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

Effective January 31, 2018, the Dana-Farber / Harvard Cancer Center (DF/HCC) Policy RCO-204 was revised to update DF/HCC requirements for review and receipt of safety reports from external sponsors. This document explains the rationale and regulatory background for the policy changes, and answers frequently asked questions from external sponsors.

What is considered an "unanticipated problem" under DF/HCC policy?

DF/HCC Policy RCO-204 section 5.12.1 states: *DF/HCC expects external study sponsors to directly notify DF/HCC Investigators of unanticipated problems and important safety information that has implications for the conduct of the research (21 CFR 312.32, 21 CFR 312.55, 21 CFR 812.46, 21 CFR 812.150).*

The DF/HCC uses the term "unanticipated problem" to refer to ""unanticipated problems involving risks to subjects or others" as understood by the Food and Drug Administration (FDA) and the Office for Human Research Protections (OHRP). While adverse events may be considered unanticipated problems, very few serious and unexpected adverse events meet the unanticipated problem definition.

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."

Why does the DF/HCC expect sponsors to directly notify investigators of unanticipated problems?

DF/HCC Policy RCO-204 section 5.12.1 states: *DF/HCC expects external study sponsors to directly notify DF/HCC Investigators of unanticipated problems and important safety information that has implications for the conduct of the research (21 CFR 312.32, 21 CFR 312.55, 21 CFR 812.46, 21 CFR*

812.150). DF/HCC Investigators are not required to check Industry, CRO, or third-party web portals for possible new information in the absence of a notification (e.g., email).

The DF/HCC expects sponsors to provide a direct notification when an unanticipated problem occurs to ensure DF/HCC investigators are aware of the event and any immediate action(s) needed to protect study participants.

Sponsors are specifically required under federal regulations to "keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use" (§ 312.55(b)). In addition, the regulations require the sponsor of an IND to "promptly review all information relevant to the safety of the drug" and to "analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information" (§ 312.32).

Unanticipated problems, according to FDA and OHRP, generally require changes to research conduct to protect the safety, welfare or rights of study participants. A timely and unambiguous notification from the sponsor is necessary for DF/HCC investigators to fulfill their responsibility "for protecting the rights, safety, and welfare of subjects under the investigator's care" (§ 312.60).

Will DF/HCC investigators acknowledge receipt of, or perform an independent review of, safety reports sent by the sponsor?

DF/HCC Policy RCO-204 section 5.12.2 states: *For phase II, II/III, III and IV trials, no action will be taken with external safety reports that do not have a clear indication of an unanticipated problem classification. Such reports will not be acknowledged, signed, printed, or retained for the study file.*

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)). However, FDA has stated that the sponsor "typically has more experience and expertise with the study drug than an investigator. Accordingly, the sponsor is in a better position to process and analyze the significance of AE information from multiple sites and…to make a determination about whether an AE is an unanticipated problem" (Guidance for Clinical Investigators, Sponsors, and IRBs - Adverse Event Reporting to IRBs).

In fact, federal regulations require sponsors to "promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor" and then "analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information" (§ 312.32). Therefore, the DF/HCC expects sponsors to fulfill their obligation to protect study participants by comprehensively reviewing new safety information in the context of all other information available to the sponsor, and clearly communicating their determination to participating investigators.

Sponsors should not attempt to transfer this regulatory obligation to participating investigators by requiring their acknowledgment or review of individual safety reports. 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).

Therefore, in implementing RCO-204, the DF/HCC and the DFCI IRB have agreed to rely on the sponsor's determination as to whether an event is an unanticipated problem that requires reporting to the IRB. This DF/HCC policy is consistent with guidance from FDA, which states "to satisfy the investigator's obligation to notify the IRB of unanticipated problems, an investigator participating in a multicenter study may rely on the sponsor's assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor" (Guidance for Clinical Investigators, Sponsors, and IRBs - Adverse Event Reporting to IRBs).

What information must sponsors provide when notifying DF/HCC investigators of an unanticipated problem?

DF/HCC Policy RCO-204 section 5.12.3 states: *It is the sponsor's responsibility to provide an explanation of why an event was determined to be an unanticipated problem and clearly indicate the implications for the conduct of the study. Sponsors must provide sufficient information to support a substantive review by investigators and the IRB for any event that results in changes to study conduct or the informed consent document.*

Since DF/HCC investigators rely on the sponsor's assessment to determine whether an event is an unanticipated problem, the DF/HCC expects that sponsors will communicate sufficient information about the event when notifying investigators that an unanticipated problem has occurred.
FDA has provided substantial guidance on safety reporting expectations in order to avoid the "submission of large numbers of reports to IRBs that are uninformative" (Guidance for Clinical Investigators, Sponsors, and IRBs - Adverse Event Reporting to IRBs). When DF/HCC Investigators and/or the DFCI IRB receive limited information from sponsors, it is difficult for the DF/HCC investigators to determine whether any action is necessary to protect study participants.

OHRP states that unanticipated problem reports to the IRB must include the following information:

1. appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
2. a detailed description of the adverse event, incident, experience, or outcome;
3. an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem; and
4. a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem. (Unanticipated Problems Involving Risks & Adverse Events Guidance)