FRED HUTCH UNIVERSITY OF WASHINGTON CANCER CONSORTIUM	Clinical Research Policies and Procedures
	Third Party Safety Reports

Approval			
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Background

FDA regulations and ICH Good Clinical Practice 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 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, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under paragraph (c)(1)(i), (c)(1)(ii), (c)(1)(iii), or (c)(1)(iv) of this section. 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 Good Clinical Practice Guidance 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 Third Party Safety Reports (i.e., MedWatch, CIOMS, SUSARS, "dear investigator" letters requiring action, or other expedited external safety reports) to investigators conducting clinical trials using an investigational product.

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 Third Party 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 constitutes 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."

Responsible Personnel

Principal Investigator

Abbreviations and Acronyms

PI: Principal Investigator

IRB: Institutional Review Board

AE: Adverse Event

FDA: Food and Drug Administration

IND: Investigational New Drug

OHRP: Office for Human Research Protections

SC: Seattle Children's

UW: University of Washington

Definitions

Adverse Event: Any harm or untoward medical occurrence in a research participant administered medical product, medical treatment or procedure even if it does not necessarily have a causal relationship with the product, treatment, or procedure. An adverse event can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporarily associated with the use of a medical product, medical treatment or procedure whether or not considered to be related.

Related or Possibly Related Adverse Event: An adverse event is "related or possibly related to the research procedures" if in the opinion of the principal investigator, it was more likely than not caused by the research procedures. Adverse events that are solely caused by an underlying disease, disorder or condition of the subject or by other circumstances unrelated to either the research or any underlying disease, disorder or condition of the subject are not "related or possibly related". If there is any question whether or not an adverse event is related or possibly related, the adverse event should be reported.

Serious Adverse Event: An adverse event that results in any of the following outcomes: Death, a life-threatening adverse event (real risk of dying), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity/or change in psychosocial status, a congenital anomaly or, requires intervention to prevent permanent impairment or damage.

Unexpected Adverse Event: An adverse event is "unexpected" when its nature, severity, or frequency are not consistent with (a) the known or foreseeable risk of adverse events associated with the research procedures described in the protocol-related documents, such as the IRB-approved research protocol, informed consent document and other relevant sources of information such as product labeling and package inserts; and are also not consistent with (b) the characteristics of the subject population being studied including the expected natural progression of any underlying disease, disorder or condition of any predisposing risk factor profile for the adverse event.

Third Party Safety Report: A report prepared by an external sponsor or coordinating center overseeing a multi-site study describing one or more adverse events or other unanticipated problems involving risks to participants or others which have occurred at one or more of the participating sites involved in the study.

Unanticipated or unexpected means that the specificity or severity of the adverse drug experience is not consistent with the Investigator's Brochure reviewed by the IRB; or, if an Investigator's Brochure was not required or not available, the specificity or severity of the adverse drug experience is not consistent with the risk information described in the general investigational plan or elsewhere in the current study documents, as amended.

Policy

The purpose of this policy is to address requirements for Consortium PI review of Third Party 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 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, relationship to the investigational agent, and whether the event represents an "unanticipated problem" as defined by Fred Hutch IRB Policy 2.6.

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 Third Party 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 Third Party 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.

Procedures

Third Party Safety Reports of individual adverse events will be subject to review by the Consortium PI if they include *all* of the following three elements:

1. Identification of the event;
2. Sponsor's assessment of causal relationship with test article; and
3. Sponsor's determination that the event represents an "unanticipated problem" (e.g., analysis in terms of other events observed with use of test article);

or

if they are identified by the Sponsor as having implications for the conduct of the study (e.g., a significant, and usually safety-related, change such as revising inclusion or exclusion criteria or including a new monitoring requirement, revisions to the informed consent, or revisions to the Investigator's Brochure).

Third Party Safety Reports may be screened by a designated and appropriately authorized member of the research team for the presence of required elements. Each report must be signed and dated upon screening.

Screened reports meeting 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 his/her 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.

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.

Applicable Regulations & Guidelines

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

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

21 CFR 312.32

ICH Good Clinical Practice Guidance (E6) 5.16, 5.17

Fred Hutch Reporting Obligations for Principal Investigators (Policy 1.11)

Fred Hutch Unanticipated Problems Involving Risks to Subjects or Others (Policy 2.6)

Version Review History	
Reviewer	**Date**
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John T. Slattery, PhD, Vice Dean for Research, University of Washington	5/31/2017