IRB Full Board Review of Noncompliance and Unanticipated Problems

DEFINITIONS

Noncompliance (NC)
Failure to comply with regulations or Emory IRB Policies and Procedures; or failure to follow the requirements or determinations of the IRB.

Serious Noncompliance (SNC)[1] *non-VA*
Noncompliance which, in the judgment of the convened IRB, significantly increases risk to participants, significantly decreases potential benefits, or compromises the integrity of the Human Research Protection Program (HRPP).

- The IRB does not have to find that harm has occurred, or was likely to occur, to make a determination of serious noncompliance.
- Multiple instances of noncompliance that are deemed not-serious individually may constitute serious noncompliance when considered collectively.
- The Board may consider mitigating factors, such as corrective action, that play a role in the determination of whether the event increased risk, decreased potential benefits, or negatively affected the integrity of the HRPP, but if despite these factors, the event's occurrence meets the definition of serious noncompliance, and then the event should be categorized as such.

Continuing Noncompliance (CNC):
A pattern of non-compliance that indicates a lack of understanding or disregard for the regulations or institutional requirements that protect the rights and welfare of participants and others, compromises the scientific integrity of a study such that important conclusions can no longer be reached, suggests a likelihood that non-compliance will continue without intervention, or involves frequent instances of minor non-compliance. Continuing non-compliance may also include failure to respond to a request from the IRB to resolve an episode of non-compliance or a pattern of minor non-compliance.

OHRP has advised that it considers noncompliance to be continuing if it persists after the investigator knew or should have known about it. In such cases, the Emory IRB holds a presumption of continuing noncompliance, placing the burden on the investigator to present compelling, mitigating circumstances. The period in which the continuing noncompliance occurred could be days or weeks (depending on the seriousness of the matter), and the IRB does not need to call an issue noncompliance before being able to call it continuing noncompliance.[2]

Unanticipated Problem (UP):
Any unanticipated problem related to the research, whether serious or not, that adversely affects the safety, rights, or welfare of subjects or others.

Generally, a UP is an event that satisfies all three following criteria:

1. Related to the research study itself;
2. Unanticipated (unexpected, not described in study docs, or higher frequency/severity); AND
3. Adversely affects the safety, rights, or welfare of subjects or others.

Breaches of confidentiality are to be considered as unexpected even if they are described in the ICF.

[1] The U.S. Office of Human Research Protections (OHRP) has advised in correspondence with the Emory IRB that it considers the following always to be serious noncompliance:
- Human subjects research conducted without IRB approval
- Substantive change to the research implemented without IRB approval

[2] Borror, Kristina. *Guidance on Reporting Incidents to OHRP*. Webinar accessible at http://videocast.nih.gov/launch.asp?18537

GUIDING EXAMPLES

SERIOUS NONCOMPLIANCE	
Example Scenario	***Key Considerations***
Research conducted without IRB review or approval: The IRB learns of a project that involved retrospective review of patients' clinical data for purposes of drawing conclusions about the efficacy of a certain genetic testing process. The study team never asked the IRB about the need for review before starting the project. The activity should have been considered research that required IRB review because it (1) aimed to draw generalized conclusions and (2) it involved human subjects by way of identifiable information.	• In-line with OHRP guidance, non-exempt research conducted without prior IRB approval is considered *presumptively serious noncompliance*. Mitigating factors that may help overcome this determination **ONLY** include: o The IRB explicitly told the researcher that IRB review was not required. o The PI made an effort to find the information themselves and mistakenly thought the research did not need IRB approval. o PI thought data were de-identified, or attempted to de-identify them. • The nature of the project itself does not mitigate the determination in any way (e.g., whether or not the study is no more than minimal risk). • Whether or not the IRB would have changed anything about the project if reviewed does not mitigate the determination in any way.
Late reporting of an unanticipated problem: The study did not report a new, unexpected and related event involving the study drug or device. The information warranted a protocol, ICF or IB modification.	• Whether or not the event was assessed by the study team in real time. If the event was assessed and considered not reportable by the PI, but later it was assessed as a UP (by the sponsor, study monitor or PI), the delayed reporting may constitute NC, not serious or continuing. • If the subjects were informed about the new risk, but the IRB was not notified, this may be a mitigating factor to consider the late reporting as NC but *not* serious.
Failure to follow the protocol: The study team reports that they have identified instances when the protocol was not followed. Specifically, the study team enrolled ineligible subjects, did not perform safety procedures or laboratory tests, enrolled subjects into the study without proper consent, or they implemented a substantive change to the research without IRB approval (unless implemented to avoid imminent harm to subjects).	• Points that may aggravate the event: o The study was a clinical trial in preliminary phase (Phase I or II) o The PI is an S-I o The deviation impairs subjects' willingness to continue participation o The deviation significantly increased the risk to subjects o The deviation compromises the integrity/effectiveness of Emory HRPP o If the deviation were to be made known to the public, it would very likely damage community trust in Emory as a research institution o Points that may mitigate the event: o The deviation was in line with the standard of care and the protocol deviated from standard of care. For example, a dose was given in a level that is more than what the protocol calls for but within standard of care. The Board should consider if the standard of care could put the subject at an increased risk (because of drug contraindication, for example) while on an investigational product or procedure. o The labs or procedures that were not done were replaced by comparable laboratory tests or procedures. For example, the protocol required a CT scan but the subject underwent an MRI.
Dose error: Wrong dose of medication was prepared to give to a subject.	• Points that may aggravate the event: o The subject received a dose that caused a serious side effect o The PI or study staff did not follow the protocol, that had specific information about the dose preparation process • Points that may mitigate the event: o If through QA measures the dose was recalled by the researcher before it was given to the patient, then the recall action could be considered in determining that the event constituted protocol noncompliance, as opposed

	to serious noncompliance. ○ The dose given was not more than what the subject may receive during the standard disease treatment and: • No contraindication exists between the standard of care and the research medication received • There are no concerns about the dose preparation process that may indicate the root cause of this issue is procedural.

CONTINUING NONCOMPLIANCE	
Example Scenario	***Key Considerations***
Protocol deviations identified during an audit: The study team reported several deviations that occurred over the course of 3 months. The events were identified during a routine monitoring visit. This is the first audit done on the study.	• Following OHRP recent guidance, the IRB does <u>not</u> need to make prior determinations of NC to call a new event CNC. In this case, because multiple events happened in the space of 3 months, this could be considered CNC • An aggravating factor could be that the investigator should have known of the noncompliance, as the approved study protocol provided for monitoring by the PI and/or sponsor. • Other examples of CNC are: ○ Repeated instances of late submission of reportable events ○ Repeated lapses of IRB approval during which human subjects research occurs ○ Repeated informed consent discrepancies, for example, missing patient signatures in consent documents, lack of HIPAA form, missing pages in consent or HIPAA document, etc.

UNANTICIPATED PROBLEMS	
Example Scenario	***Key Considerations***
Breaches of Confidentiality: The study team is reporting that a member of the team lost a laptop or other device that contained subject PHI or other identifiable data that could put their well-being at risk (for example, a social security number). The device was not encrypted. The device also was not recovered or the information was accessed by unauthorized people. PHI was inadvertently emailed to people inside or outside our institution who are not listed as groups who may access PHI on the HIPAA form.	• <u>A confidentiality breach should never be considered anticipated, despite being disclosed as a risk in the ICF.</u> • If the information that was released is very unlikely to damage the subject's well-being (for example, the only information released was the subject's name, with no PHI associated with it), then the event may be considered NC and not a UP. • If the information was released inside Emory and it is clear that the information was not accessed, then the event may be considered NC and not a UP. • If the device and/or the file containing identifiable data were encrypted (not just password-protected) then the event may be considered NC and not a UP
Serious, Unexpected, and Adverse Event: An investigator reports that one subject (at Emory or at an external location, and regardless of whether or not Emory is the lead site) experienced a new, unknown, and serious adverse event while participating in the trial, or that a known risk is happening at a greater frequency, severity, or duration than expected. This applies to SUSARs and UADE's where the event cannot be explained by the underlying medical condition or its progression, and the sponsor or PI thinks that changes to the ICF, IB, and/or protocol are required.	• Consider if the event is anticipated. Anticipated events should be outlined in the IC, IB, or protocol or should be associated with the underlying disease/disorder, past medical history, or concomitant medications • Consider if the event is related to the research, meaning that it was caused by participation in the research or directly related to the study drug or device, rather than from the underlying disease or its progression • Consider if the research places subjects or others at a greater risk of harm than was previously known. Besides fulfilling the above criteria, it may also prompt an action from the PI and study team. For example, it may require notification to subjects or changes to the study documents.

Reportable Events for VA Studies

More information can be found at VHA DIRECTIVE 1058.01, version (October 22, 2020)

Unanticipated SAEs and Deaths

An unanticipated problem involving risks to subjects or others (UPIRTSO) in human subjects research is an incident, experience or outcome that is: unexpected; related or possibly related to participation in the research; and indicative of the research placing subjects or others at substantively greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

Deaths believed to be both unexpected and related or possibly related to participation in a VA non-exempt human subjects research study are the deaths to which we refer in this guidance.

Serious and Continuing Noncompliance

Serious Noncompliance is any failure to adhere to requirements for conducting research that may reasonably be regarded as:

1) Presenting a genuine risk of substantive harm to the safety, rights, or welfare of human research subjects or others, including their rights to privacy and confidentiality of identifiable private information;
2) Presenting a genuine risk of substantive harm to the safety, rights, or welfare of research personnel who conduct research;
3) Presenting a genuine risk of substantive harm to the health or welfare of animals used in research;
4) Presenting a genuine risk of substantive reputational harm to VA; or
5) Substantively compromising a VA medical facility's Animal Care and Use Program (ACUP), Human Research Protection Program (HRPP), Research Safety and Security Program (RSSP), or research information security processes.

Continuing Noncompliance: means repeated instances of noncompliance with applicable laws, regulations, policies, agreements, or determinations of a research review committee or the prolonged persistence of noncompliance occurring after its identification, awareness, or implementation of a corrective action intended to effectively resolve the noncompliance.

Study Team Required Actions

- For deaths, study team should inform the IRB within one hour via a phone call and in writing with an Other Event within one day
- For UPIRTSOs, or possible serious or continuing noncompliance, the study team should submit an Other Event within five business days after becoming aware.

IRB Required Actions

- The Team Q member triaging Other Events will send death, and potential UPIRTSOs and serious/continuing noncompliance to the CoRe team for a determination per the timelines below:
    - Deaths: the IRB must review within one business day after receiving an Other Event submission. The IRB Chair or another qualified IRB voting member must assess and document whether any actions are warranted to eliminate apparent immediate hazards to subjects and, if so, initiate those actions.
    - UPIRTSOs, potentially serious or continuing noncompliance: the IRB must review within five business days after receiving the Other Event submission. The IRB Chair or another qualified IRB voting member must assess and document whether any actions are warranted to eliminate apparent immediate hazards to subjects and, if so, initiate those actions.
- After CoRe determination, the IRB will review the event at next convened meeting, not to exceed 30 calendar days (60 days for serious or continuing noncompliance events) after the date of written notification. NOTE: *Incidents covered by this paragraph may call for immediate attention and require the IRB to convene an emergency session prior to its next scheduled meeting.*
- Ensure that the minutes captured all required documentation per VHA DIRECTIVE 1058.01
- The IRB will copy the HRPP Manager, the facility director and the Research Compliance Officer who will report this event, as applicable, to the RCO, and the ACOS/R&D.

If modification to the protocol, informed consent form or investigational brochure is required, the convened IRB must determine whether previously enrolled subjects must be notified, and if so, when and how notification and documentation must occur.