
REPORTABLE EVENTS:

Recommendations for Investigator-initiated Multisite Studies



Reportable Event Working Group of the
SMART IRB Harmonization Steering Committee

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INTRODUCTION

This document was produced by the SMART IRB Harmonization Steering Committee's Reportable Events Working Group, which is composed of researchers and administrators with a range of experience and expertise from academia, industry, and government.

Through a series of conference calls, working group members gained an understanding of the challenges the represented organizations face with regards to reportable events and prioritized targets and topics for harmonization. In addition, the group surveyed representatives from more than 20 academic medical centers in the US and several independent IRBs to identify variations in practice related to noncompliance and unanticipated events. Identified variations in requirements, roles, and timeframes for reporting are summarized below.

The development of *Reportable Events: Recommendations for Investigator-Initiated Multisite Studies* also involved posting a draft for public review and comment. Following the review period, the working group discussed the feedback received, incorporated some, but not all, of the suggested revisions, and issued this finalized document. Of note, several recommendations from our colleagues contradicted one another, underscoring the variability in approaches to noncompliance across institutions and emphasizing the need for our community to harmonize approaches to reportable events.

The finalized recommendations provided in this guidance were determined through group discussion and consensus; where possible, priority was given to existing statutes or other standards. In acknowledgement of the thoughtful feedback received, we provide here some background regarding the working group's approach to certain aspects of the final document.

Terminology. Because the Food and Drug Administration (FDA) and Office for Human Research Protections (OHRP) do not define *noncompliance*, *serious noncompliance*, or *continuing noncompliance* within their regulations, institutions were obligated to develop their own definitions, resulting in significant variation across institutions, as noted by the working group. In developing definitions for the finalized recommendations that follow, the working group tried to use phrasing and terms found within the regulations whenever possible—an approach similar to that of many institutions. For example, while several commenters suggested deleting “adversely affects the integrity of the data and research” from the recommended definition of *serious noncompliance*, the language was retained in the final document because it matches language used within FDA device regulations.

In the case of the proposed definitions of “apparent serious noncompliance” or “apparent continuing noncompliance,” we followed the conventions from the Veterans Health Administration (VHA) Handbook 1200.05, which helps to distinguish between a report that has yet to be assessed by an IRB and one for which an IRB has made a determination of serious or continuing noncompliance. Because OHRP and FDA provide more detailed guidance regarding what constitutes an unanticipated problem, the working group did not think the “apparent” qualifier was necessary for the definition of unanticipated problems.

Other feedback from the community included a recommendation that the use of “increases risk of harm to subjects or others...” should be eliminated from the *serious noncompliance* definition because this concept is more suggestive of an unanticipated problem. The working group respectfully disagreed with this recommendation, because we thought that an increased risk of harm can be a hallmark of serious noncompliance; the final recommendations note that serious noncompliance may also be an unanticipated problem.

The working group spent significant time discussing and debating the definition of *continuing noncompliance*. Ultimately, the group agreed to define *continuing noncompliance* as “a pattern of repeated noncompliance that continues after initial discovery, including inadequate efforts to take corrective actions within a reasonable timeframe,” a definition that parallels those used by several institutions. Several other institutions, and some

commenters on early drafts of the recommendations, include language in their definitions that continuing noncompliance “indicates an inability or unwillingness to comply,” which the working group found to be too impracticable to apply (i.e., how would the inability or unwillingness on the part of a research team be discerned?). Additionally, the working group discussed the approach that many institutions adopt, which is to include in the definition of continuing noncompliance cases in which a study team has repeated the same or similar events before those events were discovered and corrected. The view in this case appears to be that noncompliance can be continuing even without first being discovered and corrective actions subsequently implemented. The working group came to consensus, however, that for noncompliance to be considered “continuing,” the events must first be *identified* as noncompliance, with a corrective action implemented, and then *continue* after this initial discovery and correction. This definition permits the possibility that the initial discovery could include a repetition of events that may be of concern. In these cases, the working group’s thinking was that noncompliance that is of sufficient breadth and depth, if not previously discovered, would be more appropriately classified as *serious* rather than *continuing noncompliance*.

Event Triage Responsibilities. The IRB community differs in regard to expectations of primary responsibility for triaging events. Some IRBs require research teams to report a wide range of events so that the IRB (including IRB staff) can determine whether they meet the definition of noncompliance and/or unanticipated problems. Others expect research teams to make an initial assessment and limit the number of events submitted for IRB review. The working group recommends that research teams triage and determine which events should be reported to the IRB because:

- Study teams should be viewed as playing a critical role in the protection of human subjects;
- Study teams have close knowledge of events that occur during their studies and should be able to assess, with appropriate guidance, whether the events meet criteria for reporting to an IRB; and
- Under the single IRB review model, the reviewing IRB could receive a significant number of reports, which may tax their resources without a gain in the protection of human subjects; IRBs should therefore leverage study team expertise to limit the number of events the IRB receives.

Based on this view of research team responsibilities, and to assist research teams in triaging events, the working group developed examples for each category of reportable event discussed. The working group thought that concrete examples were critical to helping study teams develop a sense of the types of events that should be reported to reviewing IRBs. One commenter noted a concern that labeling the list of example events as apparent serious noncompliance, apparent continuing noncompliance, and unanticipated problems may discourage study teams from reporting such events to the IRB. If institutions think that study teams will be less likely to report an event due to labeling (i.e., that study teams may avoid reporting events that might meet these definitions), they could instead describe them as “examples of events that require prompt reporting to an appropriate IRB.”

One commentator on this document’s draft noted that many site coordinators receive multiple “safety reports” from sponsors and recommended that this term should be addressed in the guidance. Although the working group acknowledges that this use of this term could present a challenge to helping research teams identify when safety reports constitute unanticipated problems, we focused in the final document on reports to the IRB rather than those from the sponsor. However, the examples provided could also assist study teams in triaging safety reports.

Reporting Timeframe. The aspect of the draft recommendations that received the most feedback was in regard to expectations for when events should be reported, both in terms how days are calculated (calendar days vs. business days) and the definition of “prompt.” The final recommended timeframes for reporting are expressed in calendar days, because, while institutions do not share the same business days, calendar days remain consistent across institutions, which is critical for clarity.

The recommendations specify timeframes for reporting an event to an IRB and for an IRB/institution to report, when applicable, to appropriate institutional officials, applicable regulatory or oversight agencies, and, when

appropriate, the sponsor or contract research organization and other performance sites involved in the research affected by the event. The working group declined to make recommendations for harmonizing the timeframe from when an IRB receives a report to when it makes a determination related to that report, because such timeframes can vary significantly depending on the nature and complexity of the events, as well as other factors.

Many commenters noted that the proposed reporting timelines were either too short or too long. The recommendation that an investigator (or investigator's designee) or others (e.g., organizational officials) should provide an *initial* report to the Reviewing IRB within seven calendar days of recognizing apparent serious or continuing noncompliance or an unanticipated problem tries to acknowledge that, while a study team (or others) may need more time to evaluate the nature of an event, in certain cases the IRB should be involved in that assessment, in order to help protect the rights and welfare of participants. Some commenters expressed concern that this seven-day timeframe would intimidate study teams who may be unsure of where to submit the report. Educating study teams regarding single IRB review and ensuring clear communication regarding which IRB has assumed responsibility for a study are critical parts of the transition to single IRB review. Should a study team provide a preliminary report to the incorrect IRB, the hope would be that this error could be recognized promptly, and that the Reviewing IRB would take into consideration that the study team intended to comply with the expected timeframe.

Other commenters suggested that there is no benefit to regulators or subjects for a limited timeframe for reporting and indicated that 30 calendar days would be a more reasonable timeframe to allow for an investigation of the allegation and to come to any conclusion as to whether noncompliance actually occurred. These commenters noted that an IRB might make a reportable determination only to overturn it after more information is received. Although the working group appreciated this thoughtful feedback, the recommended timeframe for an initial report tries to ensure that IRBs are alerted to those events that may require timely action to protect subjects (e.g., suspending the study until more information is received), but the recommendations do not require IRBs to make a determination in that timeframe, as they may need more time to obtain information to adequately assess the event.

In response to commenters' feedback, the working group lengthened the recommended timeframe from 14 to 21 calendar days for reporting final determinations of serious noncompliance, continuing noncompliance, or unanticipated problems to appropriate institutional officials, applicable regulatory or oversight agencies, and, when appropriate, the sponsor or contract research organization and other performance sites involved in the research affected by the event. The working group agreed that obtaining comments on proposed reports from organizational officials, legal counsels, and other institutions does not always occur as promptly as desired. Furthermore, the working group distinguished between any preliminary determinations an IRB might make (e.g., that an event appears to be an unanticipated problem or serious noncompliance) and a final decision regarding an event(s) based on what the IRB assesses as sufficient information to support that determination.

We thank those who took the time to provide their expertise and insights on the earlier draft recommendations, and we hope that these final recommendations accomplish what they intended – harmonizing our approach to the reporting of serious and continuing noncompliance and unanticipated problems.

REPORTING EXPECTATIONS FOR SERIOUS OR CONTINUING NONCOMPLIANCE AND UNANTICIPATED PROBLEMS: Recommendations for Investigator-initiated Studies

The recommendations contained in this document are intended to provide Reviewing IRBs and Relying Institutions participating in the SMART IRB Agreement with harmonized definitions, policies, and procedures for prompt reporting of noncompliance and unanticipated problems. *Prompt reporting* is defined as an unplanned activity a responsible party performs without delay to initially notify applicable entities of a reportable event (serious or continuing noncompliance or an unanticipated problem) within a specified period of time. The document concentrates on serious or continuing noncompliance, not on noncompliance (including protocol deviations) that is neither serious nor continuing, because federal regulations (with the exception of FDA device regulations) outline requirements for the former, but not the latter. Although many institutions require research teams to report non-serious, non-continuing noncompliance and protocol deviations to the IRB (e.g., a summary at continuing review), such reporting is not required under federal regulations. In the case of protocol deviations, we refer the reader to [Recommendation on Protocol Deviations](#), developed by the Secretary's Advisory Committee on Human Research Protections, which provides an excellent basis from which institutions can implement harmonized approaches at least to protocol deviations.

For purposes of this document, *investigator-initiated* studies are those initiated and managed by a researcher, with little or no oversight from a pharmaceutical company on the design, conduct, or interpretation of results. Although the document focuses on investigator-initiated research, principles in this document regarding noncompliance and unanticipated problems may broadly apply irrespective of the origination of the research.

We recognize that although institutions vary in their approach to reporting serious or continuing noncompliance and unanticipated problems, successful implementation of the SMART IRB Agreement hinges on harmonizing the policies and procedures used by all parties. The larger goal for these harmonization efforts is to help achieve uniformity and efficiency in how IRBs handle their responsibilities, communicate with investigators, and help ensure participant safety in multisite research.

Background

Noncompliance

Federal regulations require institutions to have and follow written procedures to ensure prompt reporting to the IRB, appropriate institutional officials, Office of Human Research Protections (OHRP), and the appropriate department or agency head of any serious or continuing noncompliance with the regulations or the IRB's requirements or determinations (see 46.108(a)(4)). The term *noncompliance* is defined as not complying with the terms of: (1) the Common Rule or (2) the requirements or determinations of the IRB. The terms *serious noncompliance* or *continuing noncompliance* are not defined.

As part of the working group's efforts to create harmonized recommendations for prompt reporting, we reviewed policies for reporting noncompliance across a range of institutions and noted the following variations, which informed our discussions.

Identified variations related to the prompt reporting and review of noncompliance, regardless of whether it is considered serious or continuing, include:

- **Which events must be promptly reported to the Reviewing IRB.** Some institutions require prompt reporting of protocol deviations/noncompliance that do not appear to be either serious or continuing noncompliance, while others limit reporting to apparent serious or continuing noncompliance.
- **Timeframe for reporting to the Reviewing IRB.** The reporting timeframe varies from five days to almost two weeks.
- **Responsible party for submitting reports to the Reviewing IRB.** Institutions vary in who they require to submit a report of noncompliance to the Reviewing IRB, regardless of whether it may be considered serious or continuing. For example, some institutions require the Principal Investigator or members of the study teams to submit reports, while others permit direct reports from study auditors or monitors.
- **Who triages and assesses reports of noncompliance.** Institutions vary in who reviews reports of noncompliance but tend to require that a convened board review events that appear to constitute serious or continuing noncompliance. At some institutions, IRB staff members review a report of noncompliance to assess severity and then assign it to an IRB chairperson or directly to a convened board. In other cases, the IRB chairperson can make non-serious or non-continuing noncompliance determinations but refers events that appear to constitute serious or continuing noncompliance to the convened board.

Unanticipated Problems

While all institutions that we reviewed follow the OHRP unanticipated problems guidance, institutions vary in whether they limit reporting of events only to those that meet the definition of unanticipated problems within that guidance.

Identified variations related to unanticipated problems include:

- **Which events must be reported to the Reviewing IRB.** Some IRBs require broad reporting of events to assess whether they constitute unanticipated problems, while others provide triage guidance to investigators and expect them to limit the events submitted to the IRB to potential unanticipated problems.
- **Timeframe for reporting to the Reviewing IRB.** The reporting timeframe varies from five days to almost two weeks.
- **Responsible party for submitting reports to the Reviewing IRB.** Institutions vary in who they require to submit an unanticipated problem report to the Reviewing IRB, with some limiting the authority to Principal Investigators.
- **Who reviews reports of unanticipated problems.** Institutions vary in who reviews reports of unanticipated problems. For example, some institutions expect IRB chairs to assess events and make determinations regarding the reports (e.g., whether the event meets the definition of an unanticipated problem, additional actions needed to address the event), whereas other institutions refer all potential unanticipated problems to the convened board to assess. Other IRBs have IRB staff who perform the initial triage.

Specific Recommendations for Reporting

The variability in institutional policy described above creates challenges for the transition to single IRB oversight of multisite research, because study teams and others must be able to identify and comply with a range of reporting policies, which can lead to confusion, frustration, and noncompliance. To help mitigate these challenges, we recommend institutions harmonize their reportable event processes for investigator-initiated multisite research that is overseen by a single IRB using the SMART IRB Agreement, even if institutions follow different policies for internally-reviewed research. Our specific recommendations are outlined below.

Although the focus in this document is on investigator-initiated research, we think these recommendations are worth considering for all research conducted under a single IRB arrangement.

Noncompliance

Recommended definitions of noncompliance, serious noncompliance, and continuing noncompliance

Noncompliance is any failure to follow:

- Applicable federal regulations, state and local laws, or institutional policies governing human subjects protections, or
- The requirements or determinations of the IRB, including the requirements of the approved investigational plan (i.e., protocol deviations).

Noncompliance can result from performing an act that violates these requirements or failing to act when required.

Serious noncompliance is any noncompliance that increases risk of harm to subjects; adversely affects the rights, safety, or welfare of subjects; or adversely affects the integrity of the data and research. **Apparent serious noncompliance** describes an event that *appears* to constitute serious noncompliance, and so requires reporting to an appropriate IRB for consideration, but the IRB has not yet made a formal assessment of the event.

Continuing noncompliance is a pattern of repeated noncompliance which continues after initial discovery, including inadequate efforts to take corrective actions within a reasonable timeframe. **Apparent continuing noncompliance** describes an event(s) that *appears* to constitute continuing noncompliance, and so requires reporting to an appropriate IRB for consideration, but the IRB has not yet made a formal assessment of the event.

Policy recommendations for serious or continuing noncompliance

As part of their policies and procedures, Reviewing IRBs (and their institutions, as applicable) should:

1. Describe the reporting requirements for apparent serious or continuing noncompliance (i.e., allegation of noncompliance).
2. Require prompt reporting by the investigator (or investigator's designee) or organizational officials and offices of any apparent serious or continuing noncompliance, and define prompt reporting as the responsible party's initial notification to the Reviewing IRB within seven calendar days of recognizing apparent serious or continuing noncompliance. The prompt reporting requirement is met once initial notification is submitted, even if all of the information is not known at the time of submission.
3. Describe the process by which the IRB reviews allegations of noncompliance and determines whether an allegation of noncompliance meets the definition of serious, continuing, or both serious and continuing noncompliance, in addition to whether the noncompliance may constitute an unanticipated problem.
4. Describe a process for alerting Relying Institutions that may be affected by the event and obtaining their input, as appropriate, regarding the event and any proposed corrective actions.
5. Identify the party(ies) responsible for reporting determinations of serious or continuing noncompliance to appropriate institutional officials, applicable regulatory or oversight agencies, and, when appropriate, the sponsor or contract research organization and other performance sites involved in the research affected by the event. For example, this responsibility can be delegated to Relying Institutions, but this delegation should be documented.
6. After the IRB makes a final determination of serious or continuing noncompliance, the designated party should promptly report the finding (within 21 calendar days) to appropriate institutional officials, applicable regulatory or

oversight agencies, and, when appropriate, the sponsor or contract research organization and other performance sites involved in the research affected by the event. This timeframe includes obtaining feedback from the affected Relying Institution(s) on the planned report. When the Reviewing IRB (or its institution) is responsible for this reporting, the SMART IRB Agreement requires that relevant Relying Institutions have the opportunity (no fewer than five business days, whenever possible) to review and comment on the draft report that is to be sent to the external recipients. Relying Institutions are expected to promptly provide any comments on the draft report to the Reviewing IRB (or Reviewing IRB Institution), though the Reviewing IRB (Reviewing IRB Institution) is under no obligation to adopt comments of a Relying Institution.

7. Make available to researchers a list of examples of apparent serious or continuing noncompliance. We suggest using a list of events that includes, but that is not limited to, the examples provided in Appendix A.
8. Adopt the SACHRP approach to protocol deviations to help identify deviations that may constitute serious or continuing noncompliance.
9. Allow flexibility, when possible, regarding who can submit the report to the Reviewing IRB, but with the expectation that the Overall Principal Investigator (PI) for a study and the local investigator at the event site (Site Investigator) are aware of the report submission. In the case of a report from a whistleblower, the Reviewing IRB would determine which study team members will be informed of the report and when.

Unanticipated Problems

Recommended definition of unanticipated problems

- Institutions should follow the Office for Human Research Protections (OHRP) guidance regarding the types of events that constitute unanticipated problems. They should not require prompt reporting of events that do not meet these criteria, such as serious adverse events (SAEs) that are expected or unrelated to study participation. OHRP considers unanticipated problems, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:
 - 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;
 - Related, or possibly related, to participation in the research (in OHRP's guidance document, "possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
 - 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.
- For research that falls under Food and Drug Administration (FDA) purview, follow FDA guidance to assist with the assessment regarding whether adverse events (AEs) or SAEs also constitute unanticipated problems under the OHRP guidance.

Policy recommendations for unanticipated problems

Reviewing IRBs (and their institutions, as applicable) should:

1. Require prompt reporting by the investigator (or investigator's designee) or organizational officials and offices of any of unanticipated problems, and define "prompt reporting" as the submission of at least a preliminary report of unanticipated problems to the Reviewing IRB within seven calendar days of the local Site Investigator determining that

the event(s) appears to meet the definition of an unanticipated problem involving risks to subjects or others.

2. Describe the process by which the IRB reviews reports to determine whether the event(s) meet the definition of an unanticipated problem, including whether the events may constitute serious or continuing noncompliance.
3. Describe a process for alerting Relying Institutions that may be affected by the event and obtaining their input, as appropriate, regarding the event and any proposed corrective actions.
4. Identify the party(ies) responsible for reporting determinations of unanticipated problems to appropriate institutional officials, applicable regulatory or oversight agencies, and, when appropriate, the sponsor or contract research organization and other performance sites involved in the research affected by the event. For example, this responsibility can be delegated to Relying Institutions, but this delegation should be documented.
5. After the IRB makes a final determination that an unanticipated problem occurred, the designated party should promptly report (within 21 calendar days) unanticipated problems to appropriate institutional officials, applicable regulatory or oversight agencies, and, when appropriate, the sponsor or contract research organization and other performance sites involved in the research affected by the event. This timeframe includes obtaining feedback from the affected Relying Institution(s) on the planned report. When the Reviewing IRB (or its institution) is responsible for this reporting, the SMART IRB Agreement requires that relevant Relying Institutions have the opportunity (no fewer than five business days, whenever possible) to review and comment on the draft report the Reviewing IRB plans to send to the external recipients. Relying Institutions are expected to promptly provide the Reviewing IRB (or Reviewing IRB Institution) any comments on the draft report, though the Reviewing IRB (Reviewing IRB Institution) is under no obligation to adopt comments of a Relying Institution.
6. Make available to researchers a list of events likely to constitute unanticipated problems, based on OHRP and FDA guidance. We suggest using a list of events that includes, but that is not limited to, the examples provided in Appendix B.
7. Allow flexibility, when possible, regarding who can submit the report to the Reviewing IRB, with the expectation that the Overall PI for a study and local Site Investigator at the site where an event occurred are aware of the submission of the event. In the case of a report from a whistleblower, the Reviewing IRB would determine which study team members will be informed of the report and when.

Other Considerations for Reportable Events

Based on the Reportable Events Working Group's review of policy and subsequent discussions, the group agreed that some general points for consideration regarding serious or continuing noncompliance and unanticipated problems could be helpful to institutions and research teams preparing for increased use of single IRB review. These considerations may also further promote broad harmonization of approaches across institutions.

Considerations for Reviewing IRBs

When an institution serves as a Reviewing IRB for other sites, we recommend the Reviewing IRB address the following in its policies or procedures:

- **Aligning policy definitions with federal regulations.** An institution's policies should be based on regulatory requirements and guidance put forth by agencies with statutory authority (e.g., OHRP and FDA), with consideration for the policies and guidance of other federal agencies (e.g., NIH and VA), given their roles in funding and collaboration in human subjects research. To support harmonization, institutions should use the definitions and terms found within federal regulatory agency regulations and guidance, to the extent possible.
- **Accounting for Relying Institutions.** An institution that has, or is, an IRB should have policies that take into the account the possibility that an external institution may rely on the institution's IRB. For example, many institutions have policies

that do not require the reporting of external events, which would not be appropriate given that reports from external sites must be reported to that IRB if they are acting as the Reviewing IRB for that site. For multisite research involving single IRB review, policies should clearly state that all reports of apparent serious or continuing noncompliance or unanticipated problems should be reported to the Reviewing IRB for any study that involves subjects, data, or specimens and for which the institution's IRB serves as the Reviewing IRB.

- **Disseminating policies for noncompliance and unanticipated problems.** A Reviewing IRB should have a mechanism in place for informing study teams of their requirements regarding reporting apparent serious or continuing noncompliance and unanticipated problems. This could be accomplished by describing or linking to the policy in approval letters or including the policy language within an investigator responsibilities document that is distributed to study teams. A Reviewing IRB could either provide this information to the Overall PI for dissemination to the study teams at each site, or the IRB can directly provide all study teams that it oversees with that information.
- **Identifying an event-reporting mechanism.** If a Reviewing IRB does not have a mechanism for study teams from Relying Institutions to directly report serious or continuing noncompliance or unanticipated problems to the Reviewing IRB (e.g., within an electronic system that all study teams can access), the Reviewing IRB should make available to study teams information about the process to promptly report these events (e.g., routing the event reporting through an entity such as a coordinating center or designated study team that has access to the Reviewing IRB's electronic system).
- **Limiting the events reported.** Reviewing IRB policies and procedures should ensure prompt reporting of unanticipated problems, but should not require study teams to report events that do not meet this definition, such as events that are expected or unrelated to study participation. Note: The SMART IRB Agreement requires Relying Institutions to report noncompliance to the Reviewing IRB and does not limit reporting to apparent serious or continuing noncompliance.
- **Triaging events.** Institutions vary in their expectations regarding who has primary responsibility for determining whether an event constitutes noncompliance or an unanticipated problem and therefore requires reporting to the Reviewing IRB. We recommend that institutions provide sufficient guidance in their policies to allow investigators to make an initial determination regarding whether an event constitutes noncompliance or an unanticipated problem (or both), and develop decision tools to help guide researchers to appropriate determinations.
- **Reporting to OHRP, FDA, and other entities.** Under the SMART IRB Agreement, unless an alternate reporting arrangement is agreed upon, the Reviewing IRB is expected to draft any reports regarding a finding of serious or continuing noncompliance or unanticipated problems. The Reviewing IRB is also expected to provide the involved Relying Institution(s) the opportunity (no fewer than five business days, whenever possible) to review and comment on the draft report before the Reviewing IRB (or Reviewing IRB's Institution) sends the report to the external recipients.
- **Notifying study teams and site personnel of determinations related to review of noncompliance and unanticipated problems.** The Reviewing IRB needs to identify a mechanism for informing study teams and relevant personnel at Relying Institutions (e.g., Points of Contact) regarding findings of serious or continuing noncompliance or of an unanticipated problem that has occurred. Under the SMART IRB Agreement, the Reviewing IRB is required to promptly notify the Overall PI, Site Investigator(s), and Relying Institution(s) of applicable review decisions as well as any findings and actions. Such notification may be made through the Reviewing IRB's designee.

Considerations for Relying Institutions

Under the single IRB review model, Relying Institutions continue to be responsible for study team compliance with the determinations of the Reviewing IRB for the approved research study. Consequently, we recommend Relying Institutions have processes and procedures to address the following in regard to reportable events:

- **Providing or having input on corrective action plans.** When an event(s) that may constitute serious or continuing

noncompliance or an unanticipated problem occurs at a Relying Institution, the institution should have processes in place to help formulate the corrective action plan(s) that will be presented to the Reviewing IRB as part of its consideration of the event(s). In addition, the Relying Institution should be prepared to provide input on corrective actions proposed by the Reviewing IRB in connection with the ceded research.

- **Ensuring events are reported to the Reviewing IRB.** When a Relying Institution identifies (e.g., through a QA/QI audit) apparent serious or continuing noncompliance or an unanticipated problem on a ceded study conducted by its own research team, or when an institution takes actions that could extend to ceded research and therefore affect oversight by an external IRB (e.g., restricting research personnel privileges), the Relying Institution should have processes in place to ensure the event and any relevant corrective actions are communicated to the Reviewing IRB.
- **Promptly providing feedback on external reports.** When the Reviewing IRB is responsible for reporting determinations of serious or continuing noncompliance or unanticipated problems to regulatory agencies (e.g., OHRP, FDA), sponsors, funding agencies, or other oversight authorities, the Relying Institution should have processes in place to provide prompt feedback on the draft communication.

Considerations for Research Teams

Study teams play an important role in recognizing, reporting, and resolving noncompliance and unanticipated problems that occur during the conduct of research. We recommend study teams have processes and procedures to address the following:

- **Triaging and assessing whether an event constitutes an unanticipated problem.** FDA guidance notes that in a multisite study, sponsors typically have more experience and expertise with the study agents than an individual investigator and, therefore, the sponsor is in a better position to process and analyze the significance of event information from multiple sites and to make a determination about whether an event is an unanticipated problem. However, in the absence of such a sponsor, research teams should have mechanisms in place to ensure events are reviewed in a timely manner (such as by the Overall PI, which may include input from a local site investigator or data monitoring entity), and to advise regarding whether an event related to a study intervention constitutes an unanticipated problem.
- **Reporting events.** Study teams should be aware of:
 - The Reviewing IRB's requirements for reporting noncompliance (including protocol deviations) and unanticipated problems, including how the Reviewing IRB defines these events, and the timeframe they require for reporting.
 - The process for local site submission of event reports to the Reviewing IRB.

APPENDIX A: Examples of Apparent Serious or Continuing Noncompliance

Examples of noncompliance events that require prompt reporting to an appropriate IRB

Note to IRBs: These events may constitute serious noncompliance as well as unanticipated problems.

- Conducting non-exempt human subjects research without IRB approval.
- Conducting human subjects research without obtaining informed consent, when a waiver of informed consent was not approved by an IRB.
- Implementing a significant modification to IRB-approved research not needed to eliminate an immediate hazard without prior IRB approval.
- Failing to adhere to eligibility criteria, such that subjects were placed at increased risk of harm or their rights or welfare were adversely affected.
- Failing to perform safety assessments within protocol-specific time frames, such that subjects were placed at increased risk of harm or their rights or welfare were adversely affected.
- Failing to communicate new information to research subjects about study participation relevant to subject rights or welfare, such as new risks that could affect subjects' willingness to participate in the study.
- Violating any conditions of IRB approval that could adversely affect subject rights or welfare.
- An event leading to a finding, such as from an audit, inspection, or inquiry by an inspector, that subjects were placed at increased risk of harm or that the subjects' rights or welfare were adversely affected.

Note to IRBs: These events may constitute continuing noncompliance as well as unanticipated problems.

- A study team repeating the same mistakes on a specific protocol, after the initial events were discovered, reported, and a corrective action plan implemented.
- The PI or study team making mistakes on multiple protocols, after the initial events were discovered, reported, and a corrective action plan implemented.

APPENDIX B:

Events that Likely Constitute Unanticipated Problems

Examples of events that likely constitute unanticipated problems that require reporting to an appropriate IRB

Note to IRBs: Some of these events may also constitute serious or continuing noncompliance.

- Identification of a new or increased risk, which could include:
 - An event occurs adversely affecting subject safety, which results in premature study closure.
 - Identification of a new risk (e.g., one not described in the protocol, consent documents, package inserts, investigational drug brochure, or device information).
 - Identification of an increased risk, including a known risk that is occurring more frequently or with greater severity than previously expected.
 - Occurrence of an event within the study that indicates an increased risk of harm and requires a change to the protocol or consent document.
 - Event that results in a withdrawal, restriction, or modification for safety reasons of a marketed approval of a drug, device, or biologic that is used in a research protocol.
 - An event leading to a finding, such as from an audit, inspection, or inquiry by a federal agency that subjects were placed at increased risk of harm.
- Malfunction of a device used as part of the research that increases risks or resulted in harm to subject(s).
- Protocol deviation that harmed a subject or placed subject at risk of actual harm or significantly increased the risk of actual harm, which could include:
 - Missed study tests or study visit(s) that could affect subject safety.
 - Enrollment of a subject who did not meet all eligibility criteria.
 - Failure to follow safety-monitoring plan.
 - Prescribing, dispensing, or administration error that results in a subject receiving an incorrect drug or dose.
- An event that leads to a protocol deviation to eliminate an immediate hazard to a subject made without prior IRB approval.
- Breach of confidentiality, where one or more research records containing private identifiable information about a subject was disclosed to persons not authorized to have access to the information.
- A stolen laptop or thumb drive with private identifiable information, if the device is not encrypted or password protected.
- Suspension of an investigator's privileges to conduct research by the researcher's institution or suspension of a physician researcher's medical license.

- Unresolved research-related complaints concerning the safety or welfare of the participant.
- Unexpected pregnancy on a study that could expose a fetus to harm.
- Incorrect imaging scan performed for research purposes that results in increased exposure of subject(s) to radiation or radiopharmaceuticals that would not have otherwise occurred.
- Errors in research-related laboratory reports that increased risks to participants.
- Instances in which subject(s) experienced physical abuse as a result of others becoming aware of their participation in the research.
- Unexpected violence by participants in a group counseling session.

REFERENCE

Sections of the SMART IRB Agreement Relevant to Noncompliance

Responsibilities of Reviewing IRB(s) and Reviewing IRB Institution(s)

5.4 IRB Review and Oversight. Perform initial and continuing reviews of submitted Research; reviews of amendments; reviews of unanticipated problems that may involve risks to subjects or others; reviews of potential noncompliance with applicable human subjects protection regulations or with the requirements or determinations of the Reviewing IRB; and reviews of other documents, requests, or information related to the approval and continuing oversight of the Research, as applicable. The review and oversight of the Research by the Reviewing IRB will be performed in accordance with the human subjects protection requirements of the Relying Institution's(s') FWA(s), any applicable federal human subjects research regulations and ethical principles referenced therein and any other applicable federal human subjects research regulations or policies.

5.11 Notification of Serious and/or Continuing Noncompliance. Promptly notify the Overall PI, Site Investigator(s), and Relying Institution(s) of any findings of serious and/or continuing noncompliance with applicable human subjects protection regulations or with the requirements or determinations of the Reviewing IRB, or of apparent serious and/or continuing noncompliance with such regulations or requirements, pertaining to the Relying Institution or its Research Personnel as well as any actions taken (including any suspension or termination of IRB approval of the Research) and the steps the Reviewing IRB deems necessary for remediation of the noncompliance at the Relying Institution. The Reviewing IRB will also notify the Overall PI, Site Investigator(s), and Relying Institution(s) of any suspension or termination of IRB approval and any remediation actions pertaining to findings of serious and/or continuing noncompliance at any other institution if such finding or actions relate to or may affect the conduct of the Research or the safety, rights, or welfare of human subjects participating in the Research at the Relying Institution(s).

If the Reviewing IRB determines that the facts of a noncompliance matter or any other matter under this Section 5.11 or under Sections 5.9 or 5.10 hereof raise issues apart from or in addition to noncompliance with human subjects protection requirements (such as a potential allegation of research misconduct), the Reviewing IRB shall notify and refer those issues to the Relying Institution for review. Any of the notifications required in this section may be made through the Reviewing IRB's designee, as determined by the Participating Institutions in connection with the specific Research.

5.13 Reporting. Notify a Relying Institution in advance if the Reviewing IRB determines that under applicable regulations or under the terms of the Relying Institution's FWA a report is required to a regulatory agency (e.g., OHRP, FDA), sponsor, funding agency, and/or other oversight authority of any unanticipated problems involving risks to human subjects or others, serious and/or continuing noncompliance with applicable human subjects protection regulations or with the requirements or determinations of the Reviewing IRB, and/or any suspensions or terminations of IRB approval.

5.13.1 Unless an alternate reporting arrangement is agreed upon, the Reviewing IRB/Reviewing IRB Institution will draft the report and will provide the involved Relying Institution(s) the opportunity (no fewer than five (5) business days, whenever possible) to review and comment on the draft report before the Reviewing IRB/Reviewing IRB Institution sends the report to the external recipients. The Relying Institution(s) will promptly provide any comments on the draft report to the Reviewing IRB/Reviewing IRB Institution. The Reviewing IRB/Reviewing IRB Institution is under no obligation to adopt comments of a Relying Institution. However, nothing in this Agreement shall prevent a Relying Institution from making its own report in addition to any report prepared by the Reviewing IRB/Reviewing IRB Institution; if a Relying Institution so elects, it will provide a copy of such report to the Reviewing IRB/Reviewing IRB Institution.

5.13.2 Alternatively, the Reviewing IRB/Reviewing IRB Institution and Relying Institution(s) may agree to make a

joint report, or, depending on the circumstances the Reviewing IRB/Reviewing IRB Institution may request the Relying Institution(s) to make the report.

5.13.3 If the Reviewing IRB/Reviewing IRB Institution requests the Relying Institution(s) to make the report, the Relying Institution(s) will promptly prepare the draft report and will provide the Reviewing IRB/Reviewing IRB Institution with the opportunity (no fewer than five (5) business days, whenever possible) to review and comment on the draft report before the Relying Institution(s) sends the report to external recipients. The Reviewing IRB/Reviewing IRB Institution will promptly provide any comments on the draft report to the Relying Institution(s). A Relying Institution is under no obligation to adopt comments of the Reviewing IRB/Reviewing IRB Institution. However, nothing in this Agreement shall prevent a Reviewing IRB/Reviewing IRB Institution from making its own report.

5.14 Notification of Communications with Regulatory Agencies. Promptly notify the Relying Institution(s) of any communications regarding unanticipated problems, suspension or termination of IRB approval, serious and/or continuing noncompliance, or other regulatory compliance concerns regarding the Research received from the FDA, OHRP, and/or other regulatory agencies.

Responsibilities of Relying Institution(s)

6.12 Notification of Noncompliance; Restriction/Suspension of Authority. Promptly notify the Reviewing IRB of any potential noncompliance with applicable human subjects protection regulations or with the requirements or determinations of the Reviewing IRB in connection with the Research at the Relying Institution, and of any suspension or restriction by the Relying Institution or any third parties of any of its Research Personnel's authority to conduct the Research.

6.14 Reporting; Notification of Communications with Regulatory Agencies. Promptly provide any comments on any draft report to external parties that will be made by the Reviewing IRB/Reviewing IRB Institution pursuant to Section 5.13.1 through 5.13.3 hereof. If the Reviewing IRB/Reviewing IRB Institution requests that the Relying Institution make the report, the Relying Institution will promptly prepare the draft report and provide the Reviewing IRB/Reviewing IRB Institution with the opportunity (no fewer than five (5) business days, whenever possible) to review and comment on the draft report, after which time the Relying Institution may finalize and send the report to external recipients. If the Relying Institution elects to make its own additional report, it will provide a copy of such report to the Reviewing IRB/Reviewing IRB Institution. The Relying Institution will also promptly notify the Reviewing IRB/Reviewing IRB Institution of communications received by the Relying Institution or between the Relying Institution and FDA, OHRP, and/or other regulatory agencies, regarding unanticipated problems, noncompliance, or other compliance concerns regarding the Research, and will require the Overall PI and Site Investigator(s) to do the same with respect to such communications between the Overall PI or Site Investigator(s) and such agencies.

Sections of the SMART IRB Agreement Relevant to Unanticipated Problems

Responsibilities of Reviewing IRB(s) and Reviewing IRB Institution(s)

5.4 IRB Review and Oversight. Perform initial and continuing reviews of submitted Research; reviews of amendments; reviews of unanticipated problems that may involve risks to subjects or others; reviews of potential noncompliance with applicable human subjects protection regulations or with the requirements or determinations of the Reviewing IRB; and reviews of other documents, requests, or information related to the approval and continuing oversight of the Research, as applicable. The review and oversight of the Research by the Reviewing IRB will be performed in accordance with the human subjects protection requirements of the Relying Institution's(s') FWA(s), any applicable federal human subjects research regulations and ethical principles referenced therein and any other applicable federal human subjects research regulations or policies.

5.10 Notification of Unanticipated Problems, Injuries, Complaints. Promptly notify the Overall PI, Site Investigator(s), and Relying Institution(s) of applicable review decisions as well as of any findings and actions (including any suspension or termination of IRB approval of the Research and required corrective actions), with respect to: (i) any unanticipated problems involving risks to human subjects or others, subject injuries related to Research participation, or significant subject complaints (e.g., those that could affect the conduct of the Research) that occurred at the Relying Institution, and (ii) such events or actions that occurred at any institution if such events or actions relate to or may affect the conduct of the Research or the safety, rights or welfare of human subjects participating in the Research at the Relying Institution(s). Such notification may be made through the Reviewing IRB's designee, as determined by the Participating Institutions in connection with the specific Research.

5.13 Reporting. Notify a Relying Institution in advance if the Reviewing IRB determines that under applicable regulations or under the terms of the Relying Institution's FWA a report is required to a regulatory agency (e.g., OHRP, FDA), sponsor, funding agency, and/or other oversight authority of any unanticipated problems involving risks to human subjects or others, serious and/or continuing noncompliance with applicable human subjects protection regulations or with the requirements or determinations of the Reviewing IRB, and/or any suspensions or terminations of IRB approval.

5.13.1 Unless an alternate reporting arrangement is agreed upon, the Reviewing IRB/Reviewing IRB Institution will draft the report and will provide the involved Relying Institution(s) the opportunity (no fewer than five (5) business days, whenever possible) to review and comment on the draft report before the Reviewing IRB/Reviewing IRB Institution sends the report to the external recipients. The Relying Institution(s) will promptly provide any comments on the draft report to the Reviewing IRB/Reviewing IRB Institution. The Reviewing IRB/Reviewing IRB Institution is under no obligation to adopt comments of a Relying Institution. However, nothing in this Agreement shall prevent a Relying Institution from making its own report in addition to any report prepared by the Reviewing IRB/Reviewing IRB Institution; if a Relying Institution so elects, it will provide a copy of such report to the Reviewing IRB/Reviewing IRB Institution.

5.13.2 Alternatively, the Reviewing IRB/Reviewing IRB Institution and Relying Institution(s) may agree to make a joint report, or, depending on the circumstances the Reviewing IRB/Reviewing IRB Institution may request the Relying Institution(s) to make the report.

5.13.3 If the Reviewing IRB/Reviewing IRB Institution requests the Relying Institution(s) to make the report, the Relying Institution(s) will promptly prepare the draft report and will provide the Reviewing IRB/Reviewing IRB Institution with the opportunity (no fewer than five (5) business days, whenever possible) to review and comment on the draft report before the Relying Institution(s) sends the report to external recipients. The Reviewing IRB/Reviewing IRB Institution will promptly provide any comments on the draft report to the Relying Institution(s). A Relying Institution is under no obligation to adopt comments of the Reviewing IRB/Reviewing IRB Institution. However, nothing in this Agreement shall prevent a Reviewing IRB/Reviewing IRB Institution from making its own report.

5.14 Notification of Communications with Regulatory Agencies. Promptly notify the Relying Institution(s) of any communications regarding unanticipated problems, suspension or termination of IRB approval, serious and/or continuing noncompliance, or other regulatory compliance concerns regarding the Research received from the FDA, OHRP, and/or other regulatory agencies.

Responsibilities of Relying Institution(s)

6.11 Notification of Unanticipated Problems, Injuries, Complaints. Require the Site Investigator(s) to promptly notify the Reviewing IRB of any unanticipated problems that may involve risks to human subjects or others, or any subject injuries related to Research participation, or any significant subject complaints that occurred at the Relying Institution.

6.14 Reporting; Notification of Communications with Regulatory Agencies. Promptly provide any comments on any draft report to external parties that will be made by the Reviewing IRB/Reviewing IRB Institution pursuant to Section 5.13.1 through 5.13.3 hereof. If the Reviewing IRB/Reviewing IRB Institution requests that the Relying Institution make the report, the Relying Institution will promptly prepare the draft report and provide the Reviewing IRB/Reviewing IRB Institution with the opportunity (no fewer than five (5) business days, whenever possible) to review and comment on the draft report, after which time the Relying Institution may finalize and send the report to external recipients. If the Relying Institution elects to make its own additional report, it will provide a copy of such report to the Reviewing IRB/Reviewing IRB Institution. The Relying Institution will also promptly notify the Reviewing IRB/Reviewing IRB Institution of communications received by the Relying Institution or between the Relying Institution and FDA, OHRP, and/or other regulatory agencies, regarding unanticipated problems, noncompliance, or other compliance concerns regarding the Research, and will require the Overall PI and Site Investigator(s) to do the same with respect to such communications between the Overall PI or Site Investigator(s) and such agencies.

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