

**University of California, San Francisco
Helen Diller Family Comprehensive Cancer Center
Investigational Trials Resource
Policy and Procedure**

Safety Reporting Policy

ITR Procedure for Processing IND Safety Reports and Other Safety Reporting Information

Purpose

The Investigational Trials Resource (ITR) of the Helen Diller Family Comprehensive Cancer Center (HDFCCC) is a shared resource and supports cancer clinical trials for all UCSF investigators belonging to programs which have joined the ITR. The ITR has a Clinical Research Support Office (CRSO) which is responsible for all regulatory management of clinical studies: protocol development for investigator-sponsored trials (ISTs); submissions to the FDA for sponsor-investigator investigational new drug applications (INDs); submissions to the UCSF Institutional Review Board, or IRB (the Committee on Human Research) for both pharmaceutical and investigator-sponsored trials; and post approval safety reporting to the CHR and safety reporting record maintenance. The IND Safety Coordinators are responsible for processing and maintaining all safety reporting information sent to the Principal Investigators conducting ISTs or clinical trials for pharmaceutical companies, including IND safety reports. The IND Safety Coordinators work with the CRSO Regulatory Support team to insure timely reporting and that informed consent risk changes are submitted to the UCSF Committee on Human Research (CHR).

The purpose of this policy is to document the responsibilities of the IND Safety Coordinators and the PI/study team where safety reporting is involved.

Background

When ITR Responsibilities Commence

The ITR may assume responsibility for safety reporting at two possible time points. For programs which joined the ITR during or prior to December 2010, the date that the ITR assumes responsibility for safety reporting is determined by the ITR. For programs joining the ITR during or after December 2010, the date that the ITR assumes responsibility for safety reporting will be the date the program officially joins the ITR.

Safety Reporting Formats

Pharmaceutical companies and manufacturers alert all investigators of potential side effects of investigational drugs by issuing safety information. This safety information comes in several formats: initial and revised Investigator Brochures (IBs); safety notifications ('Dear

Doctor' letters); written reports known as Investigational New Drug Safety Reports (IND safety reports); Data Safety Monitoring (DSMC/DSMB) reports; and holds on study activity.

Pharmaceutical companies, cooperative groups and the Food and Drug Administration (FDA) or other regulatory bodies may also conduct audits, and issue audit reports at the end of the audit. The UCSF DSMC may issue monitoring reports.

FDA Safety Reporting Requirements

The phrase IND safety report originates in the FDA Code of Federal Regulations 21CFR 312.32. An IND safety report is a report issued to the Principal Investigator (PI) by a sponsor, sponsor-investigator, or drug manufacturer describing any adverse experience associated with the use of the drug that is both serious and unexpected, or any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity. Regulations require a sponsor or sponsor-investigator (i.e., not the participating PI), to submit IND safety reports to the FDA and to participating investigators. However, if the PI holds the IND, then the PI is the sponsor-investigator and is considered the sponsor of the study (IST trials only); sponsor-investigators of cross-referenced INDs will receive letters from the manufacturer who holds the master IND for the agent(s), but the sponsor-investigator is also responsible for reporting safety events occurring at the sponsor-investigator's site, and must follow the same steps in reviewing and reporting as identified in 21CFR 312.32.

IRB Reporting Requirements

Sponsors send IND Safety Reports to investigators, often with instructions to send each report to the IRB of record. IRBs are required by FDA and DHHS human subject protection regulations to review "unanticipated problems" involving risk to participants or others. CHR, the UCSF IRB, has its own reporting criteria for IND safety reports, and defines as an external or off-site adverse event (AE) any IND safety report from a sponsor or sponsor-investigator about safety information for a participant who is not a UCSF or affiliate site participant. IRB reporting of external IND safety reports is required when the UCSF PI determines that the event described:

- Changes the study risks or benefits, *OR*
- Necessitates modification to the CHR-approved consent document(s) and/or the CHR-approved application or protocol.

The CHR also requires reporting for other safety information:

- Audit or Monitoring Report with significant findings
- Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) reports
- Other safety information or publication that suggests a change to the risk or benefit of the research
- Hold on study activities due to an unexpected risk
- Updated Investigator Brochures.

All UCSF HRPP safety reporting guidelines are found at the following web link:
http://www.research.ucsf.edu/chr/Guide/Adverse_Events_Guidelines.asp#external

Sponsor Reporting Requirements (AE Summary Logs)

The Protocol Project Manager (PPM) is asked to identify all sponsors/manufacturers (and applicable studies) who will require their IND safety reports not meeting CHR's 10-day reporting requirements to be submitted in summary form to CHR at the time of annual continuing review or study close-out; for each such study, the IND Safety Coordinator will maintain an AE summary log. At the time the ITR assumes responsibility for safety reporting, the IND Safety Coordinator will obtain existing AE summary logs from the PPM (for existing studies). Once the ITR has assumed responsibility for safety reporting, the IND Safety Coordinator will create new AE summary logs 1) when the ITR takes on regulatory responsibility for a new protocol for which no AE summary log previously exists, or 2) when the AE summary log has been submitted to CHR as part of an annual continuing review application.

When there is an industry sponsor who requires IRB review of IND safety reports regardless of the UCSF CHR's guidelines for non-reporting, the IND Safety Coordinator adds all non-reportable events to the CHR's AE summary log. The IND Safety Coordinator provides the AE summary logs to the Regulatory Affairs Specialists to include in the submission of the next annual continuing review or close-out report. This form is found at the following website: http://www.research.ucsf.edu/chr/Forms/AE_Summary_Log.doc

If the study team discovers any internal (UCSF patient) deaths unrelated to the research as determined by the UCSF PI, they should send the applicable information (date of death, subject ID and brief description of the death) to the IND Safety Coordinators (interventional studies only). The IND Safety Coordinators will enter data on internal (UCSF patient) deaths unrelated to the research (as determined by the UCSF PI) onto the AE summary log for the next CHR annual continuing review or close-out report.

If a study is terminated prior to any UCSF subjects enrolling, then submission of the AE summary log should not be required by the sponsor.

IST Protocol Development

IST sponsor-investigators should always follow the safety reporting requirements of the CHR and the FDA, plus they should discuss with the manufacturer of the study agent(s) any manufacturer-specific reporting requirements. All reporting requirements should be spelled out clearly in the IST protocol before study start-up.

Required Duration for Safety Reporting

The responsibility for safety information reporting begins at the time of initial submission to the CHR for initial approval, all the way up until the moment the protocol is retired/terminated at the CHR. Only the current IB is submitted to CHR with the initial

submission. All safety information received after the IB has been sent into CHR with the initial submission should be tracked and processed. When a study is closed to enrollment at UCSF with all subjects off study, the PI is still obligated to review IND safety reports. Once the close out visit is complete, and the study is retired at the UCSF CHR, only then is the PI under no further obligation to review IND safety reports for that study. Any exceptions to these general reporting requirements need to be clarified with the individual sponsor of each study and documented appropriately.

Procedures

Safety reporting timelines are by definition very tight. All study team personnel, including the PI and PPM, should be prepared to closely follow all instructions from the IND Safety Coordinators and be sure to respond to all IND Safety Coordinator queries in a timely fashion.

Study Management

The IND Safety Coordinators will keep a record of all applicable studies, with start and stop dates for applicable safety reporting. The IND Safety Coordinator will also track whether the manufacturer will require CHR reporting of events that do not meet CHR's reporting criteria. The IND Safety Coordinators will provide a record of IND safety reports processed to the post-award team for billing purposes.

The PPM will keep the IND Safety Coordinators apprised of all study closures in real time, as the IND Safety Coordinators must be aware at all times of which studies require reporting and which do not. The PPM is responsible for working out timing issues should the IND Safety Coordinators have difficulty obtaining timely PI assessments.

Upon first receipt of any safety reporting information (including Investigator Brochures), the IND Safety Coordinators will process the item for all applicable studies, as outlined below. Items will only be reported under the protocol for which they were received. (E.g., if one protocol generates a safety event relating to an agent used by five protocols, only the protocol for which the report was received will report on the event.)

Investigator Brochures

At study start-up a Regulatory Affairs Specialist submits the current IB with the initial CHR submission; the IND Safety Coordinators file a copy of this IB in the ITR binder along with proof of CHR submission. The PPM is responsible for explaining this ITR policy to the sponsor; any exceptions to this policy must be discussed with the Regulatory Affairs and Protocol Development teams. The PPM should ensure that all revised IBs received thereafter are passed to the IND Safety Coordinators immediately, and without performing assessment of the event/document beforehand. The PPM should also ensure that each revised IB has a summary of changes with it, and if it does not, the PPM will obtain a summary of changes from the sponsor/manufacturer. The PPM can request that sponsors communicate directly with the IND Safety Coordinators.

The IND Safety Coordinators will report the revised IBs and assess if the PI has multiple studies with the same study drug and will process it accordingly. Beginning February 2012, the IND Safety Coordinators will place an Investigator Brochure/Dear Dr. Letter/Other Safety

Information Label (Safety Information Label) on the front page of each IB for PI assessment. The IND Safety Coordinators will deliver the IB with the Safety Information Label to the PI for completion.

It is the responsibility of the PI to:

- Review the IB
- Determine whether the revised IB would require a revision to the protocol (ISTs only) and consent form (i.e., cause a change in study risk)
- Complete the Safety Information Label
- Beginning February 2012, the PI will also assess the degree of risk and indicate when verbal notification of the new risk is required. Please review the Verbal Notification of New Risk Policy dated 17Jan2012.
- Answer any questions posed by the IND Safety Coordinators
- Sign and date the Safety Information Label.

Please note: The PI should not assess any IB without a Safety Information Label attached to it.

Following receipt of the PI's completed Safety Information Label, the IND Safety Coordinators will:

- Submit the IB and the completed CHR reporting form to the CHR
- If the PI has indicated one or more new risks should be added to CHR-approved documents, the IND Safety Coordinators will send via email a scan of the front page of the document with the completed Safety Information label to the PI, the PPM, the Lead Clinical Research Coordinator, the Protocol Development and Regulatory Support teams, and the Regulatory Affairs Supervisor.
- File the IB with the CHR submission documentation in the ITR binder.

IND Safety Reports

At study start-up a Regulatory Affairs Specialist submits the current IB with the initial CHR submission; no IND safety reports are submitted to the CHR at that time. All safety reports received after the initial CHR submission are considered reportable to CHR. The PPM should ensure that all such IND safety reports received thereafter are passed to the IND Safety Coordinators immediately, and without performing assessment of the event/document beforehand. The PPM can request that sponsors communicate directly with the IND Safety Coordinators.

The IND Safety Coordinators will assess if the PI has multiple studies with the same study drug and group the reports accordingly. The IND Safety Coordinators will review the IND safety report, log it in on the ITR's tracking system, highlight pertinent information, and affix an IND Safety Label (fluorescent colored) to the front of each report. The IND Safety Coordinator will forward the IND safety report with the IND Safety Label to the PI for completion and signature.

It is the responsibility of the PI to:

- Review the External IND Reports
- Determine whether the External IND Report/s would require a revision to the protocol (ISTs only) and consent form (i.e., cause a change in study risk)
- Complete the IND Safety Label
- Beginning February 2012, the PI will also assess the degree of risk and indicate when verbal notification of the new risk is required. Please review the Verbal Notification of New Risk Policy dated 17Jan2012.
- Answer any questions posed by the IND Safety Coordinators
- Sign and date the IND Safety Label

Guidance for the PI on reporting requirements is on CHR's website.

http://www.research.ucsf.edu/chr/Guide/Adverse_Events_Guidelines.asp

While it is the PI's responsibility to ensure that the consent form is updated as soon as any information is received about increased risks to subjects, the IND Safety Coordinators will manage this responsibility (i.e., when programs join the ITR, the PIs delegate this authority to the IND Safety Coordinators). This action should not wait until the next study continuation review for any information that increases risks to subjects; per CHR policy, a 10-day external (off-site) AE reporting form is submitted, along with the modifications to the protocol or consent form in a modification application. If modifications to the protocol or consent form are not possible within the 10-day reporting timeframe, the CHR submission should explain that the modifications will follow. Per HDFCCC policy, verbal notification may be required; this will be documented by the PI at the time of assessment – refer to

http://cancer.ucsf.edu/docs//itr_forms/Risk_Notification_Policy.pdf for more detail.

Following receipt of the PI's completed IND Safety Label, the IND Safety Coordinators will:

- Determine whether the IND safety report requires immediate submission to the CHR
 - If immediate CHR submission is required, the IND safety report with the completed IND Safety Label will be submitted to the CHR via iMedRIS.
- If the PI has indicated one or more new risks should be added to CHR-approved documents, the IND Safety Coordinators will send via email a scan of the front page of the document with the completed IND Safety Label to the PI, the PPM, the Lead Clinical Research Coordinator, the Protocol Development and Regulatory Support teams, and the Regulatory Affairs Supervisor.
- File the External IND Report with the CHR submission documentation in the study specific binder.
- If immediate CHR submission is not required (no change in risk), the External IND will be recorded on the AE summary log* if CHR reporting is required by the sponsor/manufacture

- File one copy of the IND safety report in the applicable ITR binder, along with one copy of each study-specific fluorescent colored label with PI signature, plus one copy of each sponsor/major manufacturer cover letter that came with the report (as proof of receipt).

* AE summary logs are allowed by CHR to capture events that do not meet CHR's 10-day reporting requirements in cases where the sponsors/manufacturers require that such IND safety reports be reported to the local IRB. See AE Summary Log section for more detail.

The PI and his/her designees on the study team are fully responsible for reporting internal (UCSF patient) adverse events to the CHR. The IND Safety Coordinators play no role in this.

As of February 2012, the IND Safety Coordinators will use the following fluorescent colored 2 x 4 inch labels:

Safety Information Label

Investigator Brochure/Dear Dr. Letter/other Safety Reports CC# _____

- 1) Cause a change in study risk? yes no
 Waiting on sponsor ICF template _____
 Risk/s to add to ICF? _____
- 2) When will patients be informed of this new risk? (This will be documented in the study chart)
 High: within 10 business days
 Intermediate: within 30 business days
 Low: within 60 business days
 Late Risk: patient's off treatment or in f/u – at PI's discretion
- 3) Does this change the Risk/Benefit ratio? yes no

P.I. Signature & Date: _____

This Safety Information will be reported to the CHR via the 10-day Reporting Form.

IND Safety Label

External IND Reports CC# _____

- 1) Cause a change in study risk? yes no
- 2) Relationship to experimental agent? (Circle one) Is event? (Circle One)
 Possible, Probable, Related, Unrelated Serious, Unexpected, or Both
- 3) When will patients be informed of this new risk? (This will be documented in the study chart)
 High: within 10 business days
 Intermediate: within 30 business days
 Low: within 60 business days
 Late Risk: patient's off treatment or in f/u – at PI's discretion
- 4) Does this change the Risk/Benefit ratio? yes no

P.I. Signature & Date: _____

*If changes are required this report will be reported to the CHR via the 10-day Off-Site AE Report
 If no changes are required this report will be reported on the AE Summary Log at time of renewal.*

Sometimes the information in the IND Safety Report has already triggered a modification by the sponsor adding the new risk to the protocol, consent and/or a new version of the Investigator Brochure. For an IST, the PI will make the determination to update the protocol documents. Only the manufacturer will create a new version of the Investigator's Brochure.

Other Safety Notifications ('Dear Doctor' Letters)

At study start-up a Regulatory Affairs Specialist submits the current IB with the initial CHR submission. All safety notifications ('Dear Doctor' letters) which are not IND safety reports and are received after the initial CHR submission are considered reportable to CHR. The PPM should ensure that all such safety notifications received thereafter are passed to the IND Safety Coordinators immediately, and without performing assessment of the event/document beforehand.

The IND Safety Coordinators will assess if the PI has multiple studies with the same study drug and group the safety information accordingly. Beginning February 2012, the IND Safety Coordinators will place an Investigator Brochure/Dear Dr Letter/Other Safety Information Label (Safety Information Label) on the front page of each notification for PI assessment. The IND Safety Coordinators will deliver the IB with the Safety Information Label to the PI for completion.

It is the responsibility of the PI to:

- Review the Safety Information
- Determine whether the Safety Information would require a revision to the protocol (ISTs only) and consent form (i.e., cause a change in study risk)
- Complete the Safety Information Label
- Beginning February 2012, the PI will also assess the degree of risk and indicate when verbal notification of the new risk is required. Please review the Verbal Notification of New Risk Policy dated 17Jan2012.
- Answer any questions posed by the IND Safety Coordinators
- Sign and date the Safety Information Label.

Please note: Starting February 2012, the PI should not assess any Safety Information without a Safety Information Label attached to it.

Following receipt of the PI's completed Safety Information Label, the IND Safety Coordinators will:

- Submit the Safety Information and the completed CHR reporting form to the CHR
- If the PI has indicated one or more new risks should be added to CHR-approved documents, the IND Safety Coordinators will send via email a scan of the front page of the document with the completed Safety Information label to the PI, the PPM, the Lead Clinical Research Coordinator, the Protocol Development and Regulatory Support teams, and the Regulatory Affairs Supervisor.
- File the Safety Information with the CHR submission documentation in the ITR binder.

ITR Binders

The ITR will maintain binders by agent. At the time the ITR assumes responsibility for safety reporting, the IND Safety Coordinators will create a binder for each agent in use by the program at that time (unless the ITR already has an existing binder for that agent). Once the ITR has assumed responsibility for safety reporting, the IND Safety Coordinators will create a new binder only when the ITR takes on regulatory responsibility for a protocol using a new agent for which no binder previously exists. Each binder will include:

- a protocol identification list*
- one copy of all IBs for that agent (with summary of changes)
- one copy of each study-specific cover letter sent with each version of the IB
- one copy of proof of CHR submission for each IB for each applicable study
- one copy of all IND safety reports for that agent
- one copy of each study-specific cover letter sent with each IND safety report
- one copy of proof of CHR submission for each IND safety report for each applicable study
- annual AE log
- one copy of all other safety notifications for that agent
- one copy of each study-specific cover letter sent with each safety notification
- one copy of proof of CHR submission for each safety notification for each applicable study.

* The protocol identification list matches the sponsor protocol identification with the Cancer Center protocol identification (i.e., protocol number matched with CC number).

The items retained in the binder, as reference above, will only include documents received for a study on or after the date that the ITR assumes responsibility for safety reporting for that study. IND safety reports and IB versions pre-dating that transfer of responsibility, for example, will be retained by the study team, not by ITR.

The IND Safety Coordinators will make the agent binder available to all monitors and auditors. It is the responsibility of the PPM to notify the IND Safety Coordinator of the anticipated date for the next monitoring or audit visit as soon as the PPM becomes aware of it.

Alternate Procedures

Due to their Parnassus campus location, an alternate procedure is in place for the Hematopoietic Malignancy (Heme) program as well as for all Heme trials conducted by the Early Phase Unit (Early Phase/Heme). The IND Safety Coordinators works with the Heme or Early Phase/Heme staff to obtain signatures. The IND Safety Coordinator will deliver and pick up items requiring PI signature whenever feasible, and the Heme or Early Phase/Heme staff will do likewise whenever they travel to the Mount Zion campus.


Policy Approval

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



Eric Small, MD
Director, Investigational Trials Resource

1/18/12
Date



Nicole Lama, MS
Director, Clinical Research Support Office,
Investigational Trials Resource

1/23/12
Date