Frequently Asked Questions:
DF/HCC Policy on Receipt of Safety Reports

As of January 1, 2022, DF/HCC research teams may begin implementing the changes in policy RCO-204 Version 12, which becomes effective on February 28, 2022. This document explains the rationale and regulatory background for the INDSR language contained within this policy.

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 sponsors do not meet this standard.

DF/HCC Policy RCO-204 section 5.3.1 states: *DF/HCC expects external study sponsors to determine which events meet the FDA requirements for IND/IDE safety reporting and to directly notify DF/HCC investigators of potential serious risks. (21 CFR 312.32, 21 CFR 312.55, 21 CFR 812.46, 21 CFR 812.150). Sponsors must analyze the significance of new safety events and provide sufficient information to support a substantive review by investigators (and the IRB, when applicable).*

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).

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: *For studies utilizing web portals, DF/HCC requires a direct notification to be sent to the research staff to alert them that a new IND/IDE safety report has been 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.

Will DF/HCC investigators document review of all IND/IDE safety reports sent by the sponsor?

The Principal Investigator must ensure that IND/IDE safety reports are reviewed in order to determine any required action. When DF/HCC sites are under separate FDA 1572 forms, each DF/HCC PI is responsible for ensuring all IND/IDE safety reports are reviewed at their site. However, this review may be delegated to another study team member.

DF/HCC Policy RCO-204 section 5.3.2.3 states: *Each DF/HCC PI is responsible ensuring that the appropriate review of IND safety reports occurs. The DF/HCC PI may delegate this task to appropriately trained and qualified sub-investigators listed on the FDA Form 1572.*

DF/HCC does not require investigators to take any action on incomplete, uninformative, unevaluable, or inappropriately reported information.

DF/HCC Policy RCO-204 section 5.3.1.3 states: *In the event that a DF/HCC investigator receives unevaluable reports (e.g., the report does not appropriately analyze or communicate the significance of new information, the event does not meet IND safety reporting criteria, or the report contains insufficient information for PI/IRB review), DF/HCC PIs are not required to acknowledge, sign, print, retain or take action.*

Furthermore, DF/HCC does not require investigators to document this review in sponsor systems, provided that adequate documentation of review exists locally.

DF/HCC Policy RCO-204 section 5.3.2.3 states: *Review of IND safety reports by a qualified investigator must be documented based on either institutional practice or via a sponsor's online web*

portal. Documentation is not required to be in a sponsor's safety reporting system or database if the review is documented locally in the research files.

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

DF/HCC investigators are required under the regulations to report all unanticipated problems 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 5.3.2 states: *DF/HCC PIs must ensure that all unanticipated problems involving risks to subjects or others are reported to the IRB of record, as required by IRB policy.*

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).