Human Subjects Post Approval Monitoring

Introduction

Post Approval Monitoring (PAM) or compliance monitoring is a program that monitors research projects to confirm that the research is being conducted as approved, thus ensuring compliance with the federal regulations and guidelines that govern research. The goal of compliance monitoring is to confirm, by observation, and direct communication with PI the accurate and consistent protocol performance in a collegial and unobtrusive manner. Another goal of the PAM program is to ensure the well-being of human subjects in research.

PAM visits and reviews are conducted by the Research Quality Assurance Unit (RQAU), a group within the Sponsored Program Services (SPS). The RQAU role is to ensure that there is no bias in the reviewing and monitoring research activity that is being performed in accordance with approved Institutional Review Board (IRB) protocols and institutional Standard Operating Procedures (SOPs) as well research administration and research regulatory compliance practices and to provide leadership when conducting comprehensive reviews of the University's compliance activities.

When conducting a PAM review the RQAU will speak to the PI as well as observe the research activity and determine if it is being performed in accordance with the approved IRB protocol and institutional Standard Operating Procedures (SOPs). The RQAU staff member will document the findings of the PAM visit and provide a memo documenting the visit to the PI as well as to the Human Research Protection Program (HRPP) Administrator and Director.

Additionally, the RQAU can assist the HRPP in identifying areas of weakness in the program or the approval process and suggest improvements.

PAM is not designed to "catch" individuals; rather, it is designed to verify that research is being conducted as approved. If noncompliance is detected, it may be a result of lack of understanding of the roles and responsibilities of individuals involved in research and/or inadequate training of staff. Monitoring will allow the IRB and HRPP to respond to any identified trends.

Post Approval Monitoring Process

The reason(s) for on-site review may include:

- random selections as part of a regular PAM cycle
- when IRB have cause that a non-compliance has occurred
- when there is unanticipated problems involving risk to subjects or others (UPIRTSO)
- projects where continuing review or reports from other sources have indicated that changes without IRB approval may have occurred or subjects were consented inappropriately
- subject or whistleblower complaints, or
- complex projects involving unusual levels or types of risks to subjects
- projects conducted by an investigator who previously failed to comply with IRB determinations
- requests by an investigator to review their human subject processes

The RQAU will be notified by the HRPP office of a need to conduct a for cause or random PAM review. The RQAU will contact the PI by email to notify them of PAM. The email will contain a pre-visit IRB assessment that the PI can use to prepare for the review. The questions included in the pre-visit IRB assessment can help PIs evaluate their own research programs. This can be a useful tool outside of a PAM review. The questions help identify potential noncompliance issues and allow the researchers to take appropriate action before items become serious and/or reportable problems.

The RQA staff will then pull the approved IRB protocols and compare procedures being conducted in the laboratory or study area with those listed in the approved protocol and any approved modifications. This will include reviewing study records, visiting with the PI to review consent documents and procedures and how subjects' confidentiality are protected.

The conduct of an on-site review may include but is not limited to:

- requests for progress report on human subjects recruited to date,
- examinations of research records, including signed informed consent documents, protocol modifications, and unexpected, serious, and/or related adverse experience reports,
- human subject compensation
- contacts with research subjects to determine their understanding of human subject procedures and processes (this will be done if RQAU is onsite during the consent process),
- observation of the consent process,
- study procedures, confidentiality measures, and general lab/record keeping.

The findings from the monitoring visit will be discussed with the Principal Investigator and the research staff. The draft memo will be submitted to the PI to review and sign prior to submitting to HRPP. The signed PAM memo will be submitted to the HRPP Director for submission to the IRB Executive Committee.

A written record of monitoring activities is maintained in the protocol study file and the RQAU file. Any of the following actions by the IRB may occur as a result of a monitoring report:

- Recommendation to implement corrective actions
- Request the post approval monitors review all active protocols of Principal Investigator
- Request subsequent post-approval monitoring visits
- Investigators to attend educational seminar
- Suspension of subject enrollment
- Suspension (protocol closed to treatment)
- Termination of IRB-HSR (Human Subjects Research) approval (protocol closed)
- Require protocol to be re-audited at specific time/ enrollment period
- Require PI to be mentored for a specific period of time
- Initiation of steps to disallow PI to conduct research for a period of time
- Require PI to notify subjects of non-compliance
- Notification of department head, dean, and institutional official
- Require PI to inform journals of noncompliance when submitting for publication
- Reporting of non-Compliance to federal agencies (required if suspension or termination occurred)
- Notification of all investigators at the Institution via education programs to ensure all are aware of regulations, so that the noncompliance would be less likely to happen again.

If there are concerns regarding scientific misconduct such as fraud notify the Research Integrity Officer.

Roles and Processes

Roles

Investigators and their staff will work with the RQAU and or HRPP Director and IRB member to observe and confirm procedures of an approved protocol.

The RQAU will observe research activity, prepare accurate reports, provide recommendations for maintaining compliance, provide information on training options when needed, and if appropriate, assist in execution of corrective and preventative actions.

The Director, HRPP, shall provide guidance to the RQAU and the Post Approval Monitoring Program, to assure that the IRB and the Institutional Official receive reports or updates on items of concern.

Protocol Selection

All studies, even those determined to qualify for exempt status, are subject to monitoring. Routine monitoring visits will *primarily* be randomly selected by the Director of the HRPP and a request sent to the RQAU; however, an emphasis may be placed on monitoring studies involving vulnerable populations, or unusual levels or types of risks to subjects.

A PI may also 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. Visits of this nature are encouraged as the goal of PAM is not to "catch" people, rather to assist investigators in conducting compliant research. When PI request a PAM review the following items are reportable:

1. Any serious non-compliance activity not approved by the protocol or amendments

2. Issues where subjects were inadequately consented
    a. subjects didn't sign consent form
    b. back dating of subjects signature
    c. falsifying subjects
    d. using a non-approved consent form

3. Any Unanticipated problems involving risks to subjects or others (UPIRTSO)
    a. unanticipated
    b. serious
    c. possibly related

Monitoring Process

The RQAU will schedule the PAM visit with PIs and their staff, making every attempt to facilitate schedules.

During the PAM visit, the RQAU will compare procedures being conducted in the laboratory or study area with those listed in the approved protocol and any approved modifications. This may include reviewing study records, visiting with the PI to review procedures being followed, observation of consent process, etc. Documented discrepancies between observed and approved activities will be brought to the attention of the PI. The RQAU will review and assess areas such as, but not limited to:

Research team composition and training
Recruitment procedures
Compensation
Screening procedures
Consent process
Study procedures
Publications from the study
Current enrollment and verification of informed consent
Reports of adverse events
Storage of study documents and data
Privacy and confidentiality issues
Subject payment
Questions and concerns from the PI and research team

Information Sharing Process
Following completion of the PAM visit, the RQAU will discuss observations with the PI and/or their staff prior to leaving the laboratory. If the PI is unavailable, the RQAU will schedule a time to discuss the results of the visit. Issues that pose an immediate threat to research participants will be brought to the immediate attention of the Director, HRPP.

A written memo of the PAM visit will be prepared by the RQA staff. This report will be signed by the PI and sent via file locker to the Administrator and Director, HRPP, who will then disseminate to the Executive committee and respective IRB board. Appropriate IRB processes will then be followed.

The HRPP Director will be informed of the progress of the review including trends, general items of concern, etc.

Recordkeeping
A copy of the final PAM memo will be kept by the RQAU, and a copy will be given to the IRB Administrator to be placed in the protocol file. Information will be tracked by the RQAU for trending. All files will be kept in a locked drawer or on server with Purdue two-factor authentication.

Pre-review Assessment for Post Approval Monitoring Program for the Protection of Human Subjects in Research

The goal of compliance monitoring is to confirm, by observation, accurate and consistent protocol performance in a collegial and unobtrusive manner. The program is also designed to help investigators, their teams, and the University prepare for external audits by granting, regulatory, and accreditation agencies.

Perhaps the most effective way to prepare for a PAM visit is to *carefully and objectively* read your approved protocol and make sure that you and your staff are performing the research activities *as described and approved by the IRB*. Many variables can play into the need for adjustment in the design, procedures, etc., of your protocol. The main thing to remember is any changes to the IRB approved protocol *must be approved by the IRB prior to implementation*. It is easy to get caught up in the progress of research and forget to submit a modification. Likewise, an issue may seem trivial to a researcher, but it may be of great concern to the IRB, federal regulators, or auditors.

The staff of the HRPP office are always willing to assist in answering questions or to help facilitate modifications to your protocol. They can be reached at 765-494-5942 or irb@purdue.edu

Questions and Tips
How many participants are currently enrolled in the study? Is the number enrolled in line with the number approved? Is a modification to add participants needed?

Are key personnel performing duties as described and approved? Are modifications needed?

Have there been early withdrawals from the study? Have they been reported during continuing review?

Have there been any adverse events? Were they reported?

Who is responsible for conducting study procedures? Are procedures in accordance with what was approved by the IRB?

Who is responsible for training study personnel? Are records of training maintained?

Is there a copy of the IRB-approved protocol on file? Including any continuing reviews and modifications? Are all personnel (i.e., PIs, co-PIs, research staff) aware of all approved modifications?

Do you have a copy of the approval letter on file?
Is the current version of the informed consent document being used? Does it have the IRB stamp?

Are waivers of documentation of consent in place for non-exempt on-line studies?

Are you using the IRB approved advertisements?

Are study documents (i.e., applications for approval, approval letters, informed consent) maintained for 3 years?

OHRP strongly recommends creating a file for each participant containing all study documents (i.e., consent, surveys, debriefings, etc.) when applicable.

Common Findings
Many common findings in noncompliance reviews center around the informed consent process and documentation. Below are examples of noncompliance findings:
The informed consent document on file is not complete (i.e., only the page containing the signature is on file).

Informed consent
- Informed consents are not dated by participants or signed by researcher
- Dates are added in by persons other than those giving or obtaining consent.
- Dates of consent occur after study procedures have begun.
- Dates of consent occur prior to receiving IRB approval of study.

Human Subject Compensation

- Logs are not kept of human subject compensation.
- Subjects who signed compensation logs are not the same as those consented.
- Compensation amount differs from that stated in the IRB.

Study records

- Study records are not STORED as indicated (i.e., storing other than removal for working on them, stored unsecured).
- Study records being reviewed by persons who are not approved or trained to do so.

Personnel

- Personnel are not CITI trained nor do they have accurate knowledge of approve protocol

If you have identified discrepancies between your current practices and those outlined in the approved protocol, please make the appropriate corrections. This may require submitting a modification to your protocol or simply implementing better documentation practices.

Remember, the goal of post approval monitoring is not to "catch" you doing something you aren't supposed to be doing. Rather, it is designed to facilitate research by making sure it is conducted in a manner where the conditions of federal regulations and University policy are met and by assisting researchers to identify and correct any deficiencies

Regulatory Agencies

The Common Rule
17 Signatory agencies, including DHHS, FDA, and DoD
Human Subjects Research
45 CFR 46
21 CFR 56
32 CFR 219

Additional FDA regulations
21CFR 312 (drug)
21CFR812 (device)

State of Indiana Regulation on administering drug for research

Office for Human Research Protections (OHRP)

U.S. Department of Health and Human Services (HHS), Office for Human Research Protection (OHRP)
Terms of the Federalwide Assurance (FWA)

Purdue Policies:

Human Research Protection - Office of the Executive Vice President for Research and Partnership

HRRP Policies, Procedures & Guidelines