Human Subjects Post Approval Monitoring

Introduction

Post Approval Monitoring (PAM) 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, 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. The program is designed to help investigators, their teams, and the University prepare for external audits by granting, regulatory, and accreditation agencies and to serve as a compliance resource to the research community.

PAM visits and reviews are conducted by the Research Quality Assurance Unit (RQAU), a group within the Office of the Vice President of Research (OVPR). The RQAU role is to review and monitor Purdue's research administration and research regulatory compliance practices and provide leadership when conducting comprehensive reviews of the University's compliance activities.

When conducting a PAM review the RQAU will 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, advise the principal investigator (PI) of any deviations from the approved protocol, provide reports to the IRB, via the HRPP Director, suggest improvements and if needed, assist in implementing any required changes.

Additionally, the RQAU can assist the Human Research Protection Program (HRRP) and IRB 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

Post-approval monitoring is conducted by Research Quality Assurance staff within the Office of the Vice President for Research in accordance with their Standard Operating Procedures.

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

- random selections as part of a regular monitoring cycle
- requests by an investigator to review their human subject processes,
- complex projects involving unusual levels or types of risks to subjects,
- projects conducted by an investigator who previously failed to comply with IRB determinations,
- 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
- request by the IRB.

The role of the RQAU is to confirm by observation that research activity is being performed in accordance with approved IRB protocols and institutional Standard Operating Procedures (SOPs).

The principal investigator will be notified of post approval monitoring selection by phone and a letter/email will follow with the details of the scheduled visit. The PI will be sent an Investigator Self-Assessment Checklist for IRB Protocol Post-Approval Monitoring. This can be use by the PI to prepare for the PAM review.

The questions included in the PI Self-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.

As part of a PAM review, there will be an initial visit by the RQAU staff member with the principal investigator to discuss the process and answer and questions.

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,

- 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 and recommendations from the monitoring visit will be discussed with the Principal Investigator and the research staff.

The draft PAM report will be submitted to the Director of the HRRP and the Institutional Official (IO).

The final PAM report will be submitted to the HRPP Director for submission to the IRB Executive Committee. Aggregate summaries of reports will be submitted to the full membership of the IRB on a periodic (quarterly or other) basis.

When accepted by the IRB, the report findings and Executive Committee recommendations are forwarded to the principal investigator for response and resolution of any outstanding issues. The report findings may also be forwarded to the VPR, and others, including federal regulatory agencies, as deemed necessary by the IRB.

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

- 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, Human Research Protection Program (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.

Monitoring visits may also be "directed" by the IRB.

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
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 report of the PAM visit will be prepared by the RQA staff. This report will be reviewed internally by the 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 visit report 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.

PI Self-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 post approval monitoring (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 Human Research Protection Program (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).

Dates

- Informed consents are not dated by participants
- 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.

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.

Master lists

- Master lists of participants are not created or maintained on studies that are large or contain different phases, making tracking of consent and procedures performed difficult.

If you have identified discrepancies between your current practices and those outlined in the approved protocol and these questions, 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.

INVESTIGATOR SELF-ASSESSMENT CHECKLIST FOR IRB PROTOCOL POST-APPROVAL MONITORING

For Expedited and Full Board IRB Protocols

Responsible Project Investigator: _____ IRB#:_____ Date:_____

Project title: _____

Approval and Record Keeping	Yes	No	NA	Corrective actions
The project has current IRB approval.				
All IRB related records (approval letter, application, signed consent forms, continuing review activities & correspondence) has been retained in an accessible location. All records must be kept for at least 3 years after completion of the research.				
All investigators listed on this project are currently certified in the human subjects protection training.				
Were there any changes to the approved project since the last continuing review? If yes, was a revision submitted to the IRB?				
Consents	**Yes**	**No**	**NA**	**Corrective actions**
Was the IRB approved (with footer or stamp) version of the consent(s)/assent(s) used to enroll subjects?				
Were all consent forms (with footer or stamp) signed by subjects prior to enrollment?				
If using an oral consent, the IRB approved script was used to enroll subjects.				
Do you have a signed and dated consent form on file for every subject enrolled in the study?				
If changes were made to the consent form, were the changes submitted and approved by the IRB?				

Recruitment	Yes	No	NA	Corrective actions
Subjects were identified and recruited according to the methods approved by the IRB.				
Any advertising or recruitment materials used to recruit subjects were approved by the IRB.				
All eligibility and ineligibility requirements as listed and approved by the IRB were followed. Any deviations were reported to the IRB.				
If subjects received any compensation is there documentation?				
Research Protocol	**Yes**	**No**	**NA**	**Corrective actions**
Research conducted complies with the project description and procedures as approved by the IRB.				
All data collection instruments used were those approved by the IRB.				
Privacy, Data Storage and Confidentiality	**Yes**	**No**	**NA**	**Corrective actions**
The subject's privacy is protected and safeguards are in place as approved by the IRB.				
If you proposed to collect the data anonymously, has anonymity been maintained in the physical or electronic records?				
Are hard copies (consent forms and data forms) stored in a secure, locked location?				
Is electronic data on a secure and protected computer? Are you aware of the security on your computer and server?				

Privacy, Data Storage and Confidentiality - Continued	Yes	No	NA	Corrective actions
Are electronic data files password protected?				
Is access to computer, electronic files, and physical files limited to appropriate study personnel?				
Was the research data (raw) stored/disposed of as described and approved by the IRB?				
Continuing Review	**Yes**	**No**	**NA**	**Corrective actions**
Are you aware of when your project expires? Have you placed a reminder on your schedule to submit a renewal form 4 weeks prior to the expiration?				
Have there been any lapses in IRB approval? If yes, did you report any research activity that was done during the lapse?				
Have there been any adverse events (AE) or unanticipated problems, complaints or subject withdrawals while conducting this research? If yes, have all details been reported to the IRB?				
Have there been any new findings to change the risk benefit ratio?				
Closure	**Yes**	**No**	**NA**	**Corrective actions**
If your project is complete, or you are performing data analysis only on anonymous or de-identified data, can you close the protocol?				

If you would like to discuss any aspects of your self-assessment contact the: IRB Staff or HRPP at 765-494-5942 or irb@purdue.edu
Or RQAU staff at 765-494-4590 or horton1@purdue.edu

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 Vice President for Research

HRRP Policies, Procedures & Guidelines