UCLA Research Administration
Human Research Protection Program

Guidance and Procedure: Post-Approval Reporting (PAR)
(revised February 12, 2020)

General Overview

Both the Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) require institutions to have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (1) any unanticipated problems involving risks to subjects or others (this could include family members of the participant or research personnel) or any serious or continuing noncompliance with this guidance or the requirements or determinations of the IRB; and (2) any suspension or termination of IRB approval (45 CFR 46 103(b)(5) and 21 CFR 56.108(b)).

The purpose of the PAR application is to provide the Principal Investigator with a mechanism to submit information relevant to the rights/welfare of research participants in a timely fashion to the IRB.

The expertise of the UCLA Principal Investigator is relied upon to make an initial assessment and determine the relationship of the event/incident/new information (hereafter referred to as "event") to the research activity and to determine if the event warrants a change to the protocol to minimize risks to human subjects and/or a change to the informed consent document to better inform subjects of the potential risks and the procedures needed to minimize such risks.

The IRB will review the Principal Investigator's assessment and either accept this assessment or ask for changes.

This guidance document:

- Provides definitions and examples of the types of information that should be submitted through the Post Approval Report (PAR) mechanism.
- Defines the requirements and time frame for Principal Investigators to prepare and submit PARs to the IRB and respond to requests for more information from the IRB.
- Outlines the IRB review processes and procedures for assessing these reports in order to make ongoing assessments of the risks and benefits of the research, the adequacy of the consent document(s), the adequacy of the safeguards to prevent future harm to subjects, and if/how information related to these reports should be provided to participants.
- Describes the IRB responsibilities to report certain events to federal agencies with oversight of human research.
- Provides information on reporting of events when the UCLA IRB is relying on another IRB for oversight of human subject research.

*Note: **This guidance document provides information on the requirements for reporting relevant new information during the conduct of the research to the UCLA IRBs.** The requirements for reporting adverse events and deviations to the DSMB, Sponsor, and/or the FDA (as applicable) may be different. Please consult with the Data Safety Monitoring Plan, Sponsor, and/or FDA regulations (as applicable) for reporting requirements to those entities. In addition, University policy (such as UCLA Policy 420: Breaches of Computerized Personal Information) may require reporting of certain events/incidents to additional UCLA departments.*

Definitions

Adverse Event: Any untoward or unfavorable medical occurrence in a human subject (physical or psychological harm) temporally associated with the subject's participation in the research (whether or not related to participation in the research).

Deviation: Any intended or unintended variance or exception from the IRB approved protocol.

Incident: An undesirable and unintended, although not necessarily unexpected, event or outcome involving any aspect of the research study.

PAR: An acronym for Post-Approval Report.

External Adverse Event or Outcome: An event or outcome that is experienced by subjects enrolled at study site(s) (e.g. multicenter clinical trial) under the jurisdiction of other IRBs.

Internal Adverse Event or Outcome: An event or outcome that is experienced by subjects enrolled at study site(s) under the jurisdiction of the UCLA IRB (as reviewing IRB).

Risk of Harm: Any situation/circumstance in which an individual (participant or other) is exposed to potential harm related to research. The potential harm may be physical, psychological, legal, economic, or social in nature.

Related (possibly related): In the opinion of the Principal investigator there is a reasonable possibility that the event or outcome may have been caused by the procedures

involved in the research.

Unexpected: The nature, specificity, severity or frequency of the event or outcome is not accurately reflected in the protocol-related documents, such as the IRB approved research protocol, informed consent document, and investigator's brochure; and/or the characteristics of the subject population being studied.

Unexpected Adverse Event: Any adverse event where the nature, specificity or frequency of the event is *not* consistent with either:

1) the known or foreseeable risk associated with the procedures involved in the research that are described in the protocol-related documents (IRB approved protocol, informed consent document, investigator's brochure), and relevant sources of information (product labeling/package inserts); or
2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

Serious Adverse Event: Any adverse event that may result in the following: death; is life threatening (places subject at immediate risk of death from the event as it occurred); a required or prolonged hospitalization, persistent or significant disability/incapacity; congenital anomaly/birth defect; or may require medical or surgical intervention to prevent one of the other outcomes previously listed in this definition. The occurrence of a serious adverse event suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

Deviation to eliminate apparent immediate hazards to the subject: A deviation from the approved protocol necessary to prevent harm to the subject. These deviations are not considered violations of the regulatory requirement to obtain prior IRB approval before implementing changes to the protocol. These necessary changes are in alignment with the Belmont report's concept of "beneficence". These occur infrequently and require after-the-fact reporting to the IRB.

Non-compliance: Failure to comply with applicable laws, regulations, or institutional policies pertaining to the protection of human subjects, and/or with the requirements or determinations of an IRB.

Continuing Noncompliance: A pattern of noncompliance that indicates an inability or unwillingness to comply with applicable laws, regulations, or institutional policies pertaining to the protection of human subjects and/or with the requirements or determinations of an IRB.

Serious Noncompliance: Failure to comply with applicable laws, regulations, or institutional policies pertaining to the protection of human subjects and/or with the requirements or determinations of an IRB that has a significant adverse impact either on the rights or welfare of participants or on the integrity of the data.

Unanticipated Problem: An incident, experience, or outcome that meets all of the following criteria:

(1) Is unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

(2) Is 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
(3) 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.

Policy

- The Principal Investigator must submit to the IRB all post approval reports (PARs) that meet the submission criteria within the proper timeframe, as described in the Principal Investigator Reporting Responsibilities.

- The IRB must review and make appropriate determinations regarding risks, potential benefits, the adequacy of the consent documents, ensure the provision of updated information to subjects, reevaluate whether adequate safeguards are in place to protect human subjects, including subject privacy and the confidentiality of data.

- The Principal Investigator must make any changes to the protocol, recruitment materials, and/or consent documents as required by the IRB.

- The IRB will report the events determined to represent an unanticipated problem involving risks to subjects or others, serious non-compliance, continuing non-compliance, suspensions, and terminations to regulatory agencies and the appropriate organizational officials. For more information on IRB reporting requirements, see OHRPP Guidance and Procedure: IRB Reporting Procedures for Unanticipated Problems, Noncompliance, Suspension, or Termination.

Principal Investigator Reporting Responsibilities

The Principal Investigator is responsible for submitting to the IRB ongoing reports of events that are unanticipated problems that may adversely affect the rights and/or welfare of participants or the conduct of the research. The expertise of the Principal investigator is relied upon to make an initial assessment and determine the relationship of the event to the research activity. The Principal Investigator is also tasked with determining whether the event warrants a change to the protocol to minimize risks to human subjects, and/or a change to the informed consent document to better inform subjects of the potential risks and the procedures needed to minimize such risks.

The Principal Investigator should submit as complete information about the event as is available within the indicated reporting timeframes listed below.

The PAR submission should include a description of the event; whether or not this event may impact current, past or future participants; any proposed changes to the study plan (including changes to the consent), if any, that may be necessary in response to the event.

If relevant information is unavailable at the time of submission, that information may be added to the current PAR submission later in a request for more information or submitted as a follow-up PAR application.

It is the Principal Investigator's responsibility to maintain regular communication with the sponsor or coordinating center for multi-site research in order to obtain DSMB reports and other safety-related information about the research in a timely fashion.

It is the Principal Investigator's responsibility to inform the Sponsor (if applicable) if the IRB suspends or terminated the research.

If the IRB requests additional information on a submitted PAR, the correspondence will indicate when a response is due.

The types of events and information that should be reported to the IRB include those described below. In addition, the IRB may request the Principal Investigator submit information via PAR application under circumstances not described below.

The PI should ***NOT*** include any direct identifiers (name, MRN, etc…) in PAR submissions.

Adverse Events (Internal and External)

Principal Investigators must report to the IRB all adverse events that meet ***all three of the following criteria***:

- Unexpected;
- Related or possibly related to research participation; AND
- Places participants or others at greater risks of harm than was previously known or recognized (not described in or of greater severity or frequency than described in the IRB-approved protocol and/or consent form)

In reviewing (internal or external) adverse events, the IRB ***may request additional follow-up information***. These can include autopsy results or terminal medical reports for an unexpected study-related death.

For all adverse events (internal or external) that meet the above criteria, the IRB ***may require additional action*** in response to the event in order to ensure that the research continues to meet the criteria for approval under 45 CFR 46.111 and/or 21 CFR 56.111. This may include:

- revision of the consent form to include risk(s) identified as a result of this event
- re-consent of enrolled participants continuing study treatment
- notification to previously enrolled participants and/or participants in long-term follow-up
- protocol changes to address and minimize newly identified risk(s)
- suspension of enrollment or all study procedures
- termination of the research

Internal Adverse Events

Those internal AEs that the IRB agrees meet the above criteria will receive the determination of *Unanticipated Problems involving risks to subjects or others* under 45 CFR 46.108(a)(4)(i), 21 CFR 56.108(b)(1), 21 CFR 312.53(c)(1)(vii) and/or 21 CFR 312.66.

- The IRB will report that determination to the appropriate federal department(s) and UCLA institutional officials as required. For more information on IRB reporting requirements, see OHRPP Guidance and Procedure: IRB Reporting Procedures for Unanticipated Problems, Noncompliance, Suspension, or Termination.

Initial and follow-up reports of internal AEs that meeting the reporting criteria should be submitted to provide the IRB with complete information on the internal adverse event.

External Adverse Events

Those external AEs that the IRB agrees meet the above criteria will **not** receive the determination of *Unanticipated Problem Involving Risks to Subjects or others*. It is the responsibility of the reviewing IRB for the site where the event took place to make that determination.

Initial reports of external AEs should only be submitted *after the Principal Investigator can definitively indicate* that all three criteria are met.

> ***Tip:*** For ***external AEs***, if the answer to the question of ***Does this problem place or suggest that other study participants or other people are at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized (i.e. a "serious adverse event")?*** is "**not sure**" ***wait*** to submit until the answer is "**yes**". At that time, all available materials (such as initial and follow-up reports from the sponsor) related to this event should be submitted in a single PAR application.

Follow-up reports of external AEs should not be submitted unless they provide new information to indicate that ***the event was of greater severity than originally reported*** to the IRB.

Deadlines for submission to the IRB *(for both internal and external adverse events)**:***

- **Within 3 business days of learning of the event:** *Internal or External Adverse events meeting the above criteria resulting in **death**, **suspension**, **suspension** or **termination of the research***

- **Within 10 business days of learning of the event:** All other *reportable adverse events meeting the above criteria*

- **No PAR submission (maintain in study files)**:
  - Internal or external adverse events that ***do not meet*** the above criteria
  - External AEs where the investigator ***does not yet know*** whether or not the event placed the participants or others at increased risk
  - Follow-up reports of external AEs that do not provide information on increased severity of the event since the initial report to the IRB

- **No PAR submission (summarize at continuing review)**:
  - Deaths that are related and expected

Data Safety Monitoring Board (DSMB) reports

Note: These reports are also known as Data Safety Monitoring Committee (DSMC) or Data Monitoring Committee (DMC), and Independent Data Monitoring Committee (IDMC) reports.

Relevant DSMB reports should be provided to the IRB in a timely fashion after receipt in order to provide the IRB with up-to-date information necessary for the IRB's ongoing risk/benefit assessment of the research.

Deadlines for submission to the IRB:

- **Within 3 business days of receipt of report:** DSMB reports ***recommending suspension or termination*** of the research

- **Within 10 business days of receipt of report:** DSMB reports that indicate ***other concerns/issues*** with the research.

- **No PAR submission (maintain in study files):**
  - DSMB reports that indicate that *the study may continue as planned* (with no changes requested or concerns identified).
  - DSMB consultations where the DSMB agrees with the assessment of the PI that a *specific adverse event does not meet the threshold for reporting to the IRB*.
  - DSMB consultations where the DSMB agrees with escalation to next dose level in accordance with the IRB-approved protocol's dose-escalation plan
  - Acknowledgement letters from the DSMB of materials reported to them by the PI, per the DSMB's guidance.

Other Reports Related to Safety or Compliance

Only the following types of other reports should be submitted to the IRB:

- Those that have an impact on the ongoing risk/benefit assessment of the research by the IRB;
- Those that could impact the safety or rights of former, current, or future participants; or
- Those that are required by the regulations to be reviewed by the IRB

Types of reports that fall into this category include:

1) FDA Clinical Holds
2) Suspension or termination of the research by the Principal Investigator for any reason
3) Suspension or termination of the research by the Sponsor for any reason
4) Newly released "Boxed warning" (a.k.a. "Black box warning") in the package insert of an approved drug used in clinical research.
5) FDA Device Recall for devices used in the research
6) FDA Drug Recall for drugs used in the research
7) FDA form 483 issued to the investigator after an inspection of the research
8) Annual progress reports for studies conducted under an IDE per 21 CFR 812.150(b)(5)
9) Semi-annual progress reports for studies conducted under a treatment IDE per 21 CFR 812.36(f)
10) Medical device reports for HDE approved devices per 21 CFR 814.126(a)
11) Any publication in the literature, interim results, or other finding ***that indicates an unexpected change to the risks and/or benefits of the research***
12) Self-monitoring report requested by the IRB as part of post-approval monitoring

Deadlines for submission to the IRB:

- **Within 3 business days of learning of the event:** FDA clinical holds or suspension or suspension/termination of the research by the sponsor.

- **Within 10 business days of learning of the event:** All other reports that meet the above criteria

- **No PAR submission (provide as progress report in Continuing Review application):**
  - Notice of escalation to next dose level in accordance with the IRB-approved protocol's dose-escalation plan

- **No PAR submission (submit via Amendment application instead):**
  - Protocol clarification memos that are related to human subjects protection concerns (these may include revisions to study procedures, risks, inclusion/exclusion criteria, etc...)
  - Investigator's brochures and device brochures
  - Notification that the short form process had been used (include that notification in the Amendment to submit the translated consent form)

- **No PAR submission (maintain in study files):**
  - Protocol clarification memos that are not human subjects protection issues (these may include regulatory clarifications relevant only to sites not under the jurisdiction of the UCLA IRBs)
  - Administrative memos from the Sponsor *not* related to the safety of participants, suspensions, or termination of research (this could include change in personnel for the sponsor's contact staff or for the medical monitor).
  - Memos from the Sponsor/Medical Monitor agreeing with the investigator's assessment that an event did not meet the criteria for IRB reporting
  - Monitoring reports. If there is a *specific finding on a monitoring report that meets the threshold for submission via PAR*, that specific finding should be submitted to the IRB via PAR. In that PAR submission, please indicate that the issue was identified from a monitoring visit.
  - Correspondence from the FDA of completion of an inspection *without* a 483 finding.

Deviations from the approved protocol to eliminate apparent immediate hazards to participants

The Principal Investigator is expected to follow the IRB-approved protocol with the exception of deviations necessary to prevent ***immediate*** hazards to participants.

Example:

A protocol requires a study drug to be administered in a single IV infusion. During an outpatient study visit in which a participant begins the study IV infusion, the clinic receives a bomb threat mid-way through the infusion process. As a result of the bomb threat, the infusion must be interrupted to evacuate the participant.

Deadlines for submission of PAR to the IRB:

- **Within 3 business days of learning of the event:** All reports of deviations ***to prevent apparent immediate hazards to participants***

- **No PAR submission (submit via Amendment application in advance of the planned change to study procedures instead):**
  - Protocol modifications related to an apparent hazard that is ***not*** immediate.

Other Protocol Deviations/Incidents

The OHRPP acknowledges that deviations from the approved protocol occur in the vast majority of research studies.

Investigators are required to keep a log of all deviations/Incidents.

Only the subset of those deviations that the PI determined have affected the rights and/or welfare of participants or others must be submitted to the IRB for review. However, the entire log may be reviewed by OHRPP Quality Improvement Unit (QIU) and the log should be submitted at continuing review for those studies that are subject to continuing review. For more information on the authority of the OHRPP QIU to conduct post-approval monitoring, see UCLA Policy 991: Protection of Human Subjects in Research

The following information/assessments should be recorded in the Investigator's deviation/incident log:

- Date of event
- Subject ID
- Date the investigator was made aware of the event
- A description of the event
- Is this an initial event or a follow-up/update on a previous event?
- Does the deviation meet the threshold for reporting to the IRB?
- Who (which member of the study team) made the assessment of whether or not the deviation met the threshold for IRB reporting via PAR?
- Date the assessment made (of whether it met the threshold for IRB reporting via PAR)
- Date of submission to the IRB (if applicable)
- PAR# (if applicable)

A subset of deviations/incidents must be submitted via PAR application for timely review:

Deviations/incidents for which the answer to ***any*** of the following questions is "yes" should be submitted to the IRB for review via PAR application:

1) **Did the deviation/incident cause the participant or someone else to be at risk of *potential* harm?**
    a. *Examples*:
        i. Did the participant receive/take an over- or under-dose of study drug (even if there were no apparent negative consequences)?
        ii. Was there a near-miss of a study procedure error that was caught by accident (and not prevented by functional checks in the system)?
        iii. Did a child in the household of a study participant ingest study medication?
        iv. Was the suicide SOP not used with a participant who indicated imminent threat of self-harm?
2) **Was the participant or someone else *actually* harmed by the deviation/incident?**
    a. *Examples*:
        i. Were research staff mugged at gunpoint for the gift cards carried for participant payments while doing field research?
        ii. Did an overdose of study drug cause adverse effects in the participant?
        iii. Did malfunctioning CT equipment expose participants to more radiation than was planned?
3) **Does the deviation/incident negatively affect the rights of participants or others?**

   a. *Examples*:
      i. Was there a breach of confidentiality of research records?
      ii. Was a participant not provided the information (i.e. results of Autism Diagnostic Observation Schedule conducted for research) or item (i.e. radiology images from a research scan) promised in the consent form for study procedures completed?
      iii. Was effective consent not obtained before study procedures were conducted?
      iv. Was effective HIPAA authorization or waiver not obtained before any medical records were reviewed/abstracted/shared with external collaborators for the research?
      v. Was the integrity of the data compromised?
      vi. Was protected information about a participant released in response to a subpoena when the study was covered by a certificate of confidentiality?
      vii. Were private records accessed/abstracted for non-participants?

4) **Does an individual deviation not meet the above criteria, but there are 4 or more of the same type of minor deviation in a study and those deviations, taken as a group, suggest a pattern of non-compliance on the part of the study team or ancillary staff?**
   a. *Examples*:
      i. Did half of participants enrolled to date decline to do a required study procedure suggesting there might be a problem with communicating study procedures during the consent conference at enrollment?
      ii. Was the consent conference conducted by someone who was not yet listed in the approved IRB application as an approved consenter on five separate occasions suggesting a breakdown in communication on the study team?

Root cause Analyses

For all PAR applications describing deviations that meet the criteria for reporting (either single occurrence or aggregate) the investigator should conduct a quality improvement review that includes a root cause analysis. This is necessary to determine if there are underlying systems problems that led to this deviation.

Corrective Action Preventive Action (CAPA) plan

Once a root cause has been identified, a CAPA plan must be developed by the investigator and included in materials submitted to the IRB. The CAPA should address two areas:

1) How will the deviation be resolved for the participant(s) who has already experienced the event? (does the participant require additional monitoring, should the participant be informed, does the participant need to be approached for re-consent or be asked to provide HIPAA authorization, etc.)

2) How will research procedures be modified to prevent similar deviations in the future? (does the study need an eligibility checklist, should the order process with pharmacy for study drug be updated, do study team members with greater clinical experience need to administer instruments, etc…)

- For deviations related to HIPAA authorizations or breach of confidentiality for UCLA Health-related research records, consult with UCLA Health Office of Compliance Services to develop the CAPA plan. The CAPA developed with UCLA Health Office of Compliance Services must be provided to the IRB for a final determination.

- For deviations related to breach of confidentiality of campus records (student academic records, employee records, student health records, etc…), consult with the UCLA Compliance Office to develop the CAPA plan. The CAPA developed with the UCLA Compliance Office must be provided to the IRB for a final determination.

Deadlines for submission to the IRB:

- **Within 3 business days of learning of the event**: All reports of deviations resulting in death

- **Within 10 business days of learning of the event**: All other reports of deviations (single or aggregate) that meet the threshold described above.

- **No PAR submission (submit in deviation log at continuing review):**
  - All other deviations that do not meet the criteria above for studies with continuing review

- **No PAR submission (maintain in study files):**
  - All other deviations that do not meet the criteria above for studies with no continuing review

Note: deviations that meet the threshold for reporting to the IRB should be reported in the timeframe indicated, regardless of the state of the CAPA plan development. If the root cause analysis has not yet been completed and/or the CAPA has not yet been developed, additional information may be submitted after initial PAR submission as a response to the IRB's request for more information.

Complaints about the research and allegations of non-compliance

In the course of research, the investigator and/or OHRPP may become aware of complaints from study participants or others regarding the conduct of the research.

For more information on this topic, please see Policy and Guidance: Complaints, Concerns, and Suggestions and Reports of Undue Influence Regarding the Conduct of Human Participants Research.

The investigator should submit PAR applications for any ***complaints*** they receive that meet the following criteria:

- Unexpected;
- Related or possibly related to research participation; AND
- Reflects one or more of the following circumstances:
  - Places participants or others at greater risks of harm than was previously known or recognized (not described in or of greater severity or frequency than described in the IRB-approved protocol and/or consent form);
  - Negatively impacts the rights of research subjects or others;
  - Results in a change to the risk/benefit profile of the research;
  - Cannot be resolved by the investigator.

OHRPP QUI staff will also create and submit PAR applications for reports of any complaints or allegations of non-compliance made directly to the OHRPP or forwarded to the OHRPP from the UC whistleblower hotline/website or the Office of Patient Experience (UCLA Health) or other entities.

Deadlines for submission to the IRB:

- **Within 3 business days of learning of the event**: All complaints meeting the criteria above that are related to a death

- **Within 10 days of learning of the complaint**: All other complaints meeting the criteria above.

- **No PAR submission (summarize at continuing review):**
  - Complaints that do not meet the criteria above (including those limited to delays in participant payment) for *studies with an expiration date for IRB approval*.

- **No PAR submission (maintain in study files):**
  - Complaints that do not meet the criteria above (including those limited to delays in participant payment) for studies that don't have a continuing review requirement.

Single Subject Exceptions

A special type of Post Approval Report is the Single Subject Exception (SSE). The purpose of SSE submitted by PAR application is to provide a fast mechanism to assess the risks and benefits of enrolling an individual into a ***treatment*** study when there is insufficient time to submit and review a modification to the inclusion/exclusion through the amendment process in advance of enrolling this participant.

When considering requesting a SSE, Principal Investigator/clinicians may also wish to consider alternative mechanisms for gaining access to investigational drugs and devices for their patients under *expanded access*. For more information on expanded access, please visit FDA expanded access information for Physicians.

Use of SSE should be limited to the following circumstances:

- ✓ The study in question is an intervention study/clinical trial
- ✓ The local investigator wishes to enroll someone who does not meet all of the inclusion criteria OR meets one or more of the exclusion criteria
- ✓ (if a multi-site study) The local investigator has obtained authorization from the Sponsor/IND holder/IDE holder/Coordinating Center for the exception to the inclusion/exclusion criteria for this specific potential participant.

The information submitted with a SSE should include:

- Documented approval from the study sponsor, medical monitor and other oversight entities as applicable
- A description of the inclusion/exclusion criteria for which an exception is requested
- An explanation why the exception is appropriate and necessary
- Assessment of whether exception increases risks or lowers anticipated benefits
- Explanation of whether an amendment will be submitted
- Assessment of whether the currently approved consent form is adequate for the enrollment of this specific potential participant
- Attachment of a modified informed consent form, if appropriate
- Plans for communicating the exception and the impact of the exception to the potential participant

- A declaration of the time sensitivity and why this request cannot be made via an Amendment application
- Assessment of the impact of the exception on data integrity

Deadlines for submission to the IRB:

- **In advance of enrollment**: any proposed exceptions to the inclusion/exclusion criteria

- **No PAR submission (submit via Amendment application instead):**
  - Any other type of *planned* change in the approved study plan for one or more study participants.

Single Events that fall into multiple categories

As the webIRB PAR application for deviations provides additional fields for providing the CAPA plan, if the event is an adverse event that resulted from a deviation, please submit as a deviation.

For other combinations, please contact the OHRPP Asst. Director, Quality Improvement Unit for guidance on how to proceed.

Grouping of multiple events in a single PAR

As events that meet the threshold for reporting should be reported within a short timeframe, reporting multiple events in a single PAR application is discouraged with the exception of the patterns of minor deviations that suggest potential continuing non-compliance.

For all other types of PARs, if there is an unusual circumstance in which it might make sense to report multiple events in a single PAR, consult with the OHRPP Asst. Director, Quality Improvement Unit before submission for guidance.

PARs on Studies where UCLA IRB is *RELYING* on another IRB

For more information on IRB reliance in general, please visit the OHRPP reliance webpage.

Events/incidents that occur at non-UCLA sites:

These events should generally *not be submitted by PAR* and instead maintained in the investigator's files.

If the event meets the threshold for IRB reporting, it should be submitted to the reviewing IRB. If the reviewing IRB requests changes to the protocol or consent, those changes should be managed first as an amendment to the reviewing IRB, then (after that review is complete) an amendment submitted through webIRB to notify UCLA of changes to the study plan.

However, if the reviewing IRB suspends or terminates the research in response to an event, that suspension or termination should be submitted as a PAR through webIRB to keep the OHRPP apprised of the status of the project.

Events/incidents that occur at UCLA sites:

In most instances, these events/incidents (at UCLA, they are called "PARs" but other IRBs have different names such as "reportable event", "reportable new information", etc…) need to be reviewed substantively ***first by the reviewing IRB***. Once the reviewing IRB has made a determination, ***the outcome of their review may then be submitted to the UCLA IRB*** (via a webIRB PAR application), depending on the determination made by the reviewing IRB.

- For some reliance agreements, the reviewing IRB will ***not*** take on the role of Privacy Board on UCLA's behalf. This means that a *breach of confidentiality or failure to obtain authorization event* will need to be reviewed and managed by the UCLA IRB in consultation with either UCLA Health compliance office or UCLA Campus compliance office (depending on the nature of the records involved in the breach). ***Even if these events don't meet the threshold for IRB review according to the guidelines of the reviewing IRB***, they will need to be submitted as a PAR through webIRB for local review of the breach of UCLA participant data.

However, this can vary from reliance agreement to reliance agreement. Please review the specific reliance agreement for any special review circumstances and/or whether or not the reviewing IRB will act as the privacy board for UCLA.

If the reliance agreement indicates that the reviewing IRB will act as the Privacy Board for the research on behalf of UCLA, please contact the OHRPP Asst. Director, Quality Improvement Unit for guidance as to whether or not this event must be submitted as a PAR through webIRB.

If the reliance agreement is silent on these issues or if the agreement specifies that UCLA will retain the responsibility of the Privacy Board for the research, **follow the process outlined below:**

1) Review the submission guidelines of the *reviewing* IRB. If the reviewing IRB's policies and guidance are not available online, contact the reviewing IRB and/or the coordinating center institution to help with navigation of their processes.
2) If the event meets the reviewing IRB's guidelines for submission to the IRB, submit that information to the reviewing IRB
3) Once the reviewing IRB has made their determination about the event, submit a PAR application, describing the event and uploading the determination of the reviewing IRB.
4) If the event does NOT meet the reviewing IRB's guidelines for submission to the IRB, but there is an issue of HIPAA non-compliance or a privacy breach, submit a PAR application to provide the CAPA plan developed in consultation with UCLA Health compliance or UCLA Campus Compliance.
5) For most PAR submissions for studies where the UCLA IRB is relying on another IRB, UCLA OHRPP staff will acknowledge the PAR to document receipt. If local privacy board review is needed (for HIPAA non-compliance or a breach of confidentiality), the PAR will be reviewed by the UCLA IRB with the most relevant scientific expertise (or Chair/ Chair's designee) acting as the privacy board for research.

Example #1:

A serious adverse event occurs on an industry-sponsored drug clinical trial and UCLA IRB is relying on Western IRB ("WIRB").

1) The UCLA investigator submits the information about this serious adverse event to WIRB for review, following WIRB's guidelines/processes.
2) WIRB issues their determination in written form.

3) If WIRB determines that this event constituted an "unanticipated problem involving risks to subjects or other", they will notify the FDA (and cc the UCLA investigator).
4) The UCLA investigator opens and submits a PAR application in webIRB. The written determination from WIRB is then uploaded into the PAR along with a description of the event and the actions the UCLA investigator (and the lead PI, if applicable) has taken in response to the event.
5) OHRPP staff reviews and acknowledges the PAR.
6) OHRPP forwards the FDA notification letter to relevant UCLA stakeholders. For more information on the reporting process, see Guidance and Procedure: IRB Reporting Procedures for Unanticipated Problems, Noncompliance, Suspension, or Termination

Example #2:

A breach of confidentiality (a laptop was stolen that contained study data with PHI) occurs on a nursing intervention study conducted at UCLA Health locations. For this protocol, the UCLA IRB is relying on the Stanford IRB. In the reliance agreement, the Stanford IRB declined to take on the role of HIPAA privacy board for UCLA.

1) The UCLA investigator submits the information about this breach to the Stanford IRB per the Stanford IRB's guidelines/processes.
2) The Stanford IRB reviews the breach of confidentiality solely as the IRB (to determine if it met the definition of unanticipated problem involving risks to subjects or others, serious and/or continuing non-compliance, and/or if the Stanford IRB requires the study be suspended or terminated at UCLA or all sites). If the Stanford IRB determines that the event meets the definition of any of the reportable events and the funding and/or nature of the research require reporting to the FDA and/or OHRP, the Stanford IRB will make that report to Federal regulators (and Cc the UCLA investigator).
3) The UCLA investigator will then need to submit a PAR application through webIRB. The purpose of this PAR will be to
    a. Submit the outcome of the Stanford IRB's review
    b. Submit a copy of the notification to federal regulators made by the reviewing IRB
    c. Manage the breach of confidentiality relevant to HIPAA
4) The UCLA IRB (acting as the privacy board) will request that the UCLA investigator notify the UCLA Health Compliance office to work on addressing the breach and developing a CAPA plan (if necessary).
    a. The outcome of this consultation (including the details of the CAPA plan, if applicable) should be included in the PAR submitted to the UCLA IRB.
5) The UCLA IRB (acting as the privacy board) will review the CAPA plan related to the breach of confidentiality worked out by the PI and the UCLA Health Compliance office and issue a determination on that part of the event.

Deadlines for submission to the IRB:

- **Within 10 days of discovering** a privacy breach of UCLA records or failure to obtain effective authorization (or a waiver) for use of UCLA records (*when the UCLA IRB retains the role of Privacy Board for research at UCLA per the reliance agreement*)

- **Within 10 days of receiving notice** that the ***reviewing*** IRB made any of the following determinations ***for the portion of the research conducted at UCLA***:
    - **Unanticipated Problem involving risks to subjects or others**
    - **Serious non-compliance**
    - **Continuing non-compliance**
    - **Suspension**
    - **Termination**

- **Within 10 days of receiving notice** that the ***reviewing*** IRB made any of the following determinations for ***the portion of the research conducted at sites other than UCLA***:
  - **Suspension**
  - **Termination**

- **No PAR submission (maintain in study files):**
  - All other reviewing IRB determinations for post approval reports/reportable new information
  - All other research-related events (adverse events and deviations) that don't meet the reviewing IRB's threshold for reporting and do not require UCLA Privacy Board for Research review

PARs on Studies where UCLA IRB is *REVIEWING* on behalf of another site

For more information on IRB reliance in general, please see the OHRPP reliance webpage.

As is the case when UCLA is relying on another IRB, the specific responsibilities for each site will be outlined in the specific reliance agreement. If the agreement is silent, assume that UCLA is not acting as the privacy board for the relying site and that the UCLA IRB will review all adverse events/reports (that meet the UCLA guidance threshold for reporting) on behalf of the relying IRB and follow the process below.

Note: Any adverse events *that occur at sites where the UCLA IRB is the reviewing IRB* are considered ***internal adverse events*** (even when they don't occur at UCLA or at sites under the management of the UCLA Investigator) and should be reported to the UCLA IRB per the guidelines above for internal AE reporting.

In general, these steps should be followed for events that meet the UCLA reporting threshold that happen at a site for which a UCLA IRB is the reviewing IRB:

1) Determine if the event meets the threshold for reporting per the PI Reporting Responsibilities described above.
2) Submit the event to the UCLA IRB (via a webIRB PAR application) with full details on the event (including at which site this event occurred).
3) The UCLA IRB will work with the relying IRB to investigate (as needed) for reports of non-compliance.
4) The UCLA IRB will make determination(s) about the event and communicate that to the UCLA PI.
5) The UCLA PI will communicate the outcome of the event to the relying site PI.
6) The relying site PI may need to forward notice of the UCLA IRB determination(s) to the relying IRB, depending on the relying IRB's policies/guidance. The relying site PI should review the reliance agreement and local site policies/guidance for any specific instructions related to submission of events to the relying IRB.

Amendment Submissions Related to PAR submissions

If the information provided in the PAR application indicates that modifications are needed to the IRB study application (protocol, consents, etc…), an amendment should be opened and submitted ***along with*** the PAR application. The IRB Chair or convened IRB may also determine,

after review of the PAR, that changes to the approved study application must be submitted for review in response to the information provided in the PAR report. For information on submitting amendment applications, please see Guidance and Procedure: IRB Review Type - Amendments to Previously Approved Research.

IRB Responsibilities and Procedures (when a UCLA IRB is the *reviewing* IRB)

The IRB is responsible for reviewing written reports of events and information, and determining if the reports meet the criteria of an unanticipated problem involving risk to subjects and others.

The IRB will consider whether risks to subjects are still minimized and reasonable in relation to the anticipated benefits. In reviewing events/incidents/new information the IRB will evaluate the risks, potential benefits, the adequacy of the protocol, recruitment and consent documents, provision of updated information to subjects, and the safeguards that are in place to protect the safety and welfare of the human subjects, including subject privacy and the confidentiality of data. If any revisions are needed in the protocol, recruitment and/or consent documents, these revisions are to be communicated to the investigator.

Upon receipt of the PAR, OHRPP staff will review the report(s) and materials submitted for completeness. If the report is incomplete, the Principal Investigator will be contacted with a request for the missing information. Review will not proceed until the requested information is received.

- If upon review by OHRPP staff the submitted PAR does not meet the submission criteria, review by the IRB Chair or Vice Chair will not proceed. The Principal Investigator will be notified by IRB staff that the submission criteria was not met and will be asked to withdraw the application.

Initial IRB Review

OHRPP staff will forward the PAR application to the appropriate IRB Chair or Chair designee for review. It is attached to the entire electronic file of all previous IRB submissions and determinations for the same protocol.

- The IRB Chair/Designee will review and evaluate the PAR and review materials to determine whether the risk-potential benefit profile of the study has changed.

- The IRB Chair/Designee will evaluate the PAR to determine whether the reported event or information meets the following criteria for an unanticipated problem involving risk to subjects or others. The criteria are as follows:

    - The event is unexpected;
    - The event is related or possibly related to the research participation; ***and***
    - Places subjects or others at a greater risk of harm than was previously known or recognized

- If the IRB Chair/Designee determines that the event does *not* meet the criteria for an unanticipated problem involving risk to subjects or others, and requires no further action, the event will be considered *not* to represent an unanticipated problem. The report will be accepted and acknowledged by the IRB Chair/Designee.

- If the IRB Chair/Designee determines that the event meets the criteria for an unanticipated problem involving risk to subjects or to others or cannot make a definitive determination, the report will be forwarded to the Full Committee, and scheduled for the next meeting of the appropriate IRB.

    - The IRB Chair/Designee may request additional information from the Principal Investigator regarding the PAR prior to present at the convened IRB meeting, in order to provide sufficient information to evaluate the event.

- If the PAR reports an event that places the safety, rights and welfare of subjects at immediate risk, the IRB Chair/Designee will contact the Principal Investigator in order to establish interim measure(s) to be taken to protect subject(s). The decision will be provided to the convened IRB meeting.

- If the PAR involves a matter of noncompliance, the review will also proceed as described by the appropriate policy (see OHRPP Policy: Noncompliance and Allegations of Noncompliance Regarding the Conduct of Human Subjects Research).

Review by a convened IRB meeting (Full Committee review)

The PARs determined to be (or possibly be) unanticipated problems involving risk to subjects or others will be distributed along with the entire electronic file of all previous IRB submissions and determinations to the primary reviewer(s) and Committee members approximately one week prior to the meeting.

- The convened IRB may request additional information from the Principal Investigator in order to facilitate a thorough review before a final determination is made.

- The convened IRB will consider and make the following determinations, which may include one or more actions which may include (but is not limited to) the following:

    - The event reviewed constitutes an unanticipated problem, serious and/or continuing noncompliance (if applicable);
    - No further action required;
    - Accept and approve the Principal Investigator's corrective action plan;
    - Modification of the research protocol to minimize risk;
    - Modification of the continuing review schedule;
    - Modification of the recruitment or informed consent documents;
    - Requirement that current subjects re-consent to participation;
    - Notification of previously enrolled subjects of new information;
    - Notification of currently enrolled subjects of new information, as such information may relate to a subject's willingness to continue participation in the research;
    - Observation of the research or the consent process (i.e., use of a consent monitor);
    - Frequent progress or status reports to the IRB;
    - Educational intervention for the investigators and support staff;
    - Referral for on-site review by the OHRPP Quality Improvement Program;
    - Referral to another University entity (i.e., institutional official, campus counsel, risk management);
    - Suspension of all or parts of the research (new enrollment, treatment, follow-up and data analysis) pending receipt of additional information from the Principal Investigator, including but not limited to a corrective action plan;

- Termination of the research;

If the convened IRB considers the suspension or termination of IRB approval, the review will also proceed as described by the appropriate guidance document (see OHRPP Guidance and Procedure: Suspension and Termination of Research).

The outcome and determinations made during the convened IRB meeting shall be documented in the correspondence to the principal investigator and the IRB meeting minutes.

Written correspondence from the IRB regarding their final action determination will be forwarded to the Principal Investigator within ten working days of the IRB determination.

- OHRPP senior staff will oversee and coordinate with the Chair all written correspondence from the IRB to the principal investigator.

OHRPP/Research Privacy Board Responsibilities and Procedures (when a UCLA IRB is the *relying* IRB)

Privacy Board Review

If, under a specific reliance agreement, the UCLA IRB retains the role of Privacy Board for Research and an event related to either a local breach of privacy/confidentiality or records obtained without authorization occurs, the submitted PAR will be reviewed by a Chair/Designee of a UCLA IRB with relevant expertise.

If the Chair/designee finds that the breach or unauthorized use of records warrants review by the convened Privacy Board for Research, the reliance PAR will be temporarily transferred to the UCLA IRB with relevant expertise. The PAR will then be reviewed by the IRB (acting solely as the Privacy Board for Research) during an upcoming convened IRB meeting.

- The convened Chair/designee or convened Privacy Board for Research may request additional information from the Principal Investigator in order to facilitate a thorough review before a final determination is made.

- The convened Privacy Board for Research will consider and make the following determinations, which may include one or more actions which may include (but is not limited to) the following:

    - Accept and approve the Principal Investigator's corrective action plan;
    - Observation of the research or the consent/authorization process (i.e., use of a consent monitor);
    - Educational intervention for the investigators and support staff;
    - Referral for on-site review by the OHRPP Quality Improvement Program;
    - Referral to another University entity (i.e., institutional official, campus counsel, risk management);
    - Suspension of all or parts of the research (new enrollment, treatment, follow-up and data analysis) pending receipt of additional information from the Principal Investigator, including but not limited to a corrective action plan;
    - Termination of the research;

Administrative Review

PARs submissions to inform the OHRPP of reportable determinations made by the reviewing IRB that do not include privacy board review, will be administratively acknowledged by OHRPP staff once complete information (the determination by the reviewing IRB and the notification letter to federal regulators, as applicable) is uploaded to the application.

The reviewing IRB's determination or notification to federal regulators will be forwarded to relevant UCLA stakeholders according to OHRPP Guidance and Procedure: IRB Reporting Procedures for Unanticipated Problems, Noncompliance, Suspension, or Termination.

IRB Reporting Requirements

Unanticipated problems involving risks to subjects or others; any serious or continuing noncompliance; and any suspension or termination of IRB approval are reportable to the appropriate federal department or agency head(s) and institutional official (45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)) and will be reported according to OHRPP Guidance and Procedure: IRB Reporting Procedures for Unanticipated Problems, Noncompliance, Suspension, or Termination.

Regulations and other References

DHHS Regulations

- 45 CFR 46.103(e)
- 45 CFR 46.108(a)(4)
- 45 CFR 46.116(c)(5)

FDA Regulations

- 21 CFR 50.25(b)(5)
- 21 CFR 56.108(b)
- 21 CFR 312.53(c)(1)(vii)
- 21 CFR 312.66
- 21 CFR 812.150(a)(1)

UCLA Policy

o UCLA Policy 991: Protection of Human Subjects in Research
o UCLA Policy 420: Notification of Breaches of Computerized Personal Information.

ICH-GCP

- 4.11.1
- 4.11.3
- 4.12.1
- 4.12.2
- 4.12.3

AAHRPP Standards & Elements

Element I.4.A.
Element I.5.D.
Standard I-9
Element II.2.G.
Element II.2.H.
Element II.2.I.
Element III.2.B.
Element III.2.C.
Element III.2.D.

OHRP Guidance

o OHRP Guidance on Reporting Incidents to OHRP (2011)

o OHRP Unanticipated Problems Involving Risks and Adverse Events Guidance (January 15, 2007)
o OHRP Guidance on Written IRB Procedures (July 1, 2011)

FDA Guidance

o FDA Guidance for IRBs, Clinical Investigators and Sponsors: IRB Continuing Review after Clinical Investigation Approval (February 2012)

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

Change history:
6/9/2016: Updates to links and references
2/12/2020: Update to limit the scope of items reviewed; add links for the Revised Common Rule; provide clarification on PAR submissions for UCLA as reviewing or relying site; include OHRPP/Privacy Board for Research responsibilities related to review of PARs for reliance studies; reference AAHRPP standards; revise/add definitions to reflect UCOP definitions of non-compliance, serious non-compliance, and continuing non-compliance; remove submission of use of the short form process; and include ICH-GCP relevant references