Issuing Department: Human Subjects Protection Program (HSPP)
Policy Number: 2009-005.0
Policy Title: Monitoring of IRB Approved Studies

Purpose

The purpose of this policy is to grant authority to the Research Compliance Monitor (RCM) within the HSPP to conduct audits of all studies approved by the Institutional Review Board (IRB), to identify the functions of the RCM, to identify the types of audits that may be conducted, and to articulate the obligations of investigators when audits, inspections or monitoring visits are conducted, including those conducted by an external body.

Definitions:

See policy 2011-007.0 for definitions of:

Non-compliance, Continuing, Termination	Non-compliance, Serious	Suspension
	Unanticipated Problem Involving Risk to Subjects or Others	

Policy

It is the policy of the HSPP that, approved studies (including those approved as exempt, and those approved under facilitated review) are subject to monitoring/audit by the RCM of the HSPP. The Education Specialist, Regulatory Specialists or other appropriate staff within the HSPP may provide coverage for or assistance with all aspects of the RCM function if necessary.

The functions of the RCM include, but are not limited to, ensuring that studies are being conducted in compliance with the approved protocol and supporting documents, that appropriate forms are being used, that consent is being appropriately obtained and documented, that modifications are receiving approval prior to implementation, that financial interests are being appropriately disclosed and when applicable managed, that unanticipated problems and non-compliance are being reported per policy, that data are being recorded accurately, that drug and device inventory is accurate, that study functions have been appropriately delegated, that HIPAA is appropriately addressed, and that procedures for safety monitoring and to protect privacy and confidentiality are being followed. The RCM may observe the consent process and the conduct of the research. The RCM also audits the IRB review process to ensure that the IRB has performed its duties in accordance with regulatory requirements and internal policies. The RCM may also provide educational services to study personnel.

The RCM shall have access to all information relevant to a study, including but not limited to, IRB files, clinical/medical records, research records including informed consent documents, adverse event reports, the initial protocol and amendments made to it, the clinical trial agreement, documents related to contact with subjects, all paper and electronic files, and the consent process. The RCM also has access to pharmacy or other relevant areas involved in the study in order to assess inventory control processes for compliance with regulations and policies regarding appropriate use of investigational drugs, biological products and medical devices. The types of audits that may be conducted are noted in Appendix A.

Investigators are expected to cooperate in all aspects of the audit process, including but not limited to, scheduling audit visits, providing necessary information and space for the audit to occur, and responding to audit letters. Cooperation is expected for both internal and external audits.

It is also the policy of the HSPP that results of external audits, inspections and/or monitoring visits be reported to the IRB.

Procedures

I. Procedures for Study Selection and Audit Scheduling

On a quarterly basis the RCM will post a listing of the studies to be audited within that quarter on a shared drive, accessible to IRB and HSPP staff. The list may be modified as need arises. The goal is to audit 5% of active studies each year. The RCM selects the majority of studies at random by exporting approved studies to excel and running a random selection program. However, the RCM may also give consideration to the following elements when selecting a study for audit:

- investigator originated vs. sponsored
- IND / IDE studies
- levels of risk
- results of previous audits
- directives of the IRB
- study populations
- principal investigators
- whether the CRC provides support for the study
- study topics
- study approval status (e.g. frequent lapses)
- funding sources
- initial review and approval categories
- complaints or concerns raised

In addition to the selection process above, the IRB may direct the RCM to audit a study. An IRB Chair may require an audit due to concerns found while conducting an expedited review. In such cases the Chair will correspond with the RCM. The convened board may require an audit due to concerns raised during a convened meeting. Such requirements are communicated to the RCM by distribution of the IRB minutes by the IRB RS to the RCM approximately 5 working days after the meeting, or by copying the RCM on an IRB outcome letter. The RCM will maintain a tickler file of IRB-mandated audits and will be responsible to schedule the audit visits as directed

Once a study is selected for audit, the RCM will send out an audit notification letter to the PI and study coordinator (and additional contacts as requested or appropriate) and will then work with the PI or Study Coordinator to schedule a time for the audit to occur. Exceptions to the notification policy may occur, for example, in the case of an unannounced or emergency audit.

II. Procedures for Conducting Audits

The audit will include a brief pre-audit interview with the PI and/or the study coordinator to discuss the research study and any related issues. After the interview, the RCM will review research records, the regulatory binder and other documents associated with the study. Generally, a sampling of 10% of the consent/HIPAA documents and research records are reviewed to start, with more records added should issues arise. Depending on the complexity of the research and the availability of the study team and RCM, the on-site review of these documents may occur over multiple days. Additional aspects of the

study may be reviewed at a separate time as appropriate (e.g., reviews of drug accountability and medical records). In IRB Directed audits, the review may be focused on and /or limited to specific areas of concern as indicated by the IRB.

When feasible, the RCM may conduct an exit interview (in person, by phone or email) to share preliminary findings, minor issues or suggestions.

If the audit reveals any concern that may involve imminent risk to subjects the RCM will report this immediately to the DHSPP by either phone, e-mail or a personal meeting and subsequently incorporate the finding into the final audit report. Upon receipt of this information the DHSPP may suspend study activity in whole or in part (refer to policy 2009-003 for imposing suspensions) or may require immediate corrective action to bring study conduct into compliance with the approved protocol to minimize the risk to subjects.

A. Correspondence

Within approximately ten working days of completion the RCM will generate a letter of the findings from the audit using the audit letter template. The Director (and/or designee) of the HSPP (DHSPP) will be given an opportunity to review and comment before the letter is issued. The DHSPP may require implementation of other corrective actions and may elect to discuss the recommendations of the RCM with the appropriate Chair prior to the RCM finalizing and issuing the letter.

The RCM will send the letter to the PI with copy to the DHSPP, Deputy DHSPP, study coordinator, and additional contacts as requested or appropriate. For studies under local IRB oversight, the IRB Chair and Regulatory Specialist will receive copy of the correspondence, as well. Other relevant parties may be copied as necessary (e.g., research pharmacy if a finding relates to dispensing of medications, research subject advocate for studies supported by the Clinical Research Center).

When corrective actions are required, the PI will be directed to respond in writing to the RCM within a reasonable time frame (e.g. 2 – 4 weeks) specified within the letter. Corrective actions required are limited to those that will bring the conduct of the study into compliance with the approved protocol, regulatory requirements (e.g. drug accountability for investigator held IND), or good clinical practice guidelines as recognized by the FDA or that require actions on the part of the staff, e.g. additional training requirements. The RCM may suggest changes to the protocol or study related documents. In such cases a recommendation will be made to the PI to submit a request for addendum/modification to the IRB for review and approval and the IRB will make the final determination as to whether to approve the request.

If the PI does not adequately address all issues in the initial response letter, this process of communication will be repeated.

If there are no audit findings and therefore no response is required from the PI, the initial audit letter sent by the RCM will indicate this and will also serve as the closeout letter and the Audit Response Form referenced below is not necessary,

B. Failure to Respond

If a PI does not respond to an audit letter by the due date the RCM will issue a reminder notice to the PI by e-mail and grant a short extension period (e.g. 1 – 2 weeks) by which a response to the audit is due. If necessary, a second reminder may be sent by the RCM to the PI with copy to the DHSPP, and/or a phone call may be placed by the DHSPP to the PI. An additional short extension period (e.g. one week) may be granted. If after that time the PI has not responded, the RCM will ask the DHSPP to contact the PI's Department Chair by phone or e-mail to enlist his/her services in soliciting a response from the PI. An additional short extension period (e.g. one week) may be granted. If the PI does not respond and the study was approved by the local IRB, the RCM will ask the IRB Chair to issue a directive to the PI to respond by a given date. If the PI does not respond to the directive of the IRB Chair, the RCM will ask the IRB RS to list the audit and the PI's failure to respond as a discussion item for the next convened IRB meeting. The failure to respond may constitute serious non-compliance. If the PI does not respond and the study was approved by an external IRB the RCM will work with the reviewing IRB to determine next steps.

If the PI fails to complete corrective actions in a timely manner, the RCM will follow the same procedures as stated above.

C. Review of Audits By Local IRB

(Note: For studies approved by an external IRB: the study team will be advised in the correspondence to inform the reviewing IRB of the audit outcome as directed in reporting policies of that IRB.)

The RCM will provide the relevant IRB chair with a copy of the audit letter, the response letter(s) from the PI and the Audit Review Form (ARF). The IRB Chair will review the audit letter and response letter and use the ARF to document whether any findings need to be brought before the convened board for review.

If a referral is made to the convened board, the RCM will send a final audit correspondence to the PI and study coordinator with copy to others (as requested and appropriate) indicating the areas of the audit designated by the Chair which require further review. The RCM will prepare the materials for review by the membership. At a minimum the material will include the audit letter and response letter(s). The RCM will provide the material to the IRB Regulatory Specialist (RS) for inclusion on the IRB agenda as a discussion item.

If review by the convened board is not required (inclusive of audits done by directive of the Chair), the Chair will indicate this on the ARF and return the form to the RCM.

If the audit was conducted at the direction of the convened board and no areas of the audit require further discussion by the convened board, the Chair will indicate this on the ARF and the RCM will inform the IRB RS to inform the Board that their directive had been followed.

D. Audit Close-Out

Once all audit findings and corrective actions have been addressed and the IRB chair has completed the ARF (when applicable), the RCM will prepare an audit close-out letter and copy those individuals on the initial audit outcome letter. If applicable, this letter may indicate that certain issues have been referred to the convened IRB for further review.

E. Filing

The RCM is responsible for filing all correspondence related to audits in the electronic IRB file. All audit correspondence will be attached as an "audit packet" with the original audit letter being the first document followed by other correspondence in date order. The audit packet should include the audit letter and, as applicable, the response from the PI, completed ARF form, and audit close out letter. For items that were referred to the convened board, the RCM will be copied on the discussion item outcome letter and include this letter in the audit packet. The audit packet will be uploaded to the electronic IRB file in iRIS under the Study Management tab, in the section Review Board Internal Documents. Investigators are responsible for keeping their own documentation of the audit with their study records.

III. Procedures for Annual Summary Review of All Internal Audits

On an annual basis the results of completed audits will be reviewed by the RCM to determine if there are consistent problem areas. If it is determined that there are consistent problem areas, the RCM will use this information to recommend to the DHSPP that policies be developed or clarified, and to work the ES to improve education of the research personnel.

IV. Procedures for External Audits, Inspections or Monitoring Reports

The PI is expected to forward to the IRB for review any audit, inspection, or monitoring report or finding issued by a regulatory agency, cooperative research group, contract research organization, the sponsor or the funding agency. If there are no findings or if the report is limited to deviations outside the control of the research team which pose no risk to subjects (e.g., subject rescheduled study visit outside of window) and no corrective actions are required, the report is to be submitted as part of the application for continuing review.

Reports which include deviations within the control of the research team /or require corrective action, are to be submitted to the IRB within 15 working days of receipt of the report. The information is to be submitted to the IRB in conjunction with the applicable IRIS form (i.e. an addendum/modification request form or problem report form) and include any corrective action plans. The PI must subsequently summarize the findings at the time of continuation.

The IRB RS will follow standard procedures for assigning the submission for review by the IRB.

V. Procedures for HIPAA Concerns

If an audit or external monitoring reveals a concern which may represent a HIPAA privacy issue, the RCM will instruct the PI and study coordinator to inform the UConn Health Privacy Officer of the issue. The PI will be instructed to include the RCM and/or IRB, as necessary in correspondence. If the concern should be of a serious nature and require immediate reporting, the RCM or IRB may contact the Privacy Officer directly and alert the PI when feasible.

VI. Procedures for IRB Actions

If necessary for subject safety, the Chair may suspend all or part of the research activity until such time as the board convenes (see policy 2009-003.0, 2009-004.0). If the Board determines there is a finding of serious or continuing non-compliance or an unanticipated problem involving risk to subjects or others, and/or suspends or terminates a study the procedures described in related policies will be followed.

VIII. Procedures for Potential Misconduct in Research

If the RCM is concerned that audit findings may rise to the level of misconduct in research the RCM will immediately bring this concern to the attention of the DHSPP. If the DHSPP concurs, the DHSPP will follow the policy for Reporting Compliance Concerns (2003-33) after which and if necessary, the UConn Health Research Domain Chief Compliance Officer or the Corporate Compliance Integrity Office will follow the policy for Review of Alleged Misconduct of Research (2003-41). Disagreement by the DHSPP does not prevent the RCM from reporting the compliance concern.

Related Content

2003-33 – Reporting Compliance Concerns (Institutional Policy)
2003-41 – Review of Alleged Misconduct of Research (Institutional Policy)
2009-001.0 – Reporting Unanticipated Problems to the IRB
2009-002.0 - Reporting Non-Compliance to the IRB
2009-003.0 - Imposing a Suspension or Termination of IRB Approval
2009-004.0 - Reporting to External Agencies and Institutional Officials
2011-007.0 – Definitions Applied to Policies
2011-023.0 – Educational Requirements

Basis

45 CFR 46,
21 CFR 56

Document Attributes

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Reviewed and Approved By:

Signed Richard H. Simon 19 June 18

_____ Date: _____

Richard Simon, MD
Director Human Subjects Protection Program

Appendix A
Policy 2009-005.0

Types of Audits

Unannounced Audit

Unannounced audits are conducted to verify that the research is being conducted in accordance with the IRB's terms of approval, that informed consent is being obtained, that records are kept under secure conditions, and that information being provided to the IRB is accurate, e.g. number of subjects enrolled, recruitment methods etc. This type of audit will not be conducted frequently.

Scheduled / Random Audit

These audits are designed to conduct a more comprehensive examination of compliance, including reviews of patient eligibility and medical oversight and may include observation of the informed consent process and conduct of the research and reviews of drug/device accountability. The PI and study coordinator will be given at least one week notice prior to the start of the audit.

Directed Audit

Directed audits are conducted at the request of the IRB. The scope of the audit depends on the directive from the IRB. The IRB may require on-going monitoring by the RCM over a period of time until satisfied that the issue of concern has been resolved.

Consent Audit

The IRB may require that the consent process by monitored by the Research Compliance Monitor or a representative of the IRB. The purpose of this is to ensure that the study is being explained well to the subjects. Examples of when this practice may be exercised include when the investigator or individual obtaining consent is inexperienced, when the study is complex or when the study is high risk. Investigators may also request this audit to ensure that the consent process is being conducted properly.

Emergency Audit

This type of audit may be conducted when concerns for subject safety or concerns or allegations relating to non-compliance with the regulations or requirements or determinations of the IRB are brought to the attention of the IRB or DHSPP. The DHSPP may elect to accompany the RCM on such audits. Audits will occur within 2 weeks of notification of the allegation. The DHSPP will determine whether the PI is to be given any advance notice. If given, advance notice will be by phone call from the DHSPP, or RCM as directed by the DHSPP, and will not exceed 24 hours. The purpose of any advance notice is to allow the PI to arrange to be present for discussion.

Depending on the nature of the expressed concern, the RCM and / or DHSPP may choose to sequester all research related files in the HSPP for further review. The DHSPP and / or RCM will discuss the concern that caused the audit with the PI and obtain his/her perspective. It will also be explained to the PI that the sequestering of the research files, if it occurs, is for his/her own protection. The DHSPP will communicate back to the PI the findings of the audit and the

corrective action to be taken if needed. The DHSPP may refer matters to the IRB for review and determination of whether the matter constitutes serious or continuing non-compliance or an unanticipated problem involving risk to subjects or others. The DHSPP will follow through with any required reporting to internal and external officials based on the determinations of the IRB.

First-Time PI Audit

This type of audit is occurs when a study is under the direction of a PI who has not previously been a PI or has never been a PI at UConn HealthThe purpose of this audit is to ensure that the investigator is aware of his/her responsibilities and obligations as PI, familiar with HSPP policies and is giving appropriate oversight to the research. A first-time PI audit will typically be conducted within the first year of IRB approval.

Follow-up Audit

This type of audit is occurs when a study has previously been audited and corrective actions were required as a result of the audit. The RCM may conduct a follow-up audit to check that corrective actions were implemented and that previously identified problems are not continuing to occur. Follow-up audits may be directed by the IRB to occur within a specific time frame following the initial audit. When warranted, these audits may occur with limited advanced notice.

IND/IDE Sponsor Pre-Approval Audit

This type of audit is conducted when a UConn Health faculty member is also the sponsor of an IND or IDE. The purpose of this audit is to ensure that the sponsor of the IND is aware of the additional obligations of the sponsor and to ensure that proper procedure will be followed for the manufacture, use, storage, and accountability of the investigational article. The pre-audit is conducted prior to submission of an IRB application that proposes to use the IND/IDE and the results of the audit become part of the application. An audit of this nature conducted by another area (e.g. Research Compliance Services) may substitute for the RCM audit.

Joint OCTR / HSPP Audit

This is a combined audit in conjunction with the Office of Clinical & Translational Research (OCTR) of UConn Health to assess compliance in the clinical research activities. The RCM will review research activities conducted under an IRB approval to ensure that proper scientific, ethical and regulatory requirements are followed. The OCTR auditors will conduct a financial compliance audit to ensure that subject billing adheres to the regulations set forth in the Medicare National Coverage Decision. While the on-site portion of the audit is conducted at the same time, the HSPP and OCTR reports will be issued separately.

Web / Recruitment Audit

The RCM may periodically review the content of the UConn Health clinical trials listing on the UConn Health web site to ensure that the information posted does not exceed that allowed per FDA guidance and HSPP/IRB policy. The RCM may also audit departmental web sites and other advertising to ensure compliance with recruitment policies. Web / Recruitment audits may be incorporated into another type of audit or done as a stand-alone audit.

Lapsed / Closed Study Audit

The RCM may conduct audits of studies which have experienced a lapse in IRB approval or were administratively closed. Such audits look to ensure that no research activity has occurred

during the lapse (with the exception of activities which received prior approval to continue). In the case where studies were administratively closed due to failure to obtain continuing approval, the RCM will seek to ensure that no research activity occurred during the lapse or since closure, and to confirm that records are retained per protocol, policy and applicable regulations. Such audits may be conducted on site or remotely.