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Sponsor Nora Olsen: NE Research Monitor
Area Cancer Consortium - Institutional
Applicability FHCC Institutional Policies

Review of Safety Reports

SCOPE:

This policy applies to all Fred Hutchinson Cancer Center (Fred Hutch), University of Washington (UW), and Seattle Children's (SC) workforce members supporting Cancer Consortium clinical research activities.

PURPOSE:

U.S. Food and Drug Administration (FDA) regulations and the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines describe Sponsor and Investigator responsibilities for the oversight, assessment, and communication of adverse events and other safety information identified during the conduct of a clinical trial.

The U.S. Code of Federal Regulations, under 21 CFR 312.32(c)(1), *IND safety reports*, states:

> *The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks […]. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.*

ICH E6(R2) Good Clinical Practice guideline states:

> *5.16.2 The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favorable opinion to continue the trial.*

and

5.17.1 The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

In fulfilling these obligations, sponsors routinely issue Safety Reports to investigators conducting clinical trials using an investigational product. These reports may be referred to as IND, third party, or external safety reports; MedWatch reports (referring to the FDA form used for reporting); CIOMS reports (referring to the Council for International Organizations of Medical Sciences form used for reporting); or SUSARs (referring to serious and unexpected suspected adverse reactions). The majority of Safety Reports issued by sponsors are reports of individual events.

Investigators must review significant new safety information issued by a sponsor in order to fulfill their obligations to protect the rights, safety, and welfare of human subjects, as well as to fulfill IRB reporting requirements related to unanticipated problems. However, it is increasingly recognized that Safety Reports related to individual adverse events do not necessarily constitute new or significant information, and there may not be sufficient information contained in an individual report for an investigator to assess significance.

The Office for Human Research Protections (OHRP) has noted that reports of individual external adverse events often lack sufficient information to allow investigators or IRBs at each institution engaged in a multicenter clinical trial to make meaningful judgments about whether the adverse events constitute an unanticipated problem. As a result, OHRP has further stated that 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. The guidance specifies that such determination should be made by an entity such as the research sponsor, a coordinating or statistical center, or a DSMB/DMC, rather than by investigators or IRBs at individual institutions.

FDA guidance similarly notes “for multicenter studies, the sponsor is in a better position to process and analyze adverse event information for the entire study and to assess whether an adverse event occurrence is both unanticipated and a problem for the study,” and further states, “Accordingly, 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.”

DEFINITIONS:

Adverse Event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Cancer-related Study: A study that meets one or more of the following characteristics:

- Funded by NCI; or
- Primary site of a multi-site trial has classified the study as cancer or cancer-related; or

- The trial cohort will include both patients with a cancer diagnosis and others without a cancer diagnosis AND includes a primary or secondary analysis of the portion of the cohort with a cancer diagnosis; or
- Research of secondary conditions related to cancer treatment in patients with a cancer diagnosis who have received that treatment; or
- Cancer prevention studies that specifically include a primary outcome of cancer diagnosis; or
- Bone Marrow Transplant (BMT) not related to cancer treatment.

IND Safety Report: A report issued by the sponsor of an IND to notify the FDA and all participating investigators about newly discovered, potential serious risks of an investigational product. Sometimes referred to as third party safety report, MedWatch report (referring to the FDA form used for reporting), or CIOMS report (referring to the Council for International Organizations of Medical Sciences form used for reporting). Reported information may include serious and unexpected suspected adverse reactions (SUSARs) or other important safety information.

Serious Adverse Event: An adverse event or suspected adverse reaction is considered 'serious' if, in the view of either the investigator or sponsor, it results in any of the following outcomes: 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/birth defect. Other important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Suspected adverse reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unanticipated Problem: Any incident, experience, or outcome that meets all of the following criteria: a) unexpected (in terms of nature, severity, or frequency) given [i] the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and [ii] the characteristics of the subject population being studied; b) related or possibly related to participation in the research (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 c) suggests that the research places research participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unexpected Adverse Event: An adverse event, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

POLICY:

The purpose of this policy is to address requirements for Consortium PI review of Safety Reports of individual adverse events. Compliance with this policy will permit investigators to fulfill their obligations to protect the rights, safety, and welfare of human subjects and comply with IRB reporting requirements related to unanticipated problems, while reducing review of reports that are issued by the sponsor without sufficient information for an individual investigator to make a meaningful assessment.

Investigators are responsible for assessing significant new information that becomes available during the course of a cancer-related study to determine whether it affects the conduct of the study and safety of participants, and whether it is subject to IRB reporting requirements. In the case of adverse events, critical elements for this determination include a description of the event that supports whether it is characterized as serious, a description of the relationship to the investigational agent that supports whether the event is identified as a suspected adverse reaction, and whether the event represents an unanticipated problem.

FDA and OHRP recommend that the sponsor, rather than individual investigators, determine whether an individual adverse event occurring on a multicenter study represents an unanticipated problem. Consortium investigators may therefore rely on the sponsor's assessment rather than making this determination independently. If a Safety Report does not indicate whether the sponsor has assessed the event as an unanticipated problem (and it is not otherwise identified by the Sponsor as having implications for the conduct of the study), the report lacks critical information needed for meaningful assessment. If a Safety Report indicates that the sponsor has assessed the event as *not* representing an unanticipated problem (and it is not otherwise identified by the Sponsor as having implications for the conduct of the study), reliance on the sponsor's assessment assures that the event does not affect study conduct or participant safety and is not subject to IRB reporting requirements for unanticipated problems.

REQUIREMENTS:

Safety Reports must be screened and reviewed from the time a study is initially submitted to the IRB, at which time the PI is representing that the safety information in study documents accurately reflects the currently available information. Screening and review are necessary after that time point to ensure that any safety-related changes to the protocol and/or informed consent form are identified and implemented. Screening and review are no longer necessary when a study is no longer enrolling or monitoring participants, as aligned with FDA Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies (December 2012).

Safety Reports may be screened by a designated and appropriately authorized member of the research team for the presence of required elements described below. The screener's name and date of screening must be recorded for each report, on paper or electronically via sponsor portal or other system, such as Florence.

Safety Reports of individual adverse events will be subject to review by the Consortium PI in either of the two situations below:

1. The Safety Report includes *all three* of the following elements:

    a. Identification/description of the event.

    b. Sponsor's assessment of causality that indicates the event was an adverse reaction (caused by the investigational product) or a suspected adverse reaction (there is evidence to suggest a causal relationship between the drug and the adverse event). This may be reflected by language such as "probably related" rather than using the term suspected adverse reaction.

    c. Sponsor's determination that the event is unexpected or represents an "unanticipated problem."

2. The Safety Report is identified by the Sponsor as having implications for the conduct of the study (e.g., a significant change such as revising inclusion or exclusion criteria, adding a safety monitoring requirement, revising the informed consent, or revising the Investigator's Brochure).

Screened reports that meet the above criteria will be reviewed by the PI within 15 days after the report is received from the sponsor. The PI should sign and date the reviewed report, affirming their review within the 15-day timeframe. IRB reporting and/or other actions will be completed as required based on the PI's assessment and IRB policy.

Screened reports that do not meet criteria for PI review will be maintained in the regulatory files but will not be further reviewed, reported, or acknowledged.

REFERENCES:

FDA Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs—Improving Human Subject Protection, January 2009

FDA Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies, December 2012

ICH E6(R2): Integrated Addendum to ICH E6(R1): Guideline For Good Clinical Practice

OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, January 15, 2007

U.S. Code of Federal Regulations Title 21 § 312.32 (IND Safety Reporting)

Approval Signatures

Step Description	Approver	Date
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