Part 12 - Quality Assurance and Research Compliance

This section describes the University's and IRBMED's quality assurance, quality improvement, and enforcement activities.

I. QUALITY ASSESSMENT AND IMPROVEMENT

Refer to HRPP OM Part 12.I

II. REPORTABLE EVENTS: ADVERSE EVENTS, UNANTICIPATED PROBLEMS, NON-COMPLIANCE, SUSPENSIONS AND TERMINATIONS OF IRB APPROVAL

A. Background

Refer to HRPP OM Part 12.II.A

B. Definitions

Refer to HRPP OM Part 12.II.B

Refer to IRBMED AE and ORIO Reporting Guidance on the IRBMED Website.

C. Roles and Responsibilities for Required Reporting of Reportable Events

1. Researchers

Refer to HRPP OM Part 12.II.C.1

As noted in the OM, guidelines and reporting procedures for reporting Adverse Events (AEs) and Other Reportable Information or Occurrences (ORIOs), including those AEs and ORIOs that are also unanticipated problems involving risks to participants or others (UaPs), are posted on the IRBMED website. This guidance is also referenced within the “Help” feature in eResearch. It provides the timelines and process for submitting reports.

Researchers are responsible for understanding and following these guidelines and reporting procedures. The IRBMED offers workshops that review the guidelines and will consult with study teams as needed in order to assist Principal Investigators (PIs) in understanding the reporting requirements.

Examples of events that may require reporting in accordance with IRBMED AE and ORIO guidance include:

- Internal AEs that are unexpected, involve new or increased risks, and are related to the research.
- External AEs that are UaPs.
- Changes made to the research without prior IRB approval in order to eliminate apparent immediate harm.
- Other unanticipated information that is related to the research and indicates that participants or others might be at increased risk of harm. For example:
  - Information that indicates a change to the risks or potential benefits of the research. For example:
    - An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRBMED
    - A paper is published from another study that shows that the risks or potential benefits of the research may be different than initially presented to the IRBMED
    - A breach of confidentiality
- Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol
- Incarceration of a participant in a protocol not approved to enroll prisoners
- Event that requires prompt reporting to the sponsor
- Sponsor imposed suspension for risk
- Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team
- Protocol violation (meaning an accidental or unintentional change to the IRB approved protocol) that harmed participants or others or that indicates participants or others may be at increased risk of harm

Failure to follow these guidelines may require the IRBMED to halt the study and/or the institution to report the noncompliance to government agencies or study sponsors.

As noted in the guidelines and the OM, PIs should be aware of their option to submit a “Study-Specific AE Reporting Plan” to the IRBMED, either with their initial IRBMED application or via an amendment on an approved study. If approved, a study-specific plan would be used to determine the required AE reporting and timing of reports, instead of the requirements in the Standard AE Timetable. Researchers who initiate an approved study using a standard adverse event reporting plan and then modify the project to a study-specific AE reporting plan must follow the standard reporting guidelines until the IRBMED approves the modification.

For studies that do not involve investigational agents, and particularly for studies that are minimal risk, a study-specific plan is recommended. Guidance for developing a study-specific plan can be found on the IRBMED website.

2. The IRBs

a) Refer to HRPP OM Part 12.II.C.2

It is essential to human participant protection to identify, analyze the causes of, and respond appropriately to AEs and ORIOs (including UaPs), and provide notification to appropriate institutional entities and external agencies/sponsors.

**IRBMED staff will consider the following when reviewing an AE or ORIO report:**
- Whether urgent notification of the IRBMED Director, Health System Legal Counsel, IRBMED Chair(s) (Co- or Vice-Chair), the Medical School Associate Deans for Research and Regulatory Affairs, the HRPP Director, or other authority is required, if there is a participant safety concern or a change in participant status (such as incarceration) that may impact study participation
- Completeness
- Whether necessary supporting documents are included
- Whether submission occurred within the required timeframe
- Whether the event or information is described in the currently approved informed consent document (when applicable)

Reports of events that are unexpected, related, or linked in a significant way to the research and indicate risks that were previously unknown or unrecognized, will be flagged to enable the reviewer to assess whether the event represents an UaP.

**The timelines for completion of review are dependent upon:**
- Completeness of the report, such that additional information is necessary before IRB review
• Whether the report is a potential UaP and other reporting deadlines may be triggered
• Whether the report indicates a subject safety concern or other serious matter

Requests for additions to incomplete reports should be sent back to the study team in a timely manner after the date of the initial assessment. However, if an incomplete report raises serious concerns related to participant protections or other protocol or regulatory violations, it may be sent to a designated reviewer while the missing information is being collected.

The IRB Chair(s) are authorized to take immediate action to protect the health and safety of research participants, as described in the OM per this section.

Reports identified as possible UaPs will receive full board review as soon as possible. Required changes to the submission or research, if any, will be communicated to the researchers. If a Single IRB Member reviewer of an AE or ORIO report requires changes to the research based upon that report, or if the report is judged to include potential UaPs, the submission must be sent for convened full-board review.

If the convened board determines an event to be an UaP, the IRBMED will prepare the UaP report. After appropriate institutional review, the IRBMED will send the required reports directly to external entities as required by regulation or sponsor agreement, with notification of the IO, the Associate Vice President for Research, the HRPP Director, the IRBMED co-chairs, the principal investigator, and institutional committees or entities as indicated.

Generally, reports to federal agencies for unanticipated problems will be made promptly (not to exceed one month absent special circumstances, such as the need for extensive data gathering or analysis).

Reports to federal agencies of serious and/or continuing noncompliance, suspensions, and terminations of IRB approval will be made by the HRPP Director.

**IRBMED board members consider the following when reviewing an AE report:**
• PI’s assessment of the AE and concurrence or disagreement with that assessment. The reviewer and board will consider:
  o Causality and relatedness of the event to the research, not just to an investigational agent that is part of the research
  o Seriousness
  o Expectedness
  o Whether the event constitutes an UaP
  o Whether urgent communication with the PI, IRBMED director, UM Office of General Counsel, UMOR, or other authority or unit is required (e.g., Office of Clinical Safety)
  o Safety of participants (including whether the study should be halted or modified)
  o Risk/benefit assessment of the study
  o Impact of AE on participants’ willingness to participate in the study

**For AEs not described in the currently approved informed consent document (ICD), the review will consider:**
• Whether the ICD needs modification
• Whether previously enrolled participants should be notified and/or re-consented
IRBMED board members consider the following when reviewing an ORIO report:

- PI’s assessment of the ORIO and concurrence or disagreement with that assessment. The reviewer and board will consider:
  - Causality and relatedness of the event to the research, not just to an investigational agent that is part of the research
  - Whether the event constitutes an UaP
  - Whether remediation is required (e.g., education of the study team or referral to risk management)
  - Whether urgent communication with the PI, IRBMED director, Office of General Counsel, IRBMED Chair(s), UMOR or other authority is required
  - Whether the report indicates that serious and/or continuing noncompliance may have occurred
  - Whether the report indicates that an UaP has been identified
  - Safety of participants (including whether the study should be halted or modified)
  - Risk/benefit assessment of the study
  - Impact of ORIO on participants’ willingness to participate in the study

For ORIOs not described in the currently approved ICD the review will consider:

- Whether the ICD needs modification
- Whether previously enrolled participants should be notified and/or re-consented

When reviewing an UaP, IRBMED Board Members consider whether the event is:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

3. Reporting Unanticipated Problems, Serious and/or Continuing Noncompliance, Suspensions, and Termination of IRB Approval

Refer to HRPP OM Part 12.II.C.3

If the convened board determines an event to be an UaP, the IRBMED will prepare the UaP report. After appropriate institutional review, the IRBMED will send the required reports directly to external entities as required by regulation or sponsor agreement, with notification of the IO, the Associate Vice President for Research, the HRPP Director, the IRBMED co-chairs, the principal investigator, and institutional committees or entities as indicated.

Generally, reports to federal agencies for unanticipated problems will be made promptly (not to exceed one month absent special circumstances, such as the need for extensive data gathering or analysis).

External reports of serious and/or continuing noncompliance, suspensions, and terminations of IRB approval will be made by the HRPP Director.
D. Compliance Oversight

Refer to HRPP OM Part 12.II.D

E. Response to Complaints or Allegations of Noncompliance

Refer to HRPP OM Part 12.II.D.1

If information brought to the attention of the IRBMED, through any source, indicates the possibility that research participants or others are exposed to unnecessary or excessive risks, or that the requirements of the IRBMED are not being met, the IRBMED shall collect any additional information necessary to evaluate the credibility or accuracy of the information and determine whether further action [such as education of the PI or the PI's research staff, or suspension or termination of the project] appears necessary. In some circumstances, in consultation with the IRBMED, the PI may place a voluntarily "hold" on new participant accrual or research-related interventions during the fact-finding period, unless to do so would place participants in immediate harm or otherwise jeopardize their well-being.

If the IRB is undertaking further inquiry, any voluntarily "hold" during this fact-finding period does not constitute a suspension of approval for purposes of the HRPP reporting to external agencies or sponsors.

Under institutional authority and federal regulations (45 CFR 46.103[b][5], 45 CFR 46.113, 21 CFR 56.113), the IRBMED is responsible for overseeing the safety of human participant research participants and has the authority to suspend or terminate human participant research that is (1) not being conducted in accordance with the federal and the IRBMED's requirements or (2) has been associated with unexpected serious harm to participants.

F. Noncompliance Review Procedures

Refer to HRPP OM Part 12.II.D.2

In the event of a credible allegation of noncompliance with applicable law or University policy, including these procedures, the matter will be handled consistent with University policies.

1. Should the allegation of noncompliance pose immediate risk to participants, the IRBMED will assure notification of the IRBMED Chairs, the Medical School Associate Dean for Regulatory Affairs, the Health System Legal Office, and the HRPP Director, as soon as possible.

2. Allegations or other indications of fabrication or falsification of research results will be reported to the Medical School Associate Dean for Regulatory Affairs, the Health System Legal Office, and the UMOR.

An IRBMED staff member initiates a review of any complaint or allegation of noncompliance made to the IRBMED. If assistance with the review is desired, the IRBMED Chairs will make a written request to UMOR (usually via the IRBMED Director) to request assistance from ORCR. The purpose of the review is fact-finding, and may involve examination of study records, including, but not limited to, source documentation, informed consents, and the study protocol. Where appropriate, the IRBMED staff member may engage in discussion with the research team, research participants, the complainant (if known), and others.

Initial fact-finding may include, but is not limited to, any or all of the following:

- Providing the IRBMED with copies of or access to:
  - Signed informed consent documents
  - Study files
  - Drug dispensement logs/IDS logs
  - Patient records
• Lab tests
• Delegation logs
• Observation of study activity (e.g., witnessing the informed consent process)
• Review of study by an outside auditor
• Interviews of study personnel
• Interviews of research participants

Upon completion of the review, the report is provided to the IRBMED Chair(s) in the context of a Chairs and Director Meeting (CDM). The Chair(s) review the information and determine whether the complaint or allegation of noncompliance constitutes potentially serious and/or continuing noncompliance. If so determined, the matter is referred to the convened board with oversight for the study in order to make a final determination as to the nature of the noncompliance.

The IRBMED shall notify the Medical School Associate Deans for Research and Regulatory Affairs and the HRPP Director of any complaints or allegations of noncompliance, as required in HRPP OM Part 12. As necessary, the HRPP Director will notify any applicable federal agencies and provide notification to institutional entities as indicated in the OM Part 12.

The IRBMED staff maintains records of all complaints and allegations of noncompliance that come to the attention of the IRBMED. These records include communications with the complainant and other parties providing information to the IRBMED, copies of source documents and other information gathered during the fact-finding activity, analysis of the fact-finding results for presentation to IRBMED Chair(s) and board members, notes and minutes of Chair and board member deliberations and determinations, and communications with the PI and relevant study personnel.

The IRBMED Chair(s) and Medical School Associate Deans for Research and Regulatory Affairs are provided with any copies of reports that are prepared for submission to the HRPP Director.

The IRBMED shall promptly notify the HRPP Director of (1) any potentially serious and/or continuing noncompliance; and (2) any suspension or termination of IRBMED approval for a project. In certain instances of alleged or apparent noncompliance, the IRBMED may choose to provide an early notification or preliminary report to the HRPP Director (i.e., where the noncompliance may pose immediate risk to participants) prior to a determination of serious and/or continuing noncompliance. As described in the HRPP OM Part 12, the HRPP Director may choose to further investigate the reports of serious and/or continuing noncompliance or to ask for additional review by the Office for Research Compliance Review (ORCR). On a quarterly basis, the IRBMED will prepare a list of all externally reportable events for review with the IRBMED Chair(s), and the Medical School Office of Regulatory Affairs for verification of appropriate reporting and follow-up.

G. How Compliance Concerns Are Brought Forward

Refer to HRPP OM Part 12.II.D.3

Reports or allegations of noncompliance are brought forward by, but are not limited to, the following means:

• Telephone
• Via electronic mail (e-mail) communications
• Anonymous communications (telephone, mail, e-mail)
• UM Compliance Telephone Hotline
• Through staff or faculty of the University

H. Receipt and Initial Handling of Allegations of Noncompliance

Refer to HRPP OM Part 12.II.D.4

I. Chair and Board Considerations and Determinations

Refer to HRPP OM Part 12.II.D.5

If, according to the results of the IRBMED fact-finding, the alleged noncompliance is evaluated by the Chair(s) or Director as credible to be potentially serious and/or continuing non-compliance, the available information will be presented to the IRBMED Chair(s) at the next available CDM Meeting, not later than thirty (30) days from the initial evaluation by the Chair(s) or Director. In reviewing the alleged noncompliance, the Chair(s) may request a meeting with the PI and others to discuss the concerns and provide an opportunity for the study team to correct or clarify the fact-finding information.

The Chair(s) determine by vote whether the activity (1) constitutes potentially serious noncompliance with IRBMED determinations or federal regulations; and/or, (2) separately constitutes potentially continuing noncompliance with IRBMED determination or federal regulations. Documentation of the outcome of a decision by the Chair(s) to refer the matter to the convened IRB will be sent to the Medical School Associate Deans for Research and Regulatory Affairs, the Health System Legal Office, and the PI.

If the convened IRB determines that the noncompliance was not serious and/or continuing, the Medical School Associate Deans for Research and Regulatory Affairs, the Health System Legal Office, and the PI will be notified. A finding of serious and/or continuing noncompliance as determined by the convened IRB will be sent to the PI, the Department Chair and Associate Chair for Research (if applicable), the Medical School Associate Deans for Research and Regulatory Affairs, the Health System Legal Office, and the HRPP Director. The IRB or other Medical School entity may request the additional collection of information or further investigation as needed in order to facilitate a determination of serious and/or continuing non-compliance. Such request may be made to the HRPP Director for the assistance of ORCR.

a) The IRBMED may also determine that additional monitoring activities are appropriate, and/or additional requirements or restrictions on either a PI or a particular study because of risk level, safety issues, conflict of interest issues, or because of findings of noncompliance.

Monitoring may include, but is not limited to, accessing and reviewing any or all of the following:

- Both clinical and research records
- Review of study by an outside auditor
- Interviews of research participants

Additional requirements or restrictions may include, but are not limited to, any or all of the following:

- Requirement for education, certification in the conduct of clinical research, i.e., the Association of Clinical Research Professionals (ACRP) or the Society of Clinical Research Associates (SoCRA), and re-certification of PEERRS
- Less than a one-year approval of the research project
- Submission of reports to the IRBMED at specific time intervals (in addition to the study’s scheduled continuing review submission for renewal of IRBMED approval)
• Submission of reports to the IRBMED at specific increments of participant participation (e.g., after every third participant completes the trial or after the first three doses of an agent)
• Restriction on location of study activities
• Requirement for additional supervision of overall study or aspects/activities of the study
• Prohibition, permanently or for a period of time, from obtaining informed consent from participants
• Prohibition, permanently or for a period of time, from conducting certain types of research
• Prohibition, permanently or for a period of time, from serving as a PI or study team member

J. Actions of the HRPP Director as Delegated by the Institutional Official

Refer to HRPP OM Part 12.II.D.6

K. Response to Determinations of Noncompliance

Refer to HRPP OM Part 12.II.D.7

One of the IRBMED Chair(s) will convey the board’s decision by telephone or e-mail to the PI at the conclusion of the board meeting and vote as to whether or not the noncompliance constitutes serious and/or continuing noncompliance. A formal letter will be sent to the PI outlining the reasons for the board’s decision and any required remediation (e.g., attendance at a designated IRBMED educational workshop).

L. Institutional Notification and External Reporting Requirements

Refer to HRPP OM Part 12.II.D.8

III. QUESTIONS AND CONTACT INFORMATION

Questions from research participants and study team members received by the IRBMED office are triaged by the IRBMED Receptionist or staff designee. The receptionist or designee will take the pertinent information and route the message to the most appropriate person to answer the question.

PIs and study team members may request representatives from the IRBMED office to meet with them to discuss a research project or regulatory question by contacting the Office Reception number listed below.

M. IRBMED Director and Office

• Director and Office Reception: (734) 763-4768
• E-mail: irbmed@umich.edu
• US Mail: IRBMED, 2800 Plymouth Rd., Building 520, Room 3214, Ann Arbor, MI 48109-2800

N. Questions Concerning University Policies and Procedures

• The Medical School Office of Research: (734) 615-1332
• The Medical School Office of Regulatory Affairs: (734) 647-1576
• The Office of the Vice President for Research: (734) 763-1289
• The Health System Legal Office: (734) 764-2178