

A. Example of an anticipated PD an IRB may waive from initial and continuing IRB reporting requirements

The protocol may stipulate that blood will be drawn at specified timepoints. The PI may anticipate that a small number of the tests may not be drawn precisely at those timepoints, but would be considered acceptable for the study outcomes. In such a case, the PI may propose, as part of the protocol, not to report those deviations within a specified rate. However, if the rate of these events exceeds the rate anticipated in the protocol, the events would be classified and reported as a Protocol Deviation and Unanticipated Problem.

One approach to reducing the number of protocol deviations is to establish less conservative parameters for study execution. For example, using the example above, the protocol might stipulate a range of timepoints within which blood draws would be acceptable. Similarly, use of a window of time for a study visit (e.g., weeks 5 – 7) rather than a specific date (e.g., day 42) would decrease unavoidable protocol deviations.

B. Examples of Not Serious Protocol Deviations

Examples include, but are not limited to:

1. Scheduling a protocol visit slightly outside of the timing in the protocol, at a time that would not compromise the interpretation of the study data or impact the health of the subject.

2. Inability to obtain a sample that is needed for exploratory analysis that does not impact the health of the subject.

C. Examples of Potential Serious Protocol Deviations

1. **The deviation has harmed or posed a significant or substantive risk of harm to the research subject. Examples include, but are not limited to:**

DHHS/NIH/OD/OIR/OHSRP

a. A research subject received the wrong treatment or incorrect dose

b. A research subject met withdrawal criteria during the study but was not withdrawn

c. A research subject received an excluded concomitant medication.

2. **The deviation compromised the scientific integrity of the data collected for the study. Examples include, but are not limited to:**

   a. A research subject was enrolled but does not meet the protocol's eligibility criteria

   b. Failure to treat research subjects per protocol procedures that specifically relate to primary efficacy outcomes (if it involves patient safety it meets the first category above)

   c. Changing the protocol without prior IRB approval

   d. Inadvertent loss of samples or data.

3. **The deviation is a breach of human subject protection regulations, or NIH policies, or procedures. Examples include, but are not limited to**:

   a. Failure to obtain informed consent prior to initiation of study-related procedures

   b. Performing tests or procedures beyond those anticipated in the protocol or by those not approved to perform such actions by the IRB.

   c. Falsifying research or medical records

4. **The deviation involves a serious or continuing noncompliance with applicable federal, state, local or institutional human subject protection laws, regulations, or policies, or procedures. Examples include, but are not limited to**:

   a. Working under an expired professional license or certification

   b. Failure to follow federal and/or local regulations, and intramural research or CC policies

c. Repeated Protocol Deviations.

5. **The deviation is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles. Examples include, but are not limited to**:

   a. A breach of confidentiality and/or privacy

   b. Inadequate or improper informed consent procedures.

DHHS/NIH/OD/OIR/OHSRP

ATTACHMENT A: NIH PROBLEM REPORT FORM

Use this form to report problems to the IRB that may be:

A. Unanticipated Problems (UPs) including Unanticipated Adverse Device Effects (UADEs)

B. Protocol Deviations (PDs) or

C. Non-compliance

For more information on UPs and PDs, see SOP 16**,** "Principal Investigator (PI) and IRB Reporting Requirements for Unanticipated Problems and Protocol Deviations". For more information on Non-compliance, see SOP 16A**,** "Allegations and Incidents of Non-compliance with the Requirements of the NIH Human Research Protection Program (HRPP)."

DEFINITIONS

Protocol Deviation (PD): Any change, divergence, or departure from the IRB-approved research protocol.

The impact of a PD is characterized by designation as serious or not serious (see SOP 16- Appendix E.) PDs include three types of protocol deviations:

A. Those that occur because a member of the research team deviates from the protocol;

B. Those that are identified before they occur, but cannot be prevented (e.g., when a subject alerts the research team that inclement weather will prevent the subject from attending a scheduled protocol visit); and

C. Those that are discovered after they occur.

Unanticipated Problem (UP): Is any incident, experience, or outcome that meets **all** of the following criteria:

A. **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;

B. **Related or possibly related** to participation in the research (**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

C. Suggests that the research places subjects or others at a **greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized.

Non-compliance: The failure to comply with applicable NIH HRPP policies, IRB requirements, or regulatory requirements for the protection of human research subjects; (See SOP 16A, "Allegations and Incidents of Non-compliance with the Requirements of the NIH Human Research Protection Program (HRPP).")

Minor non-compliance: Non-compliance that, is neither serious nor continuing.

Serious: A UP or PD is serious if it meets the definition of a Serious Adverse Event* or if it compromises the safety, welfare or rights of subjects or others.

* **Serious Adverse Event (SAE):** is any Adverse Event that: 1. Results in death; 2. Is life-threatening (places the subject at immediate risk of death from the event as it occurred); 3. Results in inpatient hospitalization or prolongation of existing hospitalization; 4. Results in a persistent or significant disability/incapacity; 5. Results in a congenital anomaly/birth defect; or 6. Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

INSTRUCTIONS TO PRINCIPAL INVESTIGATORS

A. Use this form to report all problems to the IRB including UPs, PDs, or Non-compliance

B. Use the appropriate electronic IRB system to complete this form (iRIS or PTMS.) If the PI is unable to access the appropriate IRB reporting system, PI may use

this NIH Problem Report Form. The PI may elect also to report events (especially if Serious) to the IRB Chair/designee and/or the CD, in person or by phone or e-mail. However, such reporting is in addition to the required reporting using the NIH Problem Report Form.

C. Any modifications to the protocol and/or consent(s) resulting from a UP, PD or Non-compliance must be submitted via a separate amendment in the appropriate IRB system (iRIS or PTMS), except when necessary to eliminate apparent immediate hazard to the subjects as explained in SOP 10 – "Amendments to IRB-approved Research".

D. Additional reporting requirements may apply, e.g., to the FDA, the NIH Office of Biotechnology Activities (OBA).

IMPORTANT: Notify the IRB and Clinical Director using the following timeframes:

A. **Serious UPs, UADEs, Serious PDs, and Serious Non-compliance:** as soon as possible, but not more than seven (7) days after the PI first learns of the event. For device research, the PI must report to the IRB any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency as soon as possible, but no later than 5 working days after the emergency occurred.

B. **Not Serious UP, Not Serious PD or Minor Non-compliance:** not more than fourteen (14) days after the PI first learns of the event.

DHHS/NIH/OD/OIR/OHSRP

NIH PROBLEM REPORT FORM

Protocol #:	**Protocol Title:**
System Ref#: [IRB system generated]	**Report version:** *(select one)* ____Initial Report ____Revised Report ____Follow-up **If revised report or follow-up, Original System Ref #: _____**
Principal Investigator: [system pull based on NED ID]	**Institute:** **Office Phone:** **E-mail:**
FDA Regulated Research [system pull from IRB system]	Study Sponsor: _____ IND/IDE# _____ IND/IDE Name: _____
Date of problem:	**Location of problem:** *(e.g., NIH Clinical Center or Name of Site/Location)* ___ NIH CC ___ Other, specify: _____
Who identified the problem? *(provide role: nurse, investigator, monitor, etc…)*	
Brief Description of Subject *(if applicable)* (*Do NOT include personal identifiers)*	Sex: ___ Male ___ Female Age: ___ Not applicable (more than subject is involved)
Diagnosis under study:	
If the subject is enrolled on any other studies, list the protocol number(s) here: *(If applicable, submit a separate report form for each protocol listed)*	
Is this problem? (*select all that apply*) [ ] An Unanticipated Problem that is: [ ] Serious [ ] Not Serious [ ] A Protocol Deviation that is: [ ] Serious [ ] Not Serious [ ] Non-compliance	
Is the problem also *(select all that apply)* [ ] AE [ ] Non-AE	
Name the problem: *(select all that apply)* [ ] Adverse drug reaction [ ] Abnormal lab value [ ] Death [ ] Cardiac Arrest/ code [ ] Anaphylaxis	

DHHS/NIH/OD/OIR/OHSRP

[ ] Sepsis/Infection
[ ] Blood product reaction
[ ] Unanticipated surgery/procedure
[ ] Change in status (e.g. increased level of care required)
[ ] Allergy (non-medication)
[ ] Fall
[ ] Injury/Accident (not fall)
[ ] Specimen collection issue
[ ] Informed consent issue
[ ] Ineligible for enrollment
[ ] Breach of PII
[ ] Tests/procedures not performed on schedule
[ ] Other, brief 1-2 word description: _____

Detailed Description of the problem: (*Include any relevant treatment, outcomes or pertinent history*):

Is this problem unexpected? *(i.e., event not described in protocol, consent, or Investigator Brochure)* __YES __NO **Please explain:**

Is this problem related or possibly related to participation in the research? __YES __NO **Please explain:**

Does the problem suggest the research places subjects or others at a greater risk of harm? __YES __NO **Please explain:**

Have similar problems occurred on this protocol? __YES __NO
If "Yes", how many? ____ Please describe:

Describe what steps have you already taken as a result of this problem?

What steps do you plan to take as a result of the problem? (*select all that apply*)
[ ] No action required
[ ] Amend consent **(*Separate amendment submission required*)**
[ ] Amend protocol **(*Separate amendment submission required*)**
[ ] Inform existing subjects **(*Include example of information to be provided to subjects*)**
[ ] Close the protocol **(*Separate closure submission required*)**
[ ] Temporarily halt the protocol **(*Provide plan for management of enrolled subjects*)**
[ ] Increase frequency/type of safety or other monitoring **(Separate amendment submission required)**
[ ] Other corrective action, describe:

DHHS/NIH/OD/OIR/OHSRP

In addition to the IRB, this problem is also being reported to: (*select all that apply*) [ ] IC Clinical Director [ ] Study Sponsor [ ] If Investigator-held IND/IDE, report to FDA [ ] Manufacturer : _____ [ ] Institutional Biosafety Committee [ ] Office of Biotechnology Activities [ ] Data Safety Monitoring Board [ ] CC Occurrence Reporting System (ORS) [ ] Other: _____ [ ] None of the above applicable	
INVESTIGATOR'S SIGNATURE:	**DATE:**
MEDICAL ADVISORY INVESTIGATOR'S SIGNATURE: *(if applicable)*	**DATE:**
CLINICAL DIRECTOR: *(If a UP, UADE, or a Serious PD)*	**DATE :**

_ _ _ _

Protocol Deviation (*select one*)
____ Serious
____ Not Serious

IRB meeting minutes:

Indicate the IRB's action in response to this event: *(specify time frames where applicable if not already addressed in the minutes)*
[ ] No action required
[ ] Follow-up report required: _____
[ ] Amend consent(s)/assent(s): _____
[ ] Amend protocol: _____
[ ] Inform existing subjects: _____
[ ] Increase frequency/type of safety or other monitoring
[ ] More frequent continuing review, specify review period: _____
[ ] Suspend the protocol:_____ (*Report to OHSRP*)
[ ] Terminate the protocol: _____ (*Report to OHSRP*)
[ ] Other corrective action, describe: _____

_ _ _ _