UCSF Helen Diller Family Comprehensive Cancer Center

University of California, San Francisco
Helen Diller Family Comprehensive Cancer Center

Policy for External Adverse Event Report Management

Table of Contents

Purpose

The purpose of this Helen Diller Family Comprehensive Cancer Center (HDFCCC) policy is to outline the procedures for processing external adverse event (AE) reports for externally and internally sponsored multi-center studies, internally sponsored single center trials, and consortium trials conducted within the HDFCCC at the University of California, San Francisco (UCSF).

Scope

This policy applies to all external AE reports, regardless of distribution method (i.e., web portals, mailing list, etc.) or medium (electronic or hard copy). External AE reports include, but are not limited to, Medwatch, Council for International Organizations of Medical Sciences form (CIOMS), suspected unexpected serious adverse reaction (SUSAR), Action Letters, IND Safety Reports (INDSR), and other reports and narratives for an adverse event (AE).

Definitions

IRB of Record – The Institutional Review Board (IRB) responsible for oversight of a trial at the trial's lead site. In the case of a single IRB study, the single IRB is the IRB of Record.

Local IRB – The IRB responsible for oversight of a trial at a subsite.

Background

The Office of Human Research Protections (OHRP) issued guidance in 2007 on Unanticipated Problems Involving Risks & Adverse Events that clarifies 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 Institutional Review Boards (IRBs) at all participating institutions conducting the research."

The 2012 FDA Guidance on Safety Reporting outlines that there must be a "reasonable possibility" that a drug caused an AE. Furthermore, "the sponsor is better positioned than the individual investigator to assess the overall safety of the investigational drug because the sponsor has access to serious adverse event reports from multiple study sites and multiple studies and is able to aggregate and analyze these reports."

For externally-sponsored studies, HDFCCC Investigators do not have access to the necessary information to assess individual external AEs (e.g., aggregate analysis, safety monitoring committee assessments, or external site's individual participant's medical history or treatment, etc.). Principal Investigators rely on the sponsor to make determinations of whether an investigational product causes a new risk; the sponsor must provide all new risk information, reportability status, and informed consent changes (if any) to the HDFCCC Investigators.

Procedures

1.0 Defining Reportable External AEs

Per federal and institutional guidelines, a reportable AE is defined as an "unanticipated problem involving risk to participants or others" or "serious or continuing noncompliance."

2.0 Criteria for Processing External AEs

HDFCCC will process external safety reports 1) after a study obtains IRB approval, and continue until 2) all three criteria are met:

- The study is closed to accrual
- There are no subjects on active treatment (≤ 30 days from last dose)
- There are no subjects in long term or survival follow-up

The HDFCCC and its affiliates will not review, acknowledge, or retain external reports that do not meet the definition of reportable external AEs indicated in section 1.0 above. This applies to reports disseminated via web portals, email, hardcopies, etc. The UCSF IRB requirements for AE reporting can be found in the reference section of this policy.

Accessing External Sponsor-Specific Portals: HDFCCC does not access portals for safety reports or any other study documents (protocols, IBs, Informed Consent Form (ICFs), participant materials, etc.). For reportable external safety reports, quality assurance and compliance measures require person-to-person transfer of documents and communication via email

3.0 Processing a Reportable External AE

Upon receipt of a reportable external safety report, the Principal Investigator (PI) or designee will review and submit the report to the IRB of Record per its reporting policy.

After the above criteria for processing an external AE has been met, all reportable external safety reports will be stored, without acknowledgement, in the study file until IRB closure. All submitted and approved IRB AE reports are available to external sponsors for review. Any external safety reports received after IRB closure will not be reviewed, acknowledged, or retained by the site.

4.0 Sponsor Responsibility for Reporting External AEs

It is the responsibility of the Sponsor (Industry-Sponsor, Cooperative Group, Academic Center Sponsor, or the Principal Investigator in an Investigator-initiated trial) to determine if an external AE meets the definition of a reportable external AE.

4.1 UCSF-Sponsored Studies

For UCSF-Sponsored, investigator-initiated studies where UCSF holds the Investigational New Drug Application (IND), it is the Sponsor-Investigator's responsibility to review external AEs (provided by participating sites or by industry partners/manufacturers) related to the investigational product(s) and determine whether the event meets the reporting criteria to the FDA and the IRB of record. If the event meets reporting criteria, then the Sponsor-Investigator will store and disseminate the event information to the FDA and IRB of record.

Note: If the Sponsor and PI are separate individuals, then it is suggested that the Sponsor and PI consult with each other to determine if the event represents a significant change in study risk. The Sponsor (not the PI) is responsible for reporting information to the FDA (21 CFR 312.32).

Multicenter Trials: If the event meets reporting criteria for the FDA and IRB of record on a multicenter trial, the UCSF Sponsor-Investigator is also responsible for storing and disseminating the event information to all participating sites. Participating sites will report to their local IRBs as applicable per local IRB reporting criteria. If the external event occurred at a participating site and is related to a study, then the Sponsor-Investigator must determine if the event meets reportable criteria to the FDA (21 CFR 312.32).

4.2 Externally Sponsored Studies

For multi-centered studies where an external sponsor holds the IND, the study sponsor or sponsor designee is responsible for notifying the UCSF site PI or PI designee of any

external safety reports that changes the study risks or benefits or necessitates modification to the IRB-approved consent document(s), and/or the IRB-approved application/protocol. External sponsors or industry partners must provide written notification in the form of a memo or Dear Investigator Letter (DIL) to accompany the corresponding safety documents. The memo and/or DIL must include a clear explanation of why the event has been determined to be an unanticipated problem. External safety documents received without the sponsor's explanation are assumed to not meet reporting criteria and will not be processed.

To ensure proper reporting, both should be included with the external safety reports:

- Copy of updated study documents (i.e., a revised protocol, informed consent form, and/or investigator's brochure), and
- Summary of the changes specifying changes for the updated documents to help quickly identify new risks and procedure changes.

Policy Exemptions

None

References

FDA Guidelines

- 21 CFR 312.32
- 45 CFR 46.103

FDA Guidance

- Safety Reporting Requirements for INDs and BA/BE Studies
- IND Application Reporting: Safety Reports

ICH

- ICH 5.16.2
- ICH 8.3.18

UCSF IRB:

- Adverse Event reporting
- Protocol Violations or Incident Page (Reporting Requirements Chart for Immediate Protocol Change to Protect Participant Safety)
- IRB Review Requirements and Submissions

Policy Approval

This policy document was approved by the following personnel on the following dates:

DocuSigned by:
Rahul Aggarwal
E879F084A5CA4CC...

Rahul Aggarwal, MD
Acting Medical Director, Clinical Research Support Office
Associate Director for Clinical Sciences
Helen Diller Family Comprehensive Cancer Center

5/22/2024
Date

DocuSigned by:
Katie Kelley
7F538467F93949B...

R. Katie Kelley, MD
Chair, Data and Safety Monitoring Committee
Helen Diller Family Comprehensive Cancer Center

5/23/2024
Date

DocuSigned by:
Eric Small
7ECB32D327E3438...

Eric Small, MD
Deputy Director
Helen Diller Family Comprehensive Cancer Center

5/22/2024
Date

DocuSigned by:
Kate Shumate
80D38159E89D41B...

Kate Shumate, MPA, CCRP
Director, Administration and Planning
Helen Diller Family Comprehensive Cancer Center

5/22/2024
Date

Policy contact:
Andrea Skafel, Clinical Research Support Office Director
Andrea.skafel@ucsf.edu; +1 415 502 5805

Clinical Research Policy Revision
Summary of Changes

Policy Title: Policy for External Adverse Event Report Management
Version Date: 05/21/2024
Version Number: Revision #1

Section(s)	Summary of Change	Rationale
All	Converted document template to match Form_Clin_Rsch_Policy_Template_Style_Guide_CURRENT	To follow Policy on Clinical Research Policies
Definitions	Added definitions for "IRB of Record" and "Local IRB"	Improved clarity when reading the policy
Background	Added paragraph about access to AEs for externally sponsored studies	Provided additional rationale requiring sponsors to assess and send information to the HDFCCC for AEs that are external to UCSF.
Procedures 2.0	Added reference to UCSF AE reporting requirements	Provide reference to requirements for the UCSF IRB external AE reporting
Procedures 2.0	HDFCCC does not access external portals	To ensure AEs are reviewed appropriately and not missed, the HDFCCC requires person-to-person transfer of safety documents
Procedures 3.0	IRB AE reports are available for sponsor review	Added statement that all IRB approved AE submissions are available for sponsor review

Procedures 4.0	Added paragraph indicating it is the responsibility of the sponsor to assess the reporting criteria for external AEs.	The HDFCCC does not have the required information to make the reporting assessment for external AE. Refer to background section.
Procedures 4.1	Added mulit-center UCSF sponsored studies information	Added procedures for AE review and dissemination of AEs for UCSF sponsored multi-center trials.
Procedures 4.2	Added additional clarification regarding sponsor's responsibility for reviewing and assessing reporting requirements for external AEs.	Refer to background section.
References	Updated links	URL changes

DocuSign

Certificate Of Completion

Envelope Id: 29CF16EC5B4140FBA90CAF7B91786168
Status: Completed
Subject: Complete with DocuSign: External_Safety_Policy_revision 1_2024MAY21.pdf
Source Envelope:
Document Pages: 7
Signatures: 4
Certificate Pages: 2
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC-08:00) Pacific Time (US & Canada)

Envelope Originator:
Andrea Skafel
1855 Folsom St
Suite 601
San Francisco, CA 94103
andrea.skafel@ucsf.edu
IP Address: 128.218.42.98

Record Tracking

Status: Original
5/21/2024 9:25:18 AM
Holder: Andrea Skafel
andrea.skafel@ucsf.edu
Location: DocuSign

Signer Events	Signature	Timestamp
Eric Small Eric.Small@ucsf.edu Professor University of California, San Francisco Security Level: Email, Account Authentication (Optional)	DocuSigned by: Eric Small 7FCB32D327E3438... Signature Adoption: Pre-selected Style Using IP Address: 128.218.42.214	Sent: 5/21/2024 9:27:37 AM Viewed: 5/22/2024 5:16:48 PM Signed: 5/22/2024 5:17:02 PM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Katherine Shumate kate.shumate@ucsf.edu Chief of Staff, Director of Administration University of California, San Francisco Security Level: Email, Account Authentication (Optional)	DocuSigned by: Kate Shumate 80D38159E89D41B... Signature Adoption: Uploaded Signature Image Using IP Address: 128.218.42.151	Sent: 5/22/2024 5:17:03 PM Viewed: 5/22/2024 5:31:58 PM Signed: 5/22/2024 5:32:13 PM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Rahul Aggarwal rahul.aggarwal@ucsf.edu Rahul Aggarwal, MD Professor of Medicine University of California, San Francisco Security Level: Email, Account Authentication (Optional)	DocuSigned by: Rahul Aggarwal E870F084A5CA4CC... Signature Adoption: Pre-selected Style Using IP Address: 128.218.42.197	Sent: 5/22/2024 5:32:14 PM Viewed: 5/22/2024 8:31:28 PM Signed: 5/22/2024 8:31:42 PM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Katie Kelley katie.kelley@ucsf.edu MD University of California, San Francisco Security Level: Email, Account Authentication (Optional)	DocuSigned by: katie kelley 7F538467F93949B... Signature Adoption: Pre-selected Style Using IP Address: 128.218.42.22	Sent: 5/22/2024 8:31:44 PM Viewed: 5/23/2024 10:00:56 AM Signed: 5/23/2024 10:03:24 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	5/21/2024 9:27:37 AM
Certified Delivered	Security Checked	5/23/2024 10:00:56 AM
Signing Complete	Security Checked	5/23/2024 10:03:24 AM
Completed	Security Checked	5/23/2024 10:03:24 AM

Payment Events	Status	Timestamps