Quality Improvement Activities

SOP 110
Revised: February 11, 2019

Purpose and Scope

This Standard Operating Procedure (SOP) describes the process to conduct quality improvement of the human research protection program, which includes procedures for external and internal compliance monitoring of research conduct

These procedures, referred to as the Quality Improvement Procedures (QIP), apply to all Human Studies Program (HSP) staff, UH Institutional Review Board (IRB) members, and UH Investigators and key research personnel (e.g., sub-investigators, study coordinators, research assistants, etc.). The HSP staff ensures completion of the QIP procedures.

Definitions

Institution refers to any public or private entity or agency (including federal, state, and other agencies).

Clinical Drug Trials

- *Phase 1 trials* refer to testing within a small group of people (20–80) to evaluate safety, determine safe dosage ranges, and begin to identify side effects.
- *Phase 2 trials* refer to testing with a larger group of people (100–300) to see if it is effective and to further evaluate its safety.
- *Phase 3 trials* refer to testing with large groups of people (1,000–3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely.

On-Site Visits

- *Routine Review* refers to a comprehensive on-site review conducted on a scheduled basis.
- *For-Cause* refers to a comprehensive or targeted on-site review to provide an assessment of study compliance.
- *Investigator-Requested* refers to an on-site review based on self-reported actual or perceived deficiencies in which there is a potential risk to human participants.

Site Visit Review Ratings

- *Acceptable* refers to a site visit that result in a finding of no deficiencies or lesser deficiencies that do not appear to involve risk to human participants.

- *Acceptable with Conditions* refers to a site visit that result in findings of multiple lesser deficiencies that presents a potential risk to human participants that needs further consideration.

- *Unacceptable* refers to a site visit that result in findings of one or more major deficiencies that impact human participant safety and welfare.

Procedures

External Compliance Monitoring of Research Conduct

To meet the objective for improving compliance of investigators with their responsibilities, the following Post Approval Monitoring (PAM) procedures will take place:

Selection Criteria

1. **"Routine Review"** refers to a comprehensive on-site review of IRB-approved protocols randomly selected by the IRB Chair, Institutional Official, HSP Manager, or a member of the PAM team, however emphasis may be placed on monitoring studies using a risk-based approach including, but not limited to, the following criteria:

    a. Research with a high degree of complexity, investigations of new drugs (INDs) or devices (IDEs), or FDA regulated trials.

    b. More than minimal risk levels to participants, high participant enrollment, participants from vulnerable populations, deception or incomplete disclosure to participants, including confidentiality and privacy concerns (see TMP 465 ICF Template: For Post-Interaction Debriefing in Research Involving Deception).

    c. Research conducted off-site, research conducted by student investigators, projects with significant changes in personnel, projects ceded to another IRB, projects requiring more than annual review by IRB, or projects not otherwise reviewed by external regulatory entities.

    d. Investigators with actual or potential conflicts of interest, Investigators with a large volume of studies, or Investigators who previously failed to comply with IRB determinations.

    e. Requested by an IRB member and with approval by the IRB Chair.

2. **"For-Cause Review"** refers to a comprehensive or targeted on-site review to provide an assessment of study compliance. The IRB can specify whether the review focuses on one aspect of the research (i.e., the consent process) or a broad review of the study conduct.

3. **"Investigator-Requested Review"** refers to review based on self-reported actual or perceived deficiencies in which there is a potential risk to human participants.

    a. A PI may request an on-site review to help keep records and procedures in compliance with federal regulations and institutional policies or to prepare for an external audit by a sponsor or federal agency.

    b. When a PI requests a PAM review the following items are reportable to the IRB:

        - Any serious non-compliance activity not approved by the protocol or amendments.
        - Issues related to obtaining a participant's consent.
        - Any Unanticipated problem[1] involving serious risks to participants.

4. **Additional Criteria.**

    a. Observation of the Informed Consent Process. Investigators can request an overview of the consent process at any time before or during initiation of a study.

    b. PAM review includes all studies, even those determined to qualify for exempt status.

Unless otherwise noted, the procedures in the Notice of Audit, Visit Review Preparation, and Site Visit, described below, will apply to Routine, For-Cause, and Investigator-Requested site visits.

Notice of Audit

For Routine and Investigator-Requested Review, the PAM Team will provide the Investigator with a fourteen (14) business days' notification of the site visit in writing or by email. In the case of a For-Cause Review or where there is a concern for study subjects' safety, the PAM Team will provide the Investigator with at least twenty-four (24) hours' notice by telephone and email of the site visit. The IRB may also specifically request an unannounced site visit.

The Investigator will cooperate with the PAM Team in scheduling the site visit at a mutually agreeable date and time. Depending on the nature of the research study, an IRB member who has experience in the study topic may participate in the site visit.

Visit Review Preparation

Prior to the Site Visit: Before the site visit, the Investigator will collect and make all documentation related to the study in the IRB file available for the research conduct assessment (see WKSH 350 Study Documentation Checklist).

[1] "An **UNANTICIPATED PROBLEM** is any unfavorable incident, experience, or outcome that is **unexpected, related or possibly related**, and suggests that the research places participants or other at **greater risk of harm** than expected for this research," (emphasis in original) available at: https://www.hawaii.edu/researchcompliance/report-protocol-violation-or-unanticipated-problem

Site Visit Checklist. The Investigator will prepare for the site visit by reviewing the checklist of questions (see WKSH 351 Site Visit Checklist). Please note that not all items on the checklist apply to all research studies.

Regulatory Requirements. Compliance with regulatory requirements is a significant component of QIP. To evaluate compliance, the PAM Team, through observation, interviews, and record review, may focus on various aspects of the regulatory requirements involved in the study (see WKSH 352 Regulatory Requirements Checklist).

Self-Assessment Checklist. The PAM specialist may provide the Self-Assessment Checklist[2] to assist the Investigator in preparing for the site visit. The checklist is intended to aid the Investigator in identifying potential issues of noncompliance and allow the Investigator to take appropriate action before items become serious and/or reportable problems.

Site Visit Process

The Site Visit will follow the process described below:

1. The Investigator will provide a brief description of the study.

2. The Investigator will provide the study files for review.

3. The PAM Team will may review all aspects of the research record, and as appropriate, focus on specific aspects of the protocol or regulatory requirement involved in the study. As an aid to the Investigator in preparing for the site visit, the PAM Team may provide checklists that describes the scope of the research record review (e.g., WKSH 350 and 351).

4. The Investigator will encourage research personnel affiliated with the protocol to participate in the audit process.

5. The Investigator will make private space available for the PAM Team's use to review study files and other documentation.

6. The PAM Team will evaluate compliance through a review of the research record, as well as though observation and interviews of the Investigator and any research personnel knowledgeable about specific aspects of the study.

7. Throughout the site visit at and at the conclusion, the PAM Team may provide recommendations and educational support to the Investigator and their research personnel based upon the site visit findings.

8. The PAM Team will notify the IRB Chair and HSP Manager immediately if any discrepancies non-compliance with approved protocols indicate that human participants are exposed to unexpected serious harm. The IRB Chair or Institutional Officer may suspend the study prior to the next regularly scheduled IRB meeting. [3]

[2] New document.

[3] In accordance with 45 CFR 46.103(b)(5) and 21 CFR 56, any unanticipated problems involving risks to participants or others must be promptly reported to the IRB, appropriate institutional officials, and the department or agency head.

9. After the site visit, the PAM Team will meet with the Investigator and provide a brief summary of findings.

10. In most cases, the Investigator should have reported serious violations that present the risk of injury to study participants immediately to the IRB. However, if a site visit demonstrates that a serious violation involving risk of injury to participants had not been reported, the PAM Team will report the event immediately to the IRB Chair, HSP Directors, and to the Assistant Vice Chancellor of Research Compliance (AVCRC), or designee.

Exit Briefing

1. At the end of the site visit, the PAM Team will meet with the Investigator or research personnel and provide a brief summary of findings and discuss any issues.

2. The purpose of the exit briefing is to confirm that the PAM Team's observations are accurate and the Investigator or research personnel agree upon the findings.

3. The exit briefing will also address corrective measures for any observed deviations from IRB-approved protocols or other deficiencies during the course of the PAM review.

Summary Report of Site Visit

1. PAM Report Elements.

    a. The Investigator's name, title of the research or study, IRB study number, and names of key research personnel.

    b. A detailed description of the monitoring activities, including any observed non-compliance or protocol violation.[4]

    c. A summary of areas requiring improvement, including recommendations for improvement (e.g., education and training).

    d. As appropriate, the IRB Worksheets and Templates, including the Investigator Self-Assessment Checklist (if submitted), will become part of the final PAM Report.

2. Comments by the Investigator.

    a. The draft PAM Report will be submitted to the Investigator for review and comment. The Investigator will submit his/her comments to the PAM Team within two weeks of the date of receipt of the draft PAM Report.

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[4] "A **PROTOCOL VIOLATION** is any **deviation or departure** from the **IRB-approved protocol** that does not have prior approval by the IRB," (emphasis in original) available at https://www.hawaii.edu/researchcompliance/report-protocol-violation-or-unanticipated-problem

b. Based upon the Investigator's comments, the PAM Team may revise the PAM Report as appropriate and prepare it in final form. The Investigator's comments will be attached to the final PAM Report

c. The PAM Team leader and Investigator will both sign the final PAM Report. The signed PAM Report will be forwarded to the HSP Director, the Investigator, and the IRB Chair.

d. When the draft PAM Report contains findings of non-compliance, the Investigator will respond with a plan of corrective action for each finding. The Investigator will submit his/her corrective action plan to the IRB within two (2) weeks of the date of receipt of the draft PAM Report.

3. IRB Review. The PAM Report, including the Investigator's comments, will be reviewed at the next convened IRB meeting. The IRB may take the following actions with respect to the PAM Report:

    a. **Acceptable** referring to a site visit that result in a finding of no deficiencies or lesser deficiencies that do not appear to involve risk to potential subjects.

    b. **Acceptable with Conditions** referring to a site visit that result in findings of multiple lessor deficiencies that presents a potential risk to potential subjects that needs further consideration.

    c. **Unacceptable** referring to a site visit that result in findings of one or more major deficiencies that impact human subjects safety and welfare.

4. The IRB will issue a letter to the Investigator after the IRB has made a decision on the PAM Report.

    a. If the IRB decision is Acceptable (i.e., the PAM Report does not identify any problems) no action will be taken.

    b. Where the IRB decision is Acceptable with Conditions or Unacceptable (i.e., the PAM Report identify findings of discrepancies or non-compliance), the possible actions that the IRB Chair, Institutional Officer, or HRPP Manager may take include, but is not limited to:

        1) Make recommendations to implement corrective actions in a time frame determined by the IRB.

        2) Request a PAM review of all active protocols of the PI.

        3) Request subsequent PAM monitoring visits at defined intervals.

        4) Require the PI and research personnel to attend educational seminar or training.

        5) Require protocol to be re-audited at a specific time or enrollment period.

        6) Require the PI to notify participants of non-compliance and get their permission to use the data.

7) Notify department chair, dean, and/or research ethics committee.

8) Notify all PIs at the University via education programs to ensure all are aware of regulations, so the noncompliance would be less likely to happen again.

9) Make determinations regarding use of data.

10) Require the PI to be mentored for a specific period of time.

11) Contact the PI to inform him/her of the allegation of non-compliance and request the PI to respond in writing.

12) Suspend participant enrollment.

13) Suspend the protocol.

14) Terminate IRB approval (protocol closed).

15) Require replacement of the PI.

16) Require additional training, education, or monitoring.

17) Disallow the PI to conduct research for a period of time.

18) Require the PI to inform journals of noncompliance when submitting for publication.

19) If non-compliance places participants at risk, the IRB may request a consultation with a specialist in the field.

20) Notify other entities (e.g., OHRP, UH General Counsel, HRPP of collaborating institution(s), other institutional officials, and other regulatory/sponsoring agencies as appropriate).

Post Visit

1. The IRB will monitor the Investigator's compliance to ensure that any corrective actions imposed on the Investigator are completed.

2. The PAM Report may then be sent to the HSP Manager, the IRB, the ORC Director, Institutional Officer, and other units within the University, as appropriate.

3. The PAM Report may also be forwarded to the UH VPRI and others Institutional Officials, including federal regulatory agencies, as deemed necessary by the IRB.

4. The PAM Team will inform the Investigator by e-mail of any actual or potential non-compliant issues and the concern or corrective actions required by the IRB.

5. The PAM Team will inform the Investigator of the IRB deadline to resolve or address any non-compliant issues and report corrective action to the PAM Team.

6. If there are no issues or concerns, the PAM Team will inform the Investigator by e-mail of a fully compliant review.

7. The IRB may/shall require a follow-up inspection to determine whether concerns have been satisfactorily resolved and corrected.

8. Copies of the final PAM report will be stored in the UH HSP study protocol files and in the master PAM archive together with related correspondence, checklists, worksheets, and Investigator comments. The PAM Report will be maintained in accordance with the UH HSP document retention policy.

Monitoring of Informed Consent/Assent Process

During an audit of consent, the PAM Team will review:

1. The timing of recruitment and screening in relation to informed consent.

2. The appropriateness of the person obtaining consent.

3. The consent process to meet the needs of vulnerable populations.

4. Steps to aid participants with barriers to understanding or lack of capacity to consent (language, reading level, etc.).

5. Steps to see if the participant understands the research purpose risks, benefits, voluntary participation, withdrawal, confidentiality, costs/compensation, and contacts for questions or injuries.

Review Rating.

Investigator-requested site visits focused on the informed consent process may include observation, interview, and record review. The monitor will provide feedback during and provide a brief summary of the findings at the conclusion of the visit.

Internal Compliance Monitoring of IRB Operations

To meet the objectives for improving compliance of IRB meeting minutes with regulatory compliance and increase efficiency of recording and finalizing minutes, the following procedures will take place:

1. The HSP Manager and/or Compliance Specialist will conduct administrative reviews of at least one set of IRB meeting minutes every other month on a rotating basis so that each IRB has at least two (2) sets of minutes reviewed per year. Minutes are assessed for completeness and adherence to the requirements outlined under 45 C.F.R. 46.115(2). These administrative reviews of the minutes will also involve verification that the IRB membership listed on the minutes for a given IRB meeting is accurate according to the master list maintained by the IRB administration as well as the roster provided to OHRP.

2. Feedback will be provided to the HSP staff members associated with the generation of minutes, and findings will be reported to the Assistant Vice Chancellor of Research Compliance and to the Institutional Official.

3. Corrective actions such as re-training of the HSP staff will occur both individually and at the monthly meetings of the research compliance administrators and the IRB administration.

4. The HSP Manager or designee will be available for every convened meeting of the IRBs to answer regulatory questions for the members and to advise on policy issues.

5. In addition to the HSP staff member assigned to record meeting minutes during a convened IRB meeting, a second HSP staff person will be in attendance to record presence and absence of members; to assure that a quorum is met and maintained; and to count and record votes. This additional staff support will help ensure the accuracy of the assessment of IRB chairs and members will be conducted annually. The HSP Manager will meet record of the IRB's activities that will be reflected in the minutes from each meeting.

6. Assessment of IRB chairs and members will be conducted annually. The HSP Manager will meet with each IRB Chair to assess the constitution of the committee as well as members performance and need for additional training.

Materials

HSP Website and the Policies and Guidance section for Quality Improvement Worksheets

- WKSH 322: Consent Observation Checklist
- WKSH 350: Study Documentation Checklist
- WKSH 351: Site Visit Checklist
- WKSH 352: Regulatory Requirements Checklist
- WKSH 353: Post-Approval Monitoring Site Visit Checklist and Report (Biomedical, Clinical Studies)
- WKSH 354: Post-Approval Monitoring Checklist (Social & Behavioral Sciences)
- WKSH 355: IRB Meeting Minutes Quality Assessment
- WKSH 357: Quorum and Expertise
- WKSH 358: Protocol Assessment – Internal Review

References

- The Organization conducts audits or surveys or uses other methods to assess compliance with organizational policies and procedures and applicable laws, regulations, codes, and guidance. The Organization makes improvements to increase compliance, when necessary (**AAHRPP Element I.5.A**.).

- The Organization conducts audits or surveys or uses other methods to assess the quality, efficiency, and effectiveness of the Human Research Protection Program. The Organization identifies strengths and weaknesses of the Human Research Protection Program and makes improvements, when necessary, to increase the quality, efficiency, and effectiveness of the program (**AAHRPP Element I.5.B**.).