

IS YOUR CAPA ROBUST ENOUGH?

Identifying and Reporting Non-Compliance and Developing
Corrective and Preventive Action Plans

IDENTIFYING NON-COMPLIANCE

NON-COMPLIANCE

Definition

Failure to comply with the requirements of an applicable law, regulation, or institutional policy pertaining to the protection of human subjects, and/or with the requirements or determinations of an IRB

HRP-001 SOP: Definitions

HRP-103 INVESTIGATOR MANUAL

Investigator Obligations

What are my obligations after IRB approval? 1) Do not start Human Research activities until you have the final IRB approval letter. 2) Do not start Human Research activities until you have obtained all other required institutional approvals, including approvals of departments or divisions that require approval prior to commencing research that involves their resources. For instance, at UC Davis when an investigational drug or biologic is involved, the UC Davis PI is required to defer responsibility for accounting, storage, dispensing, etc. to the UC Davis Health Investigational Drug Services (IDS) Pharmacy. 3) Ensure that there are adequate resources to carry out the research safely. This includes, but is not limited to, sufficient investigator time, appropriately qualified research team members, equipment, and space. 4) Ensure that Research Staff are qualified (e.g., including but not limited to appropriate training, education, expertise, credentials, protocol requirements and, when relevant, privileges) to perform procedures and duties assigned to them during the study. 5) Update the appropriate IRB office with any changes to the list of study personnel (other than PI and Co-PI) at time of continuing review, if applicable or annually. To change the PI and/or Co-PI, a modification must be submitted and approved by the UC Davis IRB before the new PI and/or CO-PI can engage in human research activities. 6) Personally conduct or supervise the Human Research. a) Conduct the Human Research in accordance with the relevant current protocol as approved by the IRB. b) When required by the IRB, ensure that consent or permission is obtained in accordance with the relevant current protocol as approved by the IRB. c) Protect the rights, safety, and welfare of subjects involved in the research. 7) Report changes in funding as soon as you receive notification of an award. 8) Do not make any modifications to approved research without first obtaining prior approval from the IRB unless the modification is necessary to protect participants from imminent harm. To request approval of a modification, see "How do I submit a modification?" 9) Respond promptly to notifications from the IRB. 10) When required, submit a continuing review application to the IRB. The expiration date for your research can be found in the approval letter. See "How do I submit a continuing review?" for instructions for submitting a continuing review report. 11) Submit a continuing review application when the Human Research is closed. See "How do I close out a study?" for more information. 12) Report to the IRB using "FORM: REPORTABLE NEW INFORMATION (HRP-214)," any of the information items in Appendix A within five to ten business days as outlined in Appendix A. Investigator Manual NUMBER DATE PAGE HRP-103 08/31/2018 15 of 48 a) The IRB will review your report to determine if any of the information items meet the definitions of serious noncompliance, continuing noncompliance or an unanticipated problem involving risks to subjects or others (UPIRTSO), as listed in "SOP: DEFINITIONS (HRP-001)." b) Examples of UPIRTSOs include: i) Internal adverse events that are unexpected, involve new or increased risks, and are related to the research. ii) Changes made to the research without prior IRB approval in order to eliminate apparent immediate harm. iii) Other unanticipated information that is related to the research and participants or others might be at increased risk of harm. 13) Submit an updated disclosure of financial interests within thirty days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new financial interest. 14) Do not accept or provide payments to professionals in exchange for referrals of potential subjects ("finder's fees.") 15) Do not accept payments designed to accelerate recruitment that are tied to the rate or timing of enrollment ("bonus payments.") 16) See additional requirements of various federal agencies in Appendix B. These represent additional requirements and do not override the baseline requirements of this section.

FDA FORM 1572

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects. I agree to personally conduct or supervise the described investigation(s). I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in [21 CFR Part 50](#) and institutional review board (IRB) review and approval in [21 CFR Part 56](#) are met. I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with [21 CFR 312.64](#). I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments. I agree to maintain adequate and accurate records in accordance with [21 CFR 312.62](#) and to make those records available for inspection in accordance with [21 CFR 312.68](#). I will ensure that an IRB that complies with the requirements of [21 CFR Part 56](#) will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects. I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in [21 CFR Part 312](#).

SPONSOR'S PROTOCOL

Investigator Attestation

By signing below, I, the Principal Investigator confirm that I have read the protocol and agree to conduct the clinical trial according to all stipulations of the protocol as specified in both the clinical and administrative sections. I agree to comply with the **ICH-GCP, local regulatory authorities** guidelines for the conduct of clinical trials, World Medical Association **Declaration of Helsinki** (and relevant updates) and all other **applicable regulations**. I agree to ensure that the confidential information contained in this document, as well as supplemental documents, issued now and in the future will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

COMMON THEMES

- Read and understand the protocol and investigator's brochure
- Personally conduct or supervise the investigation
- Ensure personnel are qualified and trained
- Control investigational product
- Document study progress
- Submit required reports
- Retain records

COMMON EXAMPLES OF NON-COMPLIANCE

- Failure to follow the protocol
- Over-enrollment
- Late Reporting
- Use of old Consent Form
- Missing signatures

IS IT NON-COMPLIANCE?

IDENTIFYING NON-COMPLIANCE

What if...

On January 10 you receive a new investigator brochure. The sponsor indicates the risk/benefit ratio has not changed, so you decide to wait until the next protocol amendment to submit the revised IB to the IRB.

On February 15 you submit a protocol amendment and the revised IB. The IRB contacts you because a new risk has been identified in the IB: abnormal heart rhythm. This risk is not described in the currently approved consent form.

Is it non-compliance?

YES

- New risk information must be reported the IRB within 5 business days

IDENTIFYING NON-COMPLIANCE

What if...

Research Compliance and Integrity completed an audit of your investigator-initiated study, and identified deficiencies in the enrollment numbers. The enrollment numbers were not calculated correctly throughout the year and you - enrolled by 2 subjects more than the IRB Approved.

Is it non-compliance?

YES

- Failure to follow the IRB-approved protocol

IDENTIFYING NON-COMPLIANCE

What if...

There is a potential subject you want to enroll in a study. You pull up the protocol and review the inclusion criteria, and the patient does not meet the platelet requirement. The PI contacts the sponsor, and the sponsor approves the enrollment of the subject. You enroll the subject in the study without consulting with the IRB.

Is it non-compliance?

YES

- Failure to follow the IRB-approved protocol

PLANNED PROTOCOL DEVIATION

Avoid non-compliance by submitting a modification to the IRB BEFORE the deviation happens.

Include:

- Requirement that will not be followed
- Proposed date of the deviation
- Rationale for the deviation
- Single subject or multiple
- Any increase in risk
- Anticipated benefit
- Impact on data integrity
- Approval from sponsor, medical monitor, etc.

PLANNED PROTOCOL DEVIATIONS

Expedited Review

- Minimal risk/ Expedited Research Procedure

Committee Review

- Greater than Minimal Risk Procedures

REPORTING NON-COMPLIANCE

REPORTING NON-COMPLIANCE

Notify the IRB

- Report within the required time frames:
 - 5 business days for safety related events/information/IB updates
 - 10 business days for all other events/information
- Ensure the form is complete and accurate:
 - Current study status
 - Description of non-compliance and a CAPA Plan
 - Total number of subjects enrolled
 - If subjects are receiving interventions
 - Will this result in a change to study documents (protocol, consent form, advertisements, surveys, etc.)

REPORTING NON-COMPLIANCE

Post Approval Submission Form

- IRBNet Document Wizard
- Replaces ALL of the following:
 - ✓ Form HRP-212 Continuing Review Progress Report
 - ✓ Form HRP-213 Modification
 - ✓ Form HRP-214 Reportable New Information

REPORTING NON-COMPLIANCE

Post Approval Submission Form

Reportable New Information *

[Click here](#) for information about what must be reported to the IRB.

Do you have any of the following to report to the IRB? You may select more than one.

- Information that indicates a new or increased risk or increase in frequency or severity of a known risk.
- Change (e.g. protocol violation) made to research to prevent imminent harm to subjects or others.
- Non-Compliance with the federal regulations governing human research, with the protocol or with the requirements or determinations of the IRB.
- Ancillary approval not previously reported (e.g. Radiation Use Committee, Institutional Biosafety Committee, etc.).
- Subject complaint that cannot be addressed by research team.
- Incarceration of a research subject.
- Other
- None of the above.

Essential Elements

- Description of non-compliance
- Root cause analysis
- Corrective and preventive action plan
- Training and evaluation

DESCRIPTION OF NON-COMPLIANCE

DESCRIBE THE NON-COMPLIANCE

Event Details

- What requirement was not met?
- What was the error and when did it occur?
- When and how was the error discovered?
- Was a subject harmed?

EXAMPLE

The IRB approved a revised consent document on November 6. The changes included new risk information.

On November 20, an old version of the consent form was used to enroll a subject.

The error was discovered on November 26, when doing data entry.

WHAT IS THE REQUIREMENT THAT WAS NOT MET?

On November 6, the IRB approved an updated consent form. All subjects consented after November 6 should receive the updated consent form.



WHAT WAS THE ERROR AND WHEN DID IT OCCUR?

*On November 20, a sub-investigator enrolled
subject XYZ using the consent document that was
approved on March 3.*



WHEN AND HOW WAS THE ERROR DISCOVERED?

On November 26, a team member noted this error when completing data entry.



WAS A SUBJECT HARMED?

The consent document updates approved on November 6 included new risk information for the study drug. The subject has not yet received study drug, therefore the subject was not harmed as a result of this event.



DESCRIPTION OF NON-COMPLIANCE

On November 6, the IRB approved a revised consent form with new risk information. All subjects consented after November 6 should receive the updated consent form. On November 20, a sub-investigator enrolled Subject XYZ using an outdated informed consent document initially approved on March 3. On November 26, a team member noted this error when conducting data entry. The subject has not yet received study drug, therefore the subject was not harmed as a result of this event.

ROOT CAUSE ANALYSIS

ROOT CAUSE ANALYSIS

Purpose: Identify the root cause of non-compliance

Procedure: Ask “why” multiple times until you identify the root cause.



WHY WAS AN OLD CONSENT FORM USED?

The sub-investigator did not know the consent document was revised.

Why?

The old consent document was in the subject's file before the visit started

Why?

The regulatory coordinator was out when the revised consent document was approved by the IRB.

Why?

There is no staffing plan to cover for out-of-office.

ROOT CAUSE

After a thorough analysis we have determined this error occurred because the sub-investigator did not know the consent document was revised. This happened because the regulatory coordinator was out on leave when the revised consent was approved by the IRB. The root cause of this non-compliance is lack of personnel designated to cover responsibilities when the regulatory coordinator is out-of-office.

CORRECTIVE AND PREVENTIVE ACTION PLANS

CORRECTIVE ACTION

Purpose: Correct the immediate problem.

Procedure: Action to address the non-compliance.



CORRECTIVE ACTION

To correct this error, Subject XYZ was re-consented using the revised consent document at his study next visit on December 12.

PREVENTIVE ACTION PLAN

Purpose: To avoid future instances of non-compliance.

Procedure: Create a plan to address the root-cause of non-compliance.



PREVENTIVE ACTION PLAN

To prevent this from happening in the future, the PI has delegated coverage of regulatory coordinator responsibilities to a second staff member, when necessary. The regulatory coordinator is responsible for notifying the second staff member of any out-of-office time.

SUGGESTED REPORTING TIMELINE

NON-COMPLIANCE REPORTING AT CONTINUING REVIEW

LATE SUBMISSION

- Root cause analysis
- Preventive action plan

OVER-ENROLLMENT

- Root cause analysis
- Preventive action plan
- Corrective action: submit a modification to update all study documents with new enrollment numbers

IRB REVIEW PROCESS

IRB REVIEW PROCESS





UNIVERSITY OF CALIFORNIA, DAVIS

BERKELEY • DAVIS • IRVINE • LOS ANGELES • MERCED • RIVERSIDE • SAN DIEGO • SAN FRANCISCO



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IRB DETERMINATION
LETTER

Found under “Reviews”
in IRBNet

September 21, 2018

Name:
Department:
Phone:
Email:

The IRB acknowledges receipt of the following information:

Type of Review:	New Information
Title:	Research Study
Investigator:	Researcher, Jane PhD
IRB ID:	555555-4
Funding:	(NIH)
Documents Submitted:	<ul style="list-style-type: none">• Protocol Deviation/Violation Report - HRP-214-FORM-Reportable New Information.docx
Comment:	The information in this report meets the UC Davis definition of non-compliance that is not serious or continuing. You must ensure that you adhere to your corrective and preventive action plan (CAPA).

TRAINING AND EVALUATION

If you don't document, it didn't happen

Training

- **Who was trained**
- **When were they trained**
- **What information was presented**

Evaluation

- **Monitor for compliance**
- **Measure outcomes**



What if?

GO TO IRBNET.ORG

- **Create a new study named “Test Study”**
- **Add the Post-approval submission form**
- **Complete the form for the following scenarios**

NON-COMPLIANCE

What if...

Today is July 17. You are meeting with Subject 0043 in 20 minutes to complete visit 4. As you're going through the subject's research binder you notice the lipid panel results that are from visit 3 are missing. Visit 3 occurred on June 1.

What should you do next?

NON-COMPLIANCE

Submit a report of non-compliance to the IRB.

DESCRIBE THE NON-COMPLIANCE

On July 17 the research coordinator was preparing for visit 4 when she discovered that lipid panel results for visit 3 were missing. Visit 3 took place on June 1. The results from the lipid panel are not used to monitor subject safety. The subject was not harmed as a result of this event.

ROOT CAUSE ANALYSIS

POSSIBLE CAUSES

- Subject refusal
- Blood hemolyzed
- Laboratory technician failed to draw the blood for the test
- Orders were incorrect
- Test was not ordered

ROOT CAUSE STATEMENT

- This event occurred because...

CORRECTIVE ACTION PLAN

The sponsor is aware that the lipid results are missing and does not require any action to correct this error.

PREVENTIVE ACTION

To prevent this from happening in the future the research team will...

AUDIT REPORTS

What if...

The sponsor monitor conducted an audit of your site. The monitor did not identify any deficiencies, and provided a letter congratulating you on a successful site visit.

What should you do next?

DO NOT REPORT

According to HRP-214, only audit and monitoring reports that include information that falls under one of the reportable categories (e.g. new risk information, protocol deviation, etc.) and has not previously been reported, must be submitted to the IRB.

CONTINUING REVIEW

What if...

You just realized one of your studies expires in two weeks. You note that you have not submitted the Continuing Review Report form that was due 31 days ago.

What should you do next?

SUBMIT A CONTINUING REVIEW REPORT

Indicate the report is late and include a preventive action plan

ROOT CAUSE ANALYSIS

POSSIBLE CAUSES

- Staff turnover
- Unaware of administrative due date
- PI out of office

ROOT CAUSE STATEMENT

- This event occurred because...

PREVENTIVE ACTION

To prevent this from happening in the future the research team will...

NON-COMPLIANCE

What if...

Today is April 20. You are a coordinator conducting an internal review of consent documents and HIPAA Authorizations. You discover that at the enrollment visit on January 21, Subject 0012 signed the approved consent document, but did not sign the HIPAA Authorization Form. On February 3 a research coordinator extracted data from the medical record for research purposes.

What should you do next?

NON-COMPLIANCE

Submit a report of non-compliance to the IRB.

DESCRIBE THE NON-COMPLIANCE

According to the IRB approved protocol, research subjects will provide informed consent and sign a HIPAA Authorization at the enrollment visit. On April 20, the regulatory coordinator was conducting a routine review of study documents and discovered that Subject 0012 did not sign a HIPAA Authorization. The HIPAA Authorization should have been signed at the enrollment visit on January 21. The research coordinator is responsible for obtaining HIPAA authorization. On February 3 a research coordinator extracted data from the medical record of the research subject. Because the medical record was accessed for research purposes without authorization, the subject's rights were impacted by this event.

ROOT CAUSE ANALYSIS

POSSIBLE CAUSES

- Coordinator forgot
- Research subject had to leave early
- HIPAA Authorization was missing from enrollment packet

ROOT CAUSE STATEMENT

- This error occurred because...

CORRECTIVE ACTION

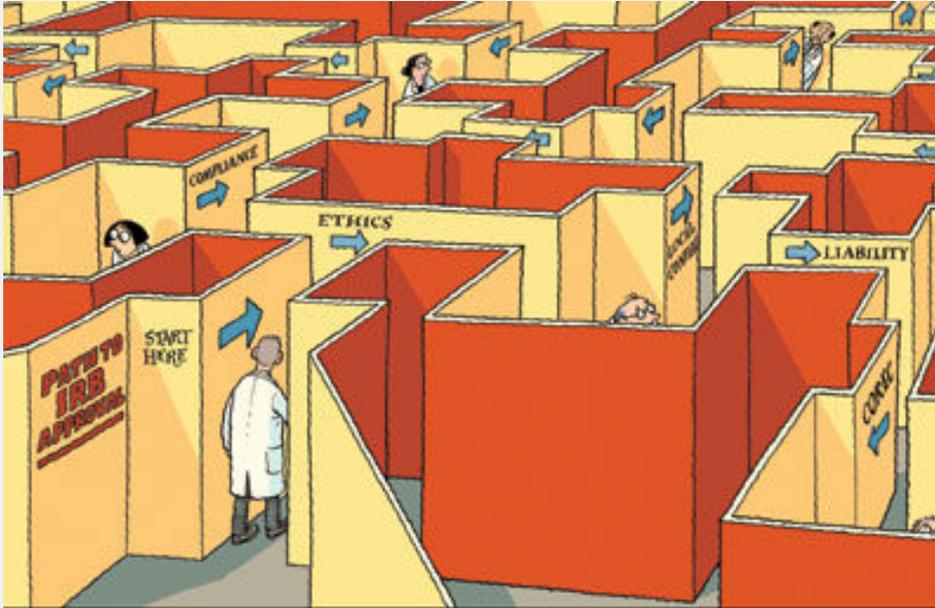
- The research subject is scheduled for visit 3 on May 15. The subject will be asked to sign a HIPAA Authorization at the time. We have notified the UCDHS Compliance Office of this situation.

PREVENTIVE ACTION PLAN

- To prevent this from happening in the future....

QUESTIONS?

Need help?



Contact the IRB

IRB Help Desk

hs-irbeducation@ucdavis.edu

916-703-9158

Website

research.ucdavis.edu/irbadmin