1. Purpose:

This policy outlines the institutional responsibilities and policies pertaining to investigating and reviewing non-compliance.

Regulation and Guideline Reference(s):

45 CFR 46.112
21 CFR 56.112

KUMC References:

KUMC Quality Assurance Program Standard Operating Procedures

2. Procedure:

17.1 Investigating Reports of Non-compliance

I. Definitions

A. Non-compliance

1. Failure on the part of investigators or other research personnel to adhere to the terms of IRB approval, or
2. Failure on the part of investigators or other research personnel to abide by applicable laws or regulations or KUMC policies, including failure to submit research for IRB review and approval prior to implementing the research.
3. Failure of the IRB to comply with requirements of 45 CFR 46.

B. Minor non-compliance is non-compliance that is neither serious nor continuing.

C. Serious non-compliance is a failure to comply with laws or regulations, KUMC policies, or the requirements or determinations of the IRB when that failure seriously increases risk of harm to participants, adversely affects the rights and welfare of the participants or undermines data integrity. A single instance of non-compliance may be serious. Any failure to comply is serious if it either increases risk of harm or adversely affects the rights and welfare of the participants. The IRB is responsible to make the final determination of whether a report is serious non-compliance. The
KUMC Quality Assurance Advisory Committee (QAAC) may be asked to review reports of non-compliance to advise the IRB.

D. **Continuing non-compliance** is a pattern of reports of minor non-compliance that, if unaddressed, may compromise the integrity of the research or may result in harm to participants. The pattern may reflect a lack of knowledge on the part of the investigator or a lack of commitment by the investigator and study team to human subjects protection. The IRB is responsible to make the final determination of whether a report is continuing non-compliance. The KUMC Quality Assurance Advisory Committee (QAAC) may be asked to review reports of non-compliance to advise the IRB.

E. **Report of non-compliance** is a notification to the IRB Office, IRB members, the HRPP Director or the Institutional Official (IO). Reports of non-compliance may come from a variety of sources, including:

1. Self report from the research team, through a Report of New Information filed with IRB through the electronic IRB system.
2. Discovery by the IRB during ongoing review (e.g., reviews of adverse events or continuing review)
3. Discovery during an internal audit of the research
4. Discovery during an internal audit of IRB records
5. Discovery during monitoring or audit by an external entity
6. Allegation from a professional colleague
7. Complaint from a research subject, subjects’ family or member of public

F. **Suspension** is the temporary closing of some or all aspects of a human research project or discontinuing some or all of an investigator's privilege to conduct human subject research short of the permanent ending of all activities related to a human research project or an investigator's privilege of conducting human subjects research. Suspension may be for serious or continuing noncompliance with IRB policies or for threats to the rights and welfare of subjects. The suspension may be partial in that certain activities may continue while others may stop or it may be complete in that no activity related to the research may proceed.

G. **Termination** is the permanent ending of all activities related to a human research project or an investigator's privilege of conducting human subject research at the University of Kansas Medical Center

II. Reportable Events

A. Prompt reporting to the IRB (within 5 days of the study team's awareness) is always required in the following circumstances:

1. Failure to obtain informed consent, or re-consent when required by the IRB
2. Modifying the protocol without IRB approval, except to avoid immediate hazard to subjects
3. Conducting the research prior to IRB approval, during an IRB suspension or after IRB approval expires

B. Additionally, prompt reporting is required for other non-compliance that the principal investigator determines causes harm, increases risk of harm, adversely affects the rights and welfare of participants or undermines the scientific integrity of the data.

C. The IRB provides investigators with specific instructions about reportable events. The instructions
are posted on the IRB website.

D. Reports to the IRB are made by submitting a Report of New Information in the electronic IRB system.

III. Initial Evaluation

A. A report or allegation of non-compliance may be received in the electronic IRB system or by written or oral communication to the HRPP. The HRPP staff first evaluates whether the report represents an imminent threat of harm to subjects or others.

1. If there is an indication of imminent threat of harm, the HRPP staff notifies the IRB Chair. In the Chair's absence, the IO or HRPP Director will be notified.

2. The Chair, IO or HRPP Director may elect to gather additional information from the study team to confirm that interim steps have been taken to address an immediate threat of harm. Any immediate threat will be adequately addressed before other steps are taken.

3. The Chair determines whether the immediate suspension is warranted. Additional information may be gathered before the determination is made. The Chair may consult with the IO and HRPP Director. In the Chair's absence, the IO or HRPP Director can suspend a study on an urgent basis.

4. When a study is suspended, the Chair or HRPP Director notifies the IO. The Chair or HRPP Director notifies the investigator by phone call and in writing.

5. For research that is federally funded or supported, the IO notifies federal authorities of the suspension. The IO files a preliminary report within five working days. The report is filed as described below in section V.B.

6. The Chair works with investigator to provide for continued safety and welfare for subjects until the report can be evaluated by the convened IRB. Depending on the nature of the non-compliance and the subjects' best interests, they may be continued on an investigational drug, transferred to clinical care, placed under additional safety monitoring, or provided with other protective measures.

7. When a study is suspended, the HRPP Director coordinates an investigation to gather further information, at the direction of the Chair and the IO.

8. The IRB is notified of the suspension and reviews it at its next meeting. The evaluation by the convened IRB follows the process outlined in section IV. below.

B. If the initial evaluation does not indicate imminent threat of harm, the HRPP staff evaluates the report to determine whether it is minor non-compliance.

1. If the event is not reportable, the HRPP staff returns the report to the investigator without review. The investigator is instructed to discard the report from the eIRB system.

2. If the report is reportable, the HRPP staff determine whether the report meets the definition of minor non-compliance. The HRPP staff may consult the QA Program in making their determination. If it is minor, HRPP staff return the report to the investigator in the eIRB system. The investigator is instructed to document the deviation or non-compliance in the study file. Additional actions may be recommended.

3. Reportable events that are not minor, and may represent serious or continuing non-compliance, are referred to the IRB Chair. In the Chair's absence, the IO or HRPP Director can be consulted.

4. The Chair or chair designee may elect to gather additional information from the study team to
confirm that interim steps have been taken to prevent immediate concerns about safety, subject welfare or integrity of study data. Any immediate concerns will be adequately addressed before other steps are taken.

5. The Chair determines whether the report should be reviewed by the convened IRB.
   
a. The Chair may determine that the event is minor non-compliance. In that case, the report is returned to the investigator as described in III.B.2 above.
   
b. The Chair may gather additional information to determine whether review by the convened IRB is warranted. Additional information may include an evaluation by the QA Program.
      
i. The Chair may elect to wait for the QA evaluation before deciding whether to refer to the convened board. If the Chair determines the event is minor non-compliance after QA input, then the report is returned to the investigator as described in III.B.2 above.
      
ii. Alternatively, the Chair may refer the event for prompt IRB review to occur in parallel to the QA review.
   
c. If the Chair determines prompt review by the IRB is warranted, the report is put on the agenda of an upcoming meeting. The evaluation by the convened IRB follows the process outlined in section IV. below.

C. If the report of new information involves a complaint or problem reported by a study subject, HRPP staff will consider the extent to which the complaint can be kept anonymous if appropriate. Depending on the nature of the complaint, guidance also may be sought from university legal counsel or risk management as the staff works collaboratively with the research team to address the problem.

IV. Evaluation by the Convened IRB

A. All IRB members receive documentation associated with the initial report, any additional documentation gathered through inquiries discussed above, and a copy of the current consent form, if applicable. Documentation may include recommendations from the QA Program or the QAAC. Primary and secondary reviewers are assigned as described in SOP 16.5. Reviewers may access copies of the study protocol or any other relevant materials in the IRB files. All members have access to the complete file, which is maintained in the electronic IRB system. During the meeting, the reviewers present the report to the committee, make an initial recommendation and begin the discussion.

B. After discussion, the IRB may defer the review in order to obtain more information before making their determination. Additional information may include evaluation by the QA Program or the QAAC.

C. If the review is not deferred, the IRB determines whether non-compliance is serious or continuing. The determination is documented in the meeting minutes. Upon finding that the event represents serious or continuing non-compliance, the IRB takes one or more of the following actions:
   
1. Require additional training or education of the investigator or research team;
2. Require additional supervision of the investigator;
3. Require modifications to the study protocol;
4. Require modifications to the informed consent document;
5. Require additional information be provided to past subjects;
6. Require notification of current subjects;
7. Require that current subjects re-consent to participation;
8. Increase the frequency of continuing review;
9. Monitor the conduct of the research;
10. Monitor the consent process;
11. Suspend the study pending further information;
12. Terminate the study.

D. If the convened IRB suspends or terminated the study, the IRB will work with investigator to provide for continued safety and welfare for subjects. Depending on the nature of the non-compliance and the subjects' best interests, they may be continued on an investigational drug, transferred to clinical care, placed under additional safety monitoring, or provided with other protective measures.

E. If the IRB directs more than minor modifications to the protocol or consent form to address the non-compliance, the changes are reviewed by the convened committee. Minor changes may be reviewed by the IRB Chair or experienced member, as described in SOP 5.2

F. If the IRB determines the event is neither serious nor continuing non-compliance, the report is accepted with no further action.

V. Action by the IO

A. When the IRB suspends or terminates a study, the IO may take additional actions, in consultation with the department chair and university leadership. Additional actions may include but are not limited to:
   1. Limiting the research of the investigator (by number of active protocols or number of active participants)
   2. Require additional education for key personnel.
   3. Withdraw or limit the privileges of the investigator to conduct human research
   4. Refer the matter to other organizational entities (such as General Counsel, Risk Management, Academic Affairs)

B. When the IRB determines the event represents serious or continuing non-compliance, the IO files a letter of notification to federal authorities and others when required. As of January 17, 2018, KUMC extends its Federalwide Assurance only to research that is funded or supported by a Common Rule department or agency. When required, the letter is drafted by the HRPP Director, with final approval by the IO. The letter is sent no longer than 30 days after the IRB’s decision. The letter of notification will include:
   1. Name of the institution
   2. Title of the research project and/or grant proposal in which the noncompliance occurred;
   3. Name of the principal investigator on the protocol;
   4. The IRB number assigned to the protocol;
   5. A detailed description of the noncompliance; and
   6. Actions the institution is taking or plans to take to address the noncompliance (including those actions described above in III.C.)

C. The notification will be sent, as applicable, to:
1. OHRP
2. FDA, if the study is subject to FDA regulations
3. Other federal agencies (if applicable) that are conducting or funding the study
4. Sponsor, if the study is sponsored
5. Principal investigator
6. Department Chair, Center Director or Dean
7. IRB Chair

17.2 Quality Assurance and Quality Improvement for the HRPP

I. The Institutional Official (IO) directs the HRPP Director and HRPP staff to ensure continuous improvement of the HRPP. Activities include both quality assurance and quality improvement.

II. Quality assurance activities are designed to assess whether the HRPP policies and procedures are followed by HRPP staff, IRB members, investigators and organizational units. Activities include:

   A. Regular meetings of IRB office staff to discuss efficient workflow, accurate administrative review and collaboration with other units.
   B. Brief presentations at IRB meetings on federal requirements, KUMC policies or current topics in human research protections.
   C. Internal reviews of IRB files by staff members, to ensure that all submissions were reviewed, all reviews were documented, and IRB requirements were fulfilled.
   D. Routine reviews of selected studies by the QA Program as outlined in the KUMC Quality Assurance SOPs.
   E. System and process audits on selected departments, including the IRB performed by the QA Program to confirm compliance with federal regulations and institutional policy.
   F. For-cause audits conducted by the QA Program as directed by the IRB, QAAC, IO and others as outlined in the KUMC Quality Assurance SOPs.
   G. Promotion of investigator's self-assessment activities

III. Quality improvement activities are designed to evaluate whether the institution is adequately protecting human subjects. These activities aim to enhance investigators’ understanding of regulatory requirements, improve the efficiency and effectiveness of IRB reviews, ensure compliance with regulations and provide information about the HRPP to research volunteers and the public. On an ongoing basis, the HRPP Director keeps the IO apprised of these quality improvement activities and any additional resources that would be needed. Resources may include physical, financial and staff resources, space, expertise of IRB members, adequacy of the number of IRBs, and access to legal counsel. The IO works with the HRPP Director on budgeting and requesting the resources through the University procedures. These activities include, but are not limited to:

   A. Analysis of the scope, volume and nature of research proposals.
   B. Coordination between the components of the HRPP, to harmonize requirements and review processes
   C. Continual assessment of the adequacy of HRPP policies, forms and review processes to meet current and pending regulatory requirements
D. Analysis of common compliance and review problems
E. Consultations with university legal counsel and with university risk management
F. Review of calls placed to the Institutional Compliance Hotline or received by other means (to report concerns, ask questions and make suggestions) and the outcomes of those calls
G. Evaluations of individual and group consultations, educational programs and web resources for investigators
H. Periodic survey of investigators on ways to improve the HRPP
   I. Analysis of timeframes from submission to final approval.
   J. Tracking of improvements made to the HRPP and analysis of their impact
K. Assessment, development and improvement of educational materials about the HRPP for research volunteers and the public, i.e., community outreach.

IV. On a regular basis, the IO, HRPP Director and IRB Chair review the performance of IRB members. The evaluation is based upon the duties outlined in SOP 1.6. The evaluation is augmented by a periodic survey of IRB members related to needs for continuing education, committee functioning, committee support, adequate expertise, and a general self-assessment.
   A. Based upon performance evaluations, adjustments are made to the IRB membership and education of IRB members, to meet regulatory and organizational requirements.
   B. The performance of IRB Chairs is evaluated collaboratively, between the IO and the Vice Chancellor for Research.

17.3 Responding to Concerns and Suggestions from Investigators
   I. Investigators and other research personnel may obtain answers to questions, express concerns, or convey suggestions regarding the HRPP by utilizing: the HRPP website, or by consulting with the IO and HRPP staff. Compliance concerns may be reported anonymously to the University’s Institutional Hotline.
   II. Any request for reconsideration of an IRB decision is handled in accordance with SOP 17.4

17.4 Request for Re-consideration of an IRB Decision
   I. When the IRB disapproves a proposed study, suspends or terminates an ongoing study for cause, the written notification to the investigator is accompanied by reasons for the decision.
   II. If an investigator disagrees with an IRB decision, he/she may request a re-consideration by the IRB. The request must be accompanied by a written summary, outlining in detail the rationale for re-consideration.
   III. The summary will be distributed to all IRB members, and the protocol will be scheduled for re-consideration at the next available meeting. The investigator may attend the meeting.
   IV. After discussion of the protocol and rationale for re-consideration, the IRB will formally re-vote. A majority vote of the members present will determine the decision.
   V. If the original decision is upheld, the protocol will not be reviewed again unless significant changes are made.
   VI. Decisions by the IRB to disapprove, suspend or terminate a project may not be overruled by another entity or institutional official.
References:

45 CFR 46.112
21 CFR 56.112
KUMC Quality Assurance Program Standard Operating Procedures

Attachments:

Approval Signatures

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<tr>
<th>Approver</th>
<th>Date</th>
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<tr>
<td>Steffani Webb: Vice Chancellor for Administration</td>
<td>12/10/2019</td>
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<tr>
<td>Lisa Hoebelheinrich: Chief Compliance Officer</td>
<td>12/10/2019</td>
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<tr>
<td>Annie Fors: QA Director</td>
<td>12/4/2019</td>
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<tr>
<td>Karen Blackwell: Director HRPP</td>
<td>11/26/2019</td>
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<td>Kyle Stephens: Assistant Director</td>
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Applicability

KU Medical Center, KU SoM Wichita