UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
AUDIT SERVICES

Human Research Protection Program
Post Approval Event Reporting
Audit Services Project #14-059

March 2014

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Research Compliance
Human Research Protection Program
Project #14-059

MANAGEMENT SUMMARY

As a supplemental audit for Fiscal Year 2014, Audit Services conducted a review of the Post-Approval Event Reporting (PAER) process and associated policies and procedures within the UCSF Human Research Protection Program (HRPP). The objectives of the review were to assess the effectiveness of the controls over the PAER process to ensure timely reporting of adverse events and protocol violations, including unanticipated problems and serious or continuing non-compliance, to the Institutional Official and outside agencies.

The Common Rule 45 CFR 46 and 21 CFR 56 is the federal regulations governing the reporting of unanticipated problems in clinical research. It requires that unanticipated problems and serious or continuing non-compliance must be reported promptly to the Institutional Review Boards, Institutional Official, and outside agencies. The purpose of prompt reporting is to ensure that appropriate and timely actions are taken to protect human subjects from avoidable harm, regardless of whether or not the research is subject to other federal regulations.

The HRPP's established PAER process is for Principal Investigators to self-report adverse events relating to human subject research that impact or change the research risks and or benefits. Submissions by Principal Investigators are initially triaged by the Quality Improvement Unit within HRPP. The Quality Improvement Unit ensures completeness of vital data and forwards potential reportable submissions to the Institutional Review Board for determination if reporting is required and approval of corrective actions, where applicable. As of December 2013, there were 245 adverse events and 322 protocol violations submitted during the year, of which 20 adverse events and 33 protocol violations were submitted to the Institutional Review Boards to review and 10 adverse events and 9 protocol violations were determined to have met the reporting requirements.

From the work performed, process improvements need to occur to ensure that submission and reporting timelines comply with existing HRPP policies and meet regulatory reporting guidelines. Tracking and monitoring mechanisms need to be in place to enable enforcement of policies and procedures as well as to measure the timely reporting of adverse events, assess the effectiveness of the processes, and identify potential issues much earlier so that remedial actions and/or resources may be deployed accordingly. Lastly, the reporting process may be enhanced through automation of some processes and greater use of the reporting system, Integrated Research Information System.

More detailed information can be found in the body of this report.

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GLOSSARY OF KEY TERMS

1. **Unanticipated problem (UP)** – involving risk to participants or others and is an unexpected, research-related event where the risk exceeds the nature, severity, or frequency described in the protocol, study consent form, Investigator's Brochure or other study information previously reviewed and approved by the CHR.

2. **Serious Noncompliance (SNC)** – failure to follow regulations, University policies or determinations of the CHR for the protection of the rights and welfare of study participants and that, in the judgment of the CHR, results in, or indicates a potential for a) a significant risk to enrolled potential participants or b) compromises the effectiveness of the UCSF HRPP or the University.

3. **Continuing Noncompliance (CNC)** – a pattern of noncompliance that continues to occur after a report of noncompliance and a corrective action plan have been reviewed and approved by the CHR.

4. **Unexpected Adverse Event (UAE)** – the event exceeds the nature, severity, or frequency described in the current CHR application including the protocol, consent form and investigator brochure (when applicable).

5. **Serious Adverse Event (SAE)** – any adverse event that resulted in death, life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, etc.

6. **Protocol Violations (PVS)** - any unapproved changes in the research study design and/or procedures that are within the investigator's control and not in accordance with the CHR-approved protocol that may affect the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. All major violations must be reported to the CHR/HRPP.

I. BACKGROUND

As a supplemental audit for Fiscal Year 2014, Audit Services conducted a review of Post-Approval Event Reporting (PAER) process and its related policies and procedures within the UCSF Human Research Protection Program (HRPP). The HRPP program is a subset of the Research Compliance Program under the Office of Ethics & Compliance and is accredited by the Association for Accreditation of HRPP (AAHRPP), an entity for evaluating and recognizing HRPPs that meet or exceed the federal regulatory requirements for protection of human subjects.

Reporting of adverse events (AEs) is governed by Federal Regulations under 45 CFR 46 and 21 CFR 56 which require that Unanticipated Problems (UPs) and Serious or Continuous Non-Compliance (S/CNCs) must be reported promptly to the Institutional Review Board (IRB), Institutional Official (IO) and outside agencies[1]. The purpose of prompt reporting is to ensure that timely actions are taken to protect human subjects from avoidable harm, regardless of whether the research is subject to federal regulation. Failure to comply may subject the institution to potential liability and enforcement, including advisory, judicial, and administrative actions depending on the seriousness of the violation.

One of the primary roles of the HRPP is to perform post-approval monitoring on the conduct of clinical research in order assure the rights and welfare of human research participants are protected. Monitoring is done in two ways: (a) proactively through Routine or Directed Site Visits of high risk research projects that are not monitored by outside agencies and (b) through Principal Investigators (PIs) self-reporting of UPs while the study is open and approved by the IRB. Both of these monitoring activities are critical in meeting regulatory requirements, institutional policies, and research protocols approved by UCSF's four IRB panels.

PAER is the established process within HRPP for PIs to self-report adverse events and protocol violations (PVs) and other events or safety information (OE/SI) relating to human subject research that impact or change the research risks and or benefits. PAER is managed by the Quality Improvement Unit (QIU) within HRPP that performs the initial triage of PAER to ensure completeness of data and forwards only potential reportable AEs and PVs to the IRB for determining and reporting. As of December 2013, the number of AEs and PVs reported during the year and their disposition was as follows:

Incidents Reported	Adverse Events	Protocol Violations
Total Submitted	245	322
Reviewed by IRB	20	33
Met Reporting requirements	10	9

Implemented in August 2010, the Integrated Research Information System (iRIS) facilitates online submission of research protocol applications and manages all aspects of human research subject protection review. Specific to the PAER process, there are three standard forms (AE, PV and OE/SI) designed to assist PIs in populating relevant information to enable the IRB chairs and the IRBs to determine and report UPs and S/CNCs.

[1] OHRP Guideline defines Unanticipated Problem as any incident that meets all three criteria: unexpected (in nature, severity or frequency), possibly related to research participation, and serious or suggested research puts the subject at greater risk of harm than previously known. Adverse event is any untoward or unfavorable medical occurrence in a human subject. Not all adverse events and protocol violations are unanticipated problems.

II. AUDIT PURPOSE AND SCOPE

The objectives of the review were to assess the PAER process and related policies and procedures to ensure that:

a) Effective internal controls exist for timely reporting of AEs and PVs including UPs and S/CNC to outside regulatory agencies;
b) HRPP policies and procedures are aligned with regulatory requirements on reporting AEs; and
c) HRPP practices for processing AEs comply with internal policies and procedures.

In order to achieve our objectives, we performed the following:

- Interviewed staff members and the management team within HRPP to understand the PAER process;
- Reviewed relevant UCOP, UCSF and other campuses' policies on UPs and S/CNCs to gain an understanding of policies, best practices, and issues relating to the PAER process;
- Reviewed federal regulations and Office of Human Research Protection (OHRP) guidelines on definitions of prompt reporting of serious AEs, UPs, and S/CNCs;
- Reviewed AAHRPP accreditation process and standards to understand accreditation procedures and standards;
- Reviewed R/DSVs in relation to UPs and S/CNCs;
- Reviewed AE and PV submissions for the scope period to determine the compliance rate with internal policies and procedures as well as adherence to outside regulatory reporting guidelines; and
- Reviewed iRIS functionalities as they relate to the PAERs process.

Work performed was limited to selected samples of AEs and PVs for calendar years 2012 and 2013; as such, this report is not intended to, nor can it be relied upon to provide an assessment of the effectiveness of controls beyond the PAER process specifically reviewed. Fieldwork was completed in December 2013.

III. CONCLUSION

Based on the work performed, submission of AE and PV reports by PIs and issuance of letters to outside agencies are not consistently meeting HRPP requirements. Additionally, the existing PAER reporting process is not effective in ensuring timely reporting of AEs, PVs, UPs and S/CNCs to the IO and outside agencies and in meeting OHRP guidelines for prompt reporting. The PAER process is duplicative; it requires review by multiple parties, including QIU staff members, PIs, IRB chairs, IRBs and the IO. Therefore, to meet OHRP guidelines, evaluation of the existing process should occur to be more streamlined to gain efficiencies. Additionally, comprehensive metrics have not been developed to measure critical PAER process points to detect, address and resolve bottlenecks.

At the time of the review, HRPP had taken some preliminary measures to improve the reporting process by initiating the tracking of turnaround times. Additionally, they have modified their triage process by expediting AE submissions directly to IRB review where there is certainty that the submission was likely to be a UP or S/CNC.

IV. OBSERVATIONS AND MANAGEMENT CORRECTIVE ACTIONS

A. Policies & Procedures

1. Policies and procedures for reporting of AEs and PVs are not being followed nor enforced.

According to HRPP policies and procedures, PIs are required to report AEs and PVs within 10 days of awareness. Additionally, QIU is required to issue a letter to the IO, outside agencies and OHRP within 7 days after IRB determination has been made and the corresponding letter is sent to the PI.

Review of AE and PV submissions between January and September 2013 indicated that:

- 31% of the 16 AEs and 45% of the 33 PVs reported are submitted more than 10 days after PI awareness. Reporting ranged from 13 to 29 days for AEs and up to 103 days for PVs.

- 42% of the 12 agency letters were issued between 7 to 14 days after IRB determination.

Additionally, we noted that HRPP does not have a monitoring process in place to identify PIs that are repeatedly reporting late. Therefore, there is limited or no enforcement of the policies and procedures.

Untimely reporting and lack of detective controls to identify non-compliance with meeting regulatory requirements can adversely affect the institution's ability to ensure appropriate and timely actions are taken to protect human subjects from avoidable harm.

Management Corrective Actions

By June 30, 2014, HRPP will take the following actions:

1. Clarify and document the specific criteria for AE and PV reporting.

2. Educate and communicate to PIs and others the importance of timely AE and PV reporting for compliance with HRPP policies and procedures and OHRP guidelines.

3. Consider automating processes, where possible, for tracking and monitoring AE and PV reporting.

4. Develop an escalation process for PIs that are repeatedly reporting untimely and/or are non-compliant with established policies and procedures.

2. The existing HRPP policies and procedures do not have provisions to meet OHRP guidelines in reporting UPs to IO and outside agencies within 30 days[2].

OHRP and FDA requires that institutions have written policies for 'prompt' reporting of UPs, without defining specific timelines as to what is considered 'prompt.' However, in 2007 OHRP published guidelines that recommended reporting of UPs that are serious AEs to the IRB within 7 days of PI awareness, any other UPs to be reported within 14 days to the IRB, and all UPs to the IO, supporting agencies, and OHRP within 30 days of receipt by IRB. Separately, FDA recommends reporting of UPs to the IRB "as soon as possible, but no event later than 10 working days from PI awareness."

Our review of the HRPP policies and procedures against the OHRP guidelines and analysis of report submission data identified the following:

a) HRPP Standard Operating Procedures do not define the reporting timelines to the IO and outside agency as within 30 days after PI submission.

   The procedures only require that AEs and PVs be submitted by PIs within 10 days of awareness and that reporting to the IO and outside agency occur within 7 days of the determination letter being issued to the PI.

b) Reports to the IO and OHRP/FDA were not always completed within 30 days of receipt by IRB.

   Review of reporting data from iRIS between February 2013 and September 2013 determined that it took a median of 33 days to issue determination letters to PIs after PI submission. Further, it took a median of 14 days to issue letters to the IO and outside agencies.

   Additionally, the established reporting process involves several critical process points that require actions by related parties or individuals outside of HRPP, including PIs, IRB chairs, IRBs, and the IO for which turnaround time has not been defined.

3. Process inefficiencies exist that are either duplicative or can significantly add to the reporting timeline.

The current process is not conducive to meeting the OHRP guidelines of 30-day turnaround time for processing AE/PV submissions and notifying the IO and outside agencies due to the following:

a) Duplicative Triage Points – AE/PV submissions are initially triaged by the QIU, and then forwarded to IRB chairs for re-evaluation before they are submitted to the IRBs for final determination and reporting. The median turnaround times for submissions are within 1 day for QIU and 8 days for IRB chairs.

b) IRB Review Schedules - Since IRBs meet every two weeks and AEs and PVs are reported only to the IRBs that approved the research protocol, the review and reporting process are prolonged and delayed.

[2] The OHRP guidelines issued in 2007 stem from The Common Rule (45 CFR 46). Both OHRP and FDA state that these are recommended guidelines that are not established to be legally enforceable.

c) Follow-up with PI - As each report submission may be different, follow up questions with PIs by either QIU or IRB chairs are common and time consuming, further delaying the reporting.

Management Corrective Actions

1. By June 30, 2014, HRPP will complete the following:
   a. Adopt the 30 day reporting guideline and reassess the viability of the current AE and PV reporting process internally and with appropriate responsible parties.
   b. Revise procedures to ensure timely reporting, including:
      i. Clarification on whether the QIU is considered part of the IRB when determining compliance with OHRP guidelines
      ii. Identification of the unit(s) that are most suited to make UP and SCNC determinations; and
      iii. Establishment of criteria that will be used for the UP and SCNC determination.

2. Communicate revised policies and procedures to all affected parties by September 30, 2014.

B. Reporting and Metrics

1. The current metrics used to track AE and PV reports are not sufficiently comprehensive for monitoring the effectiveness and timeliness of reporting of UPs and S/CNC.

Two metrics specific to PAERs transactions, volume and median approval time, are shared regularly at Group Policy meetings and with IRB representatives. However, there are no comprehensive metrics developed and reported that allow management to fully monitor and assess the process. Such metrics should include volume of reports submitted, statuses of the reports, aging of the various hand-offs, report outcomes, etc. Having useful metrics will allow management to monitor for compliance with regulatory requirements, identify potential bottlenecks in the reporting process and prioritize resources, when necessary, to meet OHRP reporting guidelines.

The lack of comprehensive metrics impairs management's ability to make business decisions to assist with meeting regulatory requirements.

Management Corrective Actions

By September 30, 2014, HRPP will determine the critical points within the reporting process that warrant monitoring and will establish appropriate metrics and reports.

2. The reporting process for Continuing Non-Compliance (CNC) events is ineffective and time consuming.

In the current environment, in order to determine CNCs, QIU has to review historical AE and PV reports, which can be time consuming. Additionally, if PIs have multiple studies with different IRBs, it can further complicate and increase resource time in identifying CNCs. Because of this labor intensive manual process, very few CNCs are identified and reported. For the period CY 2010-2013 a total of 9 CNCs was reported.

The lack of an effective process for identifying CNCs increases the risk that all CNCs may not be reported to the IO and outside agencies.

Management Corrective Actions

By December 31, 2014, HRPP will evaluate and revise their current process for recording, monitoring, and tracking of non-compliance reports to improve the identification and reporting of CNCs. The evaluation will include consultation with the iRIS System Administrator for system automation capabilities for the tracking of non-compliance outcomes for AEs and PVs by categories to improve efficiency.

3. PVs are not properly categorized for CNC reporting.

The PV form is designed for PIs to report major PVs and major incidents to the IRB. Since most major PVs meet the regulatory and the University definition of non-compliance events, it would be more accurate to mark these as “non-compliance” as opposed to the current designation of “acknowledged.” This change in designation to “non-compliance” would enable better and more accurate tracking and reporting of CNCs. Additionally, IRB chairs currently only have the authority to mark PVs as “acknowledged” if the event is not an UP.

Incorrect or vague classification prohibits proper tracking and detection of continuing non-compliance reportable to the IO and outside agencies.

Management Corrective Actions

By December 31, 2014, HRPP will assess the appropriateness and feasibility of replacing ‘acknowledged’ with ‘non-compliance’. In conjunction with this assessment, delegations to IRB chairs will be evaluated to allow for non-compliance determination.

C. System Enhancements

Opportunities may exist for greater utilization of the iRIS system to improve the reporting process.

Our review identified a number of areas (listed below) where greater use and/or enhancements to the iRIS system can create efficiencies as follows:

1. Dates for notifying and obtaining approval from the IO and letters sent to outside agencies are recorded outside of the iRIS system. As such, QIU manually captures

this data in order to track and monitor the timeliness of reporting, which can be cumbersome, time consuming, and prone to human error.

2. PV forms do not capture information such as PV event date and specific deviation details in order to reduce follow-up time with PIs by QIU.

3. Date fields are not configured as required fields; consequently, they can be left blank, which hinders calculation and tracking of timeliness. Also, date fields do not have data integrity check, so dates entered may be earlier than the submission date, causing negative day calculations.

Management Corrective Actions

By December 31, 2014, HRPP will consult with the iRIS system administrator to evaluate and implement system enhancements to improve the tracking and monitoring process. If system enhancements are not feasible, a more streamlined manual tracking and monitoring process will be developed.

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