

Guidance and Procedures Number: 55
Title: On-Site Reviews of Human Research Studies
Date of Last Revision: February 26, 2009

I. General Overview

- A. ***HRPP Quality Improvement and Assurance:*** As part of its quality assurance and quality improvement efforts, the UCLA Human Research Protection Program (HRPP) has developed a plan to measure and improve the effectiveness, quality and compliance with organizational policies and procedures and applicable federal, state, and local laws. A major part of this plan is the implementation of a Quality Improvement Program (QIP) within the OPRS HRPP. The HRPP has the authority and responsibility for continuing oversight of approved human research protocols based on federal regulations, University policy and UCLA's Federal Wide Assurance (FWA) with the federal Office for Human Research Protections (OHRP). The charge of the HRPP QIP includes the conduct of on-site reviews of IRB approved-protocols as well as ongoing random reviews of IRB decisions, determinations and documentation.
- B. ***On-Site Reviews of Human Research Studies:*** On-site reviews may be either routine or for-cause. The on-site review function is a core component of the UCLA HRPP and is performed to promote quality and integrity in the conduct and methodology of human subjects research. On-site reviews will also be conducted by the School of Medicine Quality Assurance Program as described below. The on-site reviews enable the HRPP to identify current trends in the implementation of human research and the dissemination to the research community of information regarding both best research practices and common findings in human research. Findings from the on-site reviews are communicated to the IRB(s) and provide an additional level of quality assurance and adherence to compliance for Principal Investigators and their research teams as well as the IRBs. The HRPP QIP and well as the School of Medicine QA Program also presents an additional level of safeguards for subjects in research at UCLA as the on-site reviews also include a targeted educational component.
- C. ***School of Medicine Quality Assurance Program:*** The UCLA School of Medicine has also developed a quality assurance program that will conduct routine on-site reviews of studies selected according to the criteria in Section III.B below.
- D. ***Coordination with Other QI/QA Units:*** The HRPP QIP coordinates activities with other Quality Assurance/Improvement Units on campus, including the School of Medicine QA Program, to make sure that all significant findings are reported to the IRB and that any corrective actions that are needed are developed and implemented in a timely manner.
- D. ***Significant Findings:*** Per federal regulations, research participants must be informed when there is a significant new finding during the course of research that may affect their willingness to participate. Examples of significant findings from site monitoring or audit activities include, but are not limited to, any of the following:

1. Conducting research without prior IRB approval (including during any period of protocol lapse).
2. Material changes to IRB-approved research without prior IRB approval.
3. Enrolling participants who did not meet key safety-related study entry criteria.
4. Enrolling vulnerable participant populations not identified and approved in the IRB-approved application.
5. Failure to report study-related information that may place participants or others at increased risk (unanticipated problems).

II. Policy

All researchers are expected to comply with the provisions of an IRB-approved protocol and to adhere to all federal and state regulations and UC/UCLA policies governing human subjects research. The Institution supports and maintains compliance with applicable federal regulations and state laws related to the protection of the safety, rights and welfare of human subjects in research under the terms of UCLA's Federal Wide Assurance (FWA).

III. QIP Process for On-Site Reviews

A. *Initiation of QIP On-Site Reviews:* On-site reviews are initiated may be initiated by but are not limited to the following ways:

1. A Department Chair or Division Chief may request a preventive on-site review for any clinical research studies in the department or division.
2. Principal Investigators may request a preventive on-site review for any of their own studies.
3. IRB Chairs and/or IRB Committees may request on-site reviews for issues that have been previously identified by the IRB.

B. *QI/QA Procedures for Routine On-Site Reviews:*

1. Selection of Studies for Routine On-Site Reviews:
 - a. The OPRS QIP will randomly select a sampling of studies that meet the following criteria:
 - i. Risk level is more than minimal according to federally definitions;
 - ii. Review and approval has occurred by one of the UCLA Medical IRBs; and
 - iii. Vulnerable populations as defined by federal regulations [45 CFR 46.111(b)], that is, Children, Pregnant Women and Neonates and/or other groups of vulnerable populations including the Cognitively Impaired or Mentally Disabled Persons, or Economically and/or Educationally Disadvantaged are included as subjects in the study.
 - b. The School of Medicine Quality Assurance Program will randomly select a sampling of the following types of studies:
 - i. Investigator Initiated Phase I, II, III studies,
 - ii. Studies involving investigational drugs and devices;
 - iii. Substance abuse studies;
 - iv. Research involving recombinant DNA;

- v. Studies in which there is a high probability that the study interventions that prevent or treat diseases may lead to irreversible morbidity or death.
- 2. Notification of the Principal Investigator: An HRPP/OPRS QIP reviewer will contact the PI in writing informing the PI of the upcoming review at least 3 weeks in advance of actual visit.
- 3. Scheduling and Coordinating the On-Site Review:
 - a. The on-site review will be scheduled at a convenient date and time for the PI.
 - b. The On-Site Review Form will be sent to the PI prior to the site visit to ensure the PI and research team's awareness of the documents that will need to be available for the review and the extent of the review.
 - c. E-mail confirmation will be sent 3 days prior to site visit.
- 4. The On-Site Review Process:
 - a. The focus of review is on subject safety and compliance with the IRB- approved protocol.
 - b. The review generally lasts from three to four hours.
 - c. Every effort will be made to minimize the impact of the visit on the PI and the research team. For example, the PI does not need to be present for the entire site visit, but will need to designate a representative to be present for the entire review. The PI does needs to be available by pager or cell phone, however.
 - d. The documents described in item #4 below will be reviewed.
 - e. The visit will provide an opportunity for the researchers to ask and have answered any particular questions about the safe conduct of their research and for the QIP staff to provide individualized training and education as needed.
 - f. An exit interview will occur at the end of the visit. If no significant findings or areas of concern are identified during the review, the PI designee may represent the PI at the exit interview. If there are significant findings, the QIP staff will discuss these ask the PI to be available during the discussion of these findings.
- 5. Document Review Details: At a minimum, the following documents and processes will be reviewed in either or both the OPRS HRPP office as well as on site:
 - a. The informed consent documents, process and the availability of the signed consent forms in the research files;
 - b. HIPAA documentation;
 - c. Subject research records (either a sample or all, the number to be determined depending on size of enrollment);
 - d. Post-approval reports (adverse events, protocol violations and/or incidents, and other safety reports (i.e., DSMB reports);
 - e. Subject eligibility (inclusion/exclusion criteria), and source documentation;
 - f. Drug/Device Accountability documents;
 - g. Assessment of the research team's workload and availability of sufficient resources.
- 6. The QIP On-Site Review Report:
 - a. The report is prepared within five wording days after the QIP review.
 - b. The report will include an assessment of the study's compliance with federal regulations, state and local laws, university policies, and the IRB-approved protocol requirements.

- c. If any significant findings as described in I.D. above are revealed, the report will recommend a corrective action plan and identify any additional education that may be needed for the research team.
7. IRB Review of the QIP Report:
- a. The report will be forwarded to the appropriate IRB Chair for review.
 - i. The Chair may approve and sign off on the report as submitted.
 - ii. The Chair may determine that the findings represent possible unanticipated problems or evidence of possible noncompliance and should be reviewed by the Full Committee.
 - b. If the Full Committee determines that the report reflects either unanticipated problems or serious and/or continuing noncompliance, these will be addressed as described in [HRPP Guidance and Procedure #57: Post Approval Reporting Requirements for Investigators](#), [HRPP Policy #53: Noncompliance and Allegations of Noncompliance Regarding the Conduct of Human Subjects Research](#) and reported as described in [HRPP Guidance and Procedure #60: IRB Reporting Procedures](#).
 - c. IRB reports are provided with five working days of IRB review.

IV. QIP Process for For-Cause On-Site Reviews:

A. ***Initiation of For-Cause On-Site Reviews:*** These reviews are performed when concerns regarding research compliance, protocol adherence, or subject safety are brought to the attention of the IRB and may be initiated as follows:

1. Internally by but not limited to any of the following:
 - a. Vice Chancellor of Research
 - b. Institutional Review Board
 - c. Department of Medicine Office of Clinical Trial Research Compliance
 - d. School of Medicine Dean's Office
 - e. Department Chairs or Division Chiefs
 - f. School of Medicine Clinical Research QA Committee
 - g. Audit and Advisory Services
 - h. Privacy and Compliance Office
 - i. Subject, Staff, Whistleblower Complaints
 - j. Claims of Subject Injury
 - k. Risk Management
 - l. Other University Officials
 - m. UCLA-IRB HS-4 Continuing Review
2. Externally by but not limited to the following:
 - a. Office of Human Research Protection (OHRP)
 - b. Food and Drug Administration (FDA)
 - c. National Institute of Health (NIH)
 - d. Department of Defense (DOD)
 - e. Department of Energy (DOE)
 - f. Department of Navy (DON)

B. ***QIP Procedures for For-Cause On-Site Reviews:*** The procedures for these reviews will be the same as those for Routine On-Site Reviews as described in III.C. above with the following exceptions:

1. If the review is initiated externally, the QIP will notify the Principal Investigator as well as the appropriate university officials including but not limited to the Vice Chancellor for Research and the Department Chair.
2. The Principal Investigator will be notified by phone at least twenty-four hours in advance of the site visit.
3. The on-site review will focus on the allegations or concerns that resulted in the for-cause review, although it will include all relevant and pertinent information as described above in III.C above.

V. Principal Investigator Responsibilities

- A. Investigators and all research personnel involved in the study are required to cooperate with any routine or for-cause on-site visits conducted by the QIP and/or on behalf of the IRB.
- B. Investigators are required have the documents available for review at the site at which they are kept and shall provide the review personnel with space there to conduct the review.
- C. Investigators are required to prepare and implement any corrective action plans as required by the IRB.

VI. Reporting Requirements

- A. Any IRB determination of serious and/or continuing noncompliance; any suspension or termination of IRB approval according to [HRPP Policy #53: Noncompliance and Allegations of Noncompliance Regarding the Conduct of Human Subjects Research](#), [HRPP Guidance and Procedure #59: Suspensions and Terminations of Research](#) or [HRPP Guidance and Procedure #57: Post Approval Reporting Requirements for Investigators](#) the outcome of the IRB's actions are reportable to the appropriate federal department or agency head(s) and Institutional official according to [HRPP Guidance and Procedure #60: IRB Reporting Procedures for Post Approval Reporting, Noncompliance, Suspension, or Termination](#).
- B. Any IRB and/or Vice Chancellor for Research determination of serious and/or continuing noncompliance with respect to the IRB or the Institution and the outcome of the IRB or Vice Chancellor's actions are also reportable to the appropriate federal department or agency head(s) and appropriate institutional officials according to [HRPP Guidance and Procedure #60: IRB Reporting Procedures for Post Approval Reporting, Noncompliance, Suspension, or Termination](#).

Regulations:

Food and Drug Administration:

- (21 CFR 56.109(f)) An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.
- (21 CFR 56.108(b)) The FDA requires that institutions follow “written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA of: (1) Any unanticipated problems involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or (3) any suspension or termination of IRB approval.”

Department of Health and Human Services:

- (45 CFR 46.103(b)(5)) requires that institutions have “written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this guidance or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval.”
- (45 CFR 46.109(e)) states that “An IRB shall conduct continuing review of research covered by this guidance at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.”
- (45 CFR 46.113) states that “An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.”

References:

Office of Human Research Protection:

- U.S. Office for Human Research Protections' (OHRP, formerly OPRR) *Protecting Human Research Subjects Guidebook (1993)*.
- OHRP, *Compliance Oversight Activities: Significant Findings and Concerns of Noncompliance*, October 12, 2005. <http://hhs.gov/ohrp/compliance/findings.pdf>
- OHRP, *Guidance on Reporting Incidents to OHRP*, May 27, 2005. http://hhs.gov/ohrp/policy/procedures_for_reporting_052505.pdf
- OHRP, *Guidance on Written IRB Procedures*, January 15, 2007. <http://hhs.gov/ohrp/humansubjects/guidance/irbqd107.pdf>

Food and Drug Administration: FDA, *IRB Information Sheet- Continuing Review after Study Approval*, September 1998. <http://www.fda.gov/oc/ohrt/irbs/review.html>