

Guidance & FAQ: DF/HCC Policy on Review of IND Safety Reports from External Sponsors

DF/HCC Policy RCO-204: Safety and Event Reporting defines DF/HCC investigator responsibilities related to IND Safety Reports. This document explains the rationale and regulatory background for the INDSR language contained within this policy, and the expectations of external sponsors when a DF/HCC investigator is serving as the PI of an externally-sponsored IND held study.

What does DF/HCC expect of sponsors?

FDA has published that sponsors frequently provide uninformative reports to investigators, and that approximately 86% of IND safety reports do not meet the regulatory criteria for reporting.

“The purpose of expedited IND safety reporting is to call attention to important safety signals of an investigational agent so that appropriate monitoring and patient management decisions are promptly instituted to ensure protection of human subjects participating in clinical trials. Reporting of uninformative adverse events is inappropriate and can consume the limited resources of investigators, IRBs, and the FDA. Moreover, large numbers of uninformative expedited safety reports, as observed in our study, can obscure important and valid safety signals.”

Jarow JP, Casak S, Chuk M, Ehrlich LA, Khozin S. The Majority of Expedited Investigational New Drug Safety Reports Are Uninformative. Clin Cancer Res. 2016 May 1;22(9):2111-3. doi: 10.1158/1078-0432.CCR-15-2082. Epub 2016 Jan 18. PMID: 26783289. <https://pubmed.ncbi.nlm.nih.gov/26783289/>

DF/HCC expects sponsors to report new information consistent with FDA regulations and FDA guidance. However, DF/HCC has found that a majority of IND safety reports received from external sponsors do not meet this standard. Sponsors should only send IND safety reports that are clearly identified as UAPs. DF/HCC Policy RCO-204 section 5.2.3.2.1 states: *DF/HCC expects external sponsors to analyze and determine which events meet the FDA requirements for IND safety reporting, and to clearly and directly notify the DF/HCC PI that these events meet the definition of an Unanticipated Problem Involving Risk to Subject or Others (UPRSO), also known as an Unanticipated Problem (UAP).*

In general, this means that individual events should only be reported in an IND safety report if they meet all 3 criteria below:

- **Serious** (resulted in death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly or birth defect)
- **Unexpected** (not listed or inconsistent with the expected specificity or severity described in the investigator brochure or the general investigational plan)

- There is **evidence to suggest a causal relationship** between the drug and the adverse event, as determined by the sponsor (FDA expects sponsors to make this causality assessment and not solely rely on the determination of the reporting investigator).

UAP's that meet the above criteria-generally will warrant 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 or others.

What does DF/HCC policy mean by “directly notify”?

FDA regulations require sponsors to notify all investigators of IND/IDE safety reports. DF/HCC expects that sponsors provide a clear and direct notification to investigators when distributing such reports (for example, an email notification clearly indicating the release of a new IND/IDE safety report).

DF/HCC Policy RCO-204 section 5.3.1.1 states: *DF/HCC requires external sponsor utilizing web portals to send a direct notification to the research team when a new IND safety report is posted to the portal.*

DF/HCC does not consider passive or silent uploading of reports to a portal as providing adequate and timely notification. Similarly, sponsor communications should unambiguously indicate in the notification that the information is safety related and how it meets the FDA criteria for reporting.

Are all IND safety reports sent by the sponsor reviewed?

Yes. The Principal Investigator is responsible for ensuring that all IND safety reports received from an external sponsor are reviewed in order to determine if they were clearly identified as a UAP and required action. When DF/HCC sites are under separate FDA 1572 forms, each DF/HCC PI is responsible for ensuring all IND safety reports are reviewed at their site. However, this review may be delegated to another study team member. The DF/HCC PI will not individually sign or otherwise document review of IND safety reports that are not clearly identified by the sponsor as a UAPs

DF/HCC Policy RCO-204 section 5.3.2.3 states: *Each DF/HCC PI listed on the Form FDA 1572 is responsible for ensuring that all IND Safety Reports received from an external sponsor are reviewed. The DF/HCC PI may delegate review of INDSRs to appropriately trained research staff members, as per the DF/HCC Key: Delegation of Tasks for Clinical Research.*

The DF/HCC PI must review all IND Safety Reports that are **clearly identified by the sponsor as meeting the criteria for a UAP**. Review of reports that are clearly identified by the sponsor as a UAP must be done by the PI and may not be delegated to other study staff.

Will DF/HCC investigators submit IND safety reports to the IRB?

DF/HCC investigators are required under the regulations to report all unanticipated problems (UAPs) to the IRB (§§ 312.66, 312.53(c)(1)(vii), and 56.108(b)(1)). Reporting to the IRB will occur in accordance with the policies of the IRB of record.

DF/HCC Policy RCO-204 section 5.2.3.3.2. states: The DF/HCC PIs must review all IND Safety Reports that are clearly identified by the sponsor as a UAP to determine reporting requirements per the IRB of record.

However, we have found that the majority of IND safety reports received from sponsors do not meet the criteria for IRB reporting.

In [Guidance for Clinical Investigators, Sponsors, and IRBs](#), FDA has stated that “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).**”

Similarly, OHRP defines an unanticipated problem as an event that is unexpected, related or possibly related to participation 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” ([Unanticipated Problems Involving Risks & Adverse Events Guidance](#)). OHRP also states that events meeting these criteria “generally will warrant 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 or others.**”

FDA has advised that “the practice of local investigators reporting individual, unanalyzed events to IRBs, including reports of events from other study sites that the investigator receives from the sponsor of a multi-center study—often with limited information and no explanation of how the event represents an unanticipated problem—has led to the submission of large numbers of reports to IRBs that are uninformative” ([Guidance for Clinical Investigators, Sponsors, and IRBs - Adverse Event Reporting to IRBs](#)).

Furthermore, “OHRP advises that it is neither useful nor necessary under the HHS regulations at 45 CFR part 46 for reports of individual adverse events occurring in subjects enrolled in multicenter studies to be distributed routinely to investigators or IRBs at all institutions conducting the research. Individual adverse events should only be reported to investigators and IRBs at all institutions when a determination has been made that the events meet the criteria for an unanticipated problem. In general, the investigators and IRBs at all these institutions are not appropriately situated to assess the significance of individual external adverse events” ([Unanticipated Problems Involving Risks & Adverse Events Guidance](#)).