TITLE: Institutional Review Board Review of Research
   RR 405 Unanticipated Problems, Protocol Deviations and Non-Compliance

ORIGINATOR: Institutional Official
APPROVAL: Institutional Official

POLICY STATEMENT: To outline the procedure to ensure prompt reporting to the IRB, appropriate institutional officials, sponsors, coordinating centers and the appropriate regulatory agency heads of all unanticipated problems, protocol deviations and non-compliance involving risks to participants and others.

GENERAL PROVISIONS

Unanticipated Problems

An unanticipated problem is any event, experience, issue, instance, problem, or outcome that meets all 3 of the following criteria:

- Unexpected in terms of nature, severity or frequency given the research procedures that are described in the protocol–related documents AND the characteristics of the subject population being studied.
- Related or possibly related to participation in the research. This means that there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in the research study.
- The event, experience, issue, instance, problem or outcome suggests that the research places the subject or others at greater risk of harm that was previously known or recognized.

A small number of adverse events are considered Unanticipated Problems. If an adverse event meets ALL 3 of the criteria listed above, then the event is considered an adverse event AND an unanticipated problem: Those events that meet the definition of both adverse event and unanticipated problem are reported to the Mercy Health Regional IRB through the IRBManager system using an Unanticipated Problem Report Form.

A small number of protocol violations are considered unanticipated problems ONLY if they meet all 3 of the criteria listed above. Events that meet the definition of both protocol violation and unanticipated problem are reported to the Mercy Health Regional IRB using the Unanticipated Problems Report Form.

The following unanticipated problems must also be reported:

- Breach of confidentiality
- New Information received that indicates a new or increased risk to participants
- A harm has been experienced by a local research participant or other individual which in the opinion of the local investigator is unexpected and is related to the Human Research procedures (This is not to be used for a serious adverse event. This choice is to be used when there is an adverse event with greater than 50% probability that the research procedure more than likely caused the harm)
- Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
Institutional Policy & Procedure

- A finding of non-compliance or continuing non-compliance
- A for-cause inspection or audit by a federal agency
- A change to the protocol has been made without prior IRB review to eliminate an immediate hazard to a participant
- A participant complaint that cannot be resolved by the research team
- A local participant has become a prisoner in a study not approved to involve prisoners
- Failure to follow protocol due to an action or inaction by the investigator or study team that affects the scientific soundness of the plan or the rights, safety or welfare of human subjects (minor protocol deviations are to be reported at the time of continuing renewal)

Unanticipated problems that that are not the result of an adverse event or protocol violation must be submitted to the Mercy Health Regional IRB within 7 calendar days from the time the study team receives knowledge of problem.

Protocol Deviations and Protocol Violations

The term “protocol deviation” is not defined by either the HHS human subject’s regulations (45 CFR 46) or the FDA human subject’s regulations (21 CFR 50). At Mercy Health, minor or administrative protocol deviations are defined as those which do not “affect the scientific soundness of the research plan or the rights, safety, or welfare of human subjects.” If a protocol deviation occurs which meets this definition, the deviation should be reported to the Mercy Health Regional IRB at the time the continuing review application is submitted. Investigators should use the Protocol Deviation Summary Sheet to report these deviations. The sheet should be uploaded in the electronic IRB submission system at the time of the continuing renewal submission as an attachment to the continuing renewal form. Examples of minor or administrative deviations could include: follow up visits that occurred outside the protocol required time frame because of the participant’s schedule, or blood samples obtained at times close to but not precisely at the time points specified in the protocol.

Investigators should be aware that sponsored research agreements may require the PI to notify the sponsor of all unplanned deviations or departures from IRB approved protocol procedures. Sponsor reporting requirements for deviations may differ from Mercy Health Regional IRB reporting requirements. It is the PI’s responsibility to comply with the reporting requirements outlined in the signed contract. Before a PI signs a research agreement, the PI is strongly advised to read and understand the contract terms.

Many sponsors require investigators to follow Good Clinical Practice (GCP) guidelines. The GCP Guidance for Industry states: “The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB...of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).”

Protocols that involve an Investigational Device Exemption (IDE)

FDA device regulations at 21 CFR 812.150(a)(4) require prior approval from the sponsor of all planned deviations, including administrative and minor deviations. Planned deviations requested of a sponsor must be submitted for IRB review and approved by the Mercy Health Regional IRB prior to instituting any IDE research planned deviations. The PI must submit a modification submission form. For device research, the PI must keep on file a copy of the written approval document from the sponsor when a deviation is granted.

Emergency Deviations

When a deviation occurs in an emergency situation, such as when a departure from the protocol is required to protect the life or physical well-being of a participant. The sponsor and the reviewing IRB must be notified as soon as possible, but not later than 5 days after the emergency situation occurred (21 CFR 812.150(a)(4)). The PI must submit a report to the Mercy Health Regional IRB using the Unanticipated Problem Report Form.

Non-Compliance, Serious Non-Compliance and Continuing Non-Compliance

Reports of non-compliance will be directed to the appropriate IRB staff and to the IRB for investigation and corrective action. Complaints about the IRB process or the conduct of research may or may not involve non-compliance with IRB policies or federal regulations and will be handled as potential unanticipated problems.
Institutional Policy & Procedure

involving risks to participants or others. Complaints that do not have elements of non-compliance should be handled in accordance with the IRB policy for addressing complaints.

It is the policy of the Mercy Health Regional IRB to address both allegations and confirmed reports of any non-compliance in accordance with 45 CFR Part 46, 21 CFR Part 50, the policies, requirements and determinations of the IRB. Members of the research community must report apparent non-compliance to the IRB. The determination that non-compliance is serious or continuing rests with the IRB.

The following cases are presumed by the Mercy Health Regional IRB to constitute serious non-compliance. The burden is on the investigator to rebut the presumption by presenting compelling evidence of error or circumstances.

- Human subjects research conducted without IRB approval
- Subjects enrolled without consent (when not eligible for a waiver of consent)
- Subjects enrolled without meeting inclusion/exclusion criteria
- Substantive change to the research implemented without IRB approval (unless implemented to avoid imminent harm to subjects)

Examples of cases that could constitute continuing non-compliance:

- Repeatedly late submissions of reportable events
- Repeated lapses of IRB approval during which human subjects research occurs
- Repeated failure to comply with an IRB-approved protocol
- Repeated informed consent discrepancies

Reports of non-compliance may be provided to the IRB Chairperson from anyone inside or outside of the Mercy Health community who has reason to believe that the non-compliance with the IRB policies has occurred.

Allegations that are presented via telephone or in person through the Office of the IRB will be directed to the IRB Chairperson. The recipient of the call should take care to record all relevant information in a thorough manner and request that the caller provide a contact number for follow-up calls, unless the caller desires to remain anonymous. The person making the allegation may choose to remain anonymous. The recipient of an anonymous call should inform the caller that the matter will be investigated to the extent possible given the information provided. The recipient of the call should ask the caller for any available evidence that the caller is willing to give that will facilitate an investigation into the matter, but should not encourage the caller to provide a name or contact information if the caller has expressed a desire to remain anonymous. It is permissible to advise the caller to provide additional information at a later date if new information becomes available or if the caller remembers details that were not presented originally.

*Not serious and not continuing*: If it is determined by the IRB Chairperson that the allegation is not serious and not continuing, the Investigator will be notified by the Office of the IRB. In addition, the IRB Chairperson will discuss the issue with the Investigator and an action plan will be drafted. The final action plan will be forwarded to the Investigator via letter or e-mail and the information will be included in the IRB agenda as an information item.

*Non-Compliance that may be Serious or continuing*: If it is determined by the IRB Chairperson that the allegation is non-compliance that may be serious or continuing, the Investigator will be notified by the IRB Coordinator or the IRB Chairperson of the findings and/or requests for information by phone call, letter, or e-mail. The Investigator will be asked to respond in writing to the allegation and depending on the response, the Investigator may be asked by the IRB Coordinator or IRB Chairperson to attend the IRB meeting and/or a meeting with the IRB Chairperson. The Investigator will have 14 consecutive days to respond. If the Investigator needs more time, an extension may be granted by the IRB Chairperson. The written response will be presented to the Full Board at a convened meeting for review.

If it is determined by the IRB Chairperson to meet the definition of continuing non-compliance or serious non-compliance, the IRB Chairperson will add the item to the next full board IRB meeting for review and the IRB committee members will be provided with the information received. The convened IRB reviews and discusses the
information during the IRB committee meeting. The IRB committee determines if the confirmed report of non-compliance represents serious non-compliance or continuing non-compliance, as defined by this policy, the IRB considers but is not limited to the following actions:

- Verification that participant selection is appropriate.
- Observation of the research and the informed consent process by an assigned IRB reviewer.
- Modifications of the protocol.
- Request an increase in monitoring of the research activity via an independent data safety monitor or board.
- Safety intervention as necessary such as visits to the activity site and continuing evaluation of the site by an IRB reviewer.
- Request audit and progress reports from the sponsor monitor or contract research organization.
- Request a directed audit of targeted areas of concern by an IRB reviewer.
- Request a status report after each participant receives intervention from the Investigator.
- Modify the frequency of the continuing review cycle.
- Request additional Investigator and staff education focused on human research protections from appropriate available sources (e.g., GCP Training, OHRP conferences, CITI tutorial, human research protections seminars).
- Notify current subjects, if the information about the non-compliance might affect their willingness to continue participation.
- Provide additional information to past participants.
- Suspend IRB approval of the respective study pending a written plan for the correction and/or prevention of the non-compliance.
- Remove the Principal Investigator of the research study.
- Suspend or terminate some or all of the research study and possibly other studies being conducted by the Principal Investigator as well.

The convened IRB must also document whether or not action is needed to prevent an immediate hazard to subjects. If modification to the protocol, informed consent form or investigational brochure are required, the convened IRB must determine whether previously enrolled subjects must be notified, and if so, when and how notification and documentation must occur. An action plan is developed and provided to the Investigator with a defined timeline for written response.

The IRB Chairperson provides all findings of serious or continuing non-compliance to the Institutional Official who is responsible for reporting to the appropriate oversight and federal authorities.

**Reporting Findings of Serious and Continuing Non-Compliance to Federal Authorities**

Under 21 CFR 56.113, an IRB shall have the 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 Food and Drug Administration.

21 CFR 56.108(b) requires that the IRB follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of:

1. Any unanticipated problems involving risks to human subjects or others;
2. any instance of serious or continuing non-compliance with these regulations or the requirements or determinations of the IRB; or
3. any suspension or termination of IRB approval.
Institutional Policy & Procedure

When reporting suspensions or terminations of IRB approval, please include the IND or IDE number, the full name of the research protocol, the name(s) of the clinical investigators, and the reason(s) for the suspension or termination. These reports may be submitted via e-mail or in hard copy by FAX or mail. Information should be submitted to the following locations/contacts:

For Drug Products:

*Please report suspension or termination of IRB approval; unanticipated problems involving risks to human subjects; or serious or continuing non-compliance with the regulations or the requirements or determinations of the IRB to:*

Ms. Dana Walters
Dana.Walters@fda.hhs.gov
Division of Scientific Investigations (HFD-45)
Office of Compliance
Center for Drug Evaluation and Research
White Oak Campus
10903 New Hampshire Ave.
BLDG 51, Rm. 5341
Silver Spring, MD 20993
Phone: (301) 796-3150
Fax: (301) 847-8748

For Biologic Products:

*Please report suspension or termination of IRB approval; unanticipated problems involving risks to human subjects; or serious or continuing non-compliance with the regulations or the requirements or determination of the IRB to:*

Ms. Patricia Holobaugh
Patricia.Holobaugh@fda.hhs.gov
Bioresearch Monitoring Branch (HFM-664)
Division of Inspections and Surveillance
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research/FDA
1401 Rockville Pike, Room 400S
Rockville, MD 20852-1448
Phone: (301) 827-6347
Fax: (301) 827-6748

For Medical Devices:

*Please report suspension or termination of IRB approval; unanticipated problems involving risks to human subjects; or serious or continuing non-compliance with the regulations or the requirements or determination of the IRB to:*

Phone (301) 796-5490
Fax: (301) 847-8136
Email: bimo@cdrh.fda.gov

DEFINITIONS

**Non-Compliance** – Failure to conduct the study according to applicable regulations or Mercy Health Institutional Policies or Mercy Health IRB Policies. Failure to comply with the requirements or determinations of the IRB.

- The IRB Chairperson reviews all allegations and self-reports of non-compliance and refers all potential cases of serious or continuing non-compliance to the full board. The full board must make the
- The convened IRB may review and make determinations on individual occurrences and/or collective occurrences, and/or on a study as a whole.

**Serious Non-Compliance** - Non-compliance, which in the judgment of the convened IRB, significantly increases risk to participants, and/or significantly decreases potential benefits, and/or compromises the integrity of the Human Research Protection Program (HRPP) or the study. Individual instances of non-compliance that are deemed not
serious may constitute serious non-compliance when considered collectively. IRB does not have to find that harm has occurred or was likely to occur to make a determination of serious non-compliance.

- The Board should review the event by itself, and consider if the event constitutes serious non-compliance. The Board may consider mitigating factors, such as corrective action, that play a role in the determination of whether the event increased risk, decreased potential benefits, or negatively affected the integrity of the HRPP, but if despite these factors, the event’s occurrence meets the definition of serious non-compliance, then the event should be categorized as such. For example, if study activities took place without IRB approval, the fact that the study was minimal risk or exempt should not play a role in the final determination, as the end result was unchanged: research without appropriate IRB review/approval took place. Alternatively, as another example, if the wrong dose of a study medication was prepared, but through quality assurance measures was recalled by the researcher before it was given to the patient, then the recall action could be considered in determining that the event constituted protocol non-compliance, as opposed to serious non-compliance.

**Continuing Non-Compliance** – A pattern of non-compliance, that, in the judgment of the convened IRB, suggests a likelihood that instances of non-compliance will continue unless intervention occurs. The OHRP has advised that it considers that non-compliance is continuing if it persists after the investigator knew or should have known about it. Non-compliance is presumed by the Mercy Health Regional IRB to constitute continuing non-compliance if it persists after the investigator knew or reasonably should have known about it. To rebut the presumption, the burden is on the investigator to present compelling evidence of error or mitigating circumstances.

**REFERENCES:**
OHRP Guidance on Reviewing and Reporting Unanticipated Problems
FDA Guidance on Adverse Event Reporting
http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ReportProblemstoFDA/ucm136102.htm
21 CFR 56.108(b)(2), 56.113
45 CFR 46.113

**ATTACHMENTS:**
- 405-A Unanticipated Problem Report Form
- 405-B IRB Acknowledgement of Receipt and Review of Unanticipated Problem
- 405-C IRB Checklist for Review of Protocol Deviations
- 405-D IRB Checklist for Review of Unanticipated Problems
- 405-E Points to Guide IRB Discussion in review of Unanticipated Problems and Non-Compliance
- 405-F Potential Non-Compliance Report Form
- 405-G Protocol Deviation Summary Report Form
- 405-H IRB Acknowledgement of Receipt and Review of Protocol Deviations-No Action Required
- 405-I IRB Acknowledgement of Receipt and Review of Non-Compliance, Serious Non-Compliance or Continuing Non-Compliance-No action required
- 405-J IRB Checklist for Review of Non-Compliance, Serious Non-Compliance or Continuing Non-Compliance
- 405-K IRB Acknowledgement of Receipt and Review of Non-Compliance-Action Required
- 405-L IRB Acknowledgement of Receipt and Review of Protocol Deviations-Action Required

**PROCEDURE: All Mercy Health Campuses**

**Procedure for Review of Unanticipated Problem Reports**

<table>
<thead>
<tr>
<th>Responsibility</th>
<th>Action</th>
</tr>
</thead>
</table>
| Investigator   | 1. Submit Unanticipated Problem Reports to the IRB within 5 working days of discovery.  
|                | 2. Follow all action plans as requested by the IRB. |

Version Date 11/02/2016
1. Upon receipt of non-compliance or discovery/admission of non-compliance, notify the IRB Chairperson.
2. Review the Unanticipated Problem submission to determine if the report includes the necessary information for the initial evaluation.
3. Return incomplete unanticipated problem submissions to the investigator with the request for more information.
4. Notify the IRB Chairperson of the receipt of the unanticipated problem notification.
5. Place the unanticipated problem report on the next Full Board IRB Meeting agenda to be reviewed.
6. Issue IRB notification to investigator after the review of the unanticipated problem has been completed.

IRB Chairperson

1. Review the unanticipated problem report and determine if the event involved risks to the participants or others.
2. Notify the appropriate parties of the unanticipated problem (i.e. legal, risk, sponsor etc.)
3. If report of non-compliance is unknown to the investigator, notify the investigator (unless notification could jeopardize the investigation) that an investigation is being conducted.
4. If the problem places current research participants at an immediate risk, contact investigator and discuss option for ensuring participant safety. If the convened IRB or IRB Chair determines that participants are at immediate risk of harm, the principal investigator may be required to suspend the study according to the IRB policy for suspension or termination of research.
5. Notify the IRB Safety Committee. IRB Chair may request a safety committee recommendation for addressing the unanticipated problem.
6. Review the IRB Safety Committee Review Team recommended action.
7. Request issuance of appropriate IRB correspondence to the Investigator.

IRB Safety Committee

1. Review the unanticipated problem report immediately upon receipt.
2. Recommend an action plan to the IRB Chairperson.

IRB Committee

1. Review the unanticipated problem report and determine if further action is required to address the unanticipated problem beyond any action the IRB Chairperson may have already taken.
2. The IRB committee should consider the actions outlined in this policy. The committee may also determine an action that is not outlined in this policy is necessary.

---

**Procedure for Review of Protocol Deviations**

**Responsibility**

**Investigator**

1. Submit minor or administrative protocol deviations to the IRB at the time of continuing renewal using the protocol deviation summary sheet RR 405-B.
2. Follow all action plans as requested by the IRB.
Institutional Policy & Procedure

IRB Specialist/IRB Coordinator

1. Review the protocol deviation summary sheet to determine if the report includes the necessary information for the initial evaluation.
2. Return incomplete protocol deviation summary sheets to the investigator with the request for more information.
3. Notify the IRB Chairperson of the receipt of the protocol deviation summary sheet.
4. Place the protocol deviation summary sheet report with the continuing renewal submission to be reviewed.
5. Issue IRB notification to investigator after the review of the protocol deviation summary sheet has been completed.

IRB Chairperson

1. Review the protocol deviation summary sheet and determine if the reported deviations meet the definition of non-compliance or continuing non-compliance.
2. Notify the appropriate parties of the determination of non-compliance or continuing non-compliance.
3. If the non-compliance or continuing non-compliance places current research participants at an immediate risk, contact investigators and discuss option for ensuring participant safety. If the convened IRB or IRB Chair determines that participants are at immediate risk of harm, the principal investigator may be required to suspend the study according to the IRB policy for suspension or termination of research and will report the continuing non-compliance to federal authorities according to the regulations and this policy.
4. Notify the IRB Safety Committee. May request a safety committee recommendation for addressing the non-compliance finding.
5. Review the IRB Safety Committee Review Team recommended action.
6. Request issuance of appropriate IRB correspondence to the Investigator.

IRB Safety Committee

1. Review the protocol deviation summary sheet upon receipt.
2. Recommend an action plan to the IRB Chairperson.

IRB Committee

1. Review the protocol deviation summary sheet and determine if further action is required to address the reported deviations beyond any action the IRB Chairperson may have already taken.
2. The IRB committee may review the IRB safety committee recommended action and should determine an appropriate action.
3. For a report of an emergency protocol deviation taken without prior IRB review, the IRB should consider if the changes were consistent with the rights and welfare of participants.
Institutional Policy & Procedure

Review of Non-Compliance, Serious Non-Compliance and Continuing Non-Compliance

<table>
<thead>
<tr>
<th>Responsibility</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRB Specialist/IRB Coordinator</td>
<td>1. Provide reports of potential non-compliance, serious non-compliance and continuing non-compliance to the IRB Chairperson for review for the initial evaluation.</td>
</tr>
<tr>
<td></td>
<td>2. Place the reports of potential non-compliance, serious non-compliance and continuing non-compliance on the next IRB meeting agenda as requested by the IRB Chairperson.</td>
</tr>
<tr>
<td></td>
<td>3. Provide all materials necessary for the IRB committee to conduct review and discussion of non-compliance.</td>
</tr>
<tr>
<td></td>
<td>4. Issue IRB notification to investigator after the review has occurred. IRB notification may request further information, outline an action plan or provide confirmation that an action plan has been completed.</td>
</tr>
<tr>
<td>IRB Chairperson (or designee)</td>
<td>1. Review the protocol deviation summary sheet or record of verbal report of allegations of non-compliance and determine if the reported deviation/s meet the definition of non-compliance, continuing non-compliance, or serious non-compliance.</td>
</tr>
<tr>
<td></td>
<td>2. Notify the IRB Specialist of report of non-compliance to be added to the next IRB meeting agenda work with them to identify the materials needed for review and further determination of non-compliance, serious non-compliance or continuing non-compliance.</td>
</tr>
<tr>
<td></td>
<td>3. If the non-compliance, serious non-compliance or continuing non-compliance places current research participants at an immediate risk, contact investigators and discuss the options for ensuring participant safety. If the convened IRB or IRB Chair determines that participants are at immediate risk of harm, the principal investigator may be required to suspend the study according to the IRB policy for suspension or termination of research. The chairperson will then report the non-compliance to federal authorities according to the regulations as outlined in this policy.</td>
</tr>
<tr>
<td></td>
<td>4. Notify the IRB Safety Committee when requesting their review of reports of non-compliance, serious non-compliance or continuing non-compliance. May request a safety committee recommendation for addressing review findings.</td>
</tr>
<tr>
<td></td>
<td>5. Review the IRB Safety Committee recommended action and present to IRB committee at convened meeting for review and discussion.</td>
</tr>
<tr>
<td></td>
<td>6. Present the report of non-compliance at the next convened IRB meeting and prepare to lead discussion and provide guidance in the actions needed to resolve the findings.</td>
</tr>
<tr>
<td></td>
<td>7. Request issuance of appropriate IRB correspondence to the Investigator.</td>
</tr>
<tr>
<td>IRB Safety Committee</td>
<td>1. May be assigned to review reports of non-compliance, continuing non-compliance and serious non-compliance upon IRB Chair or IRB committee request.</td>
</tr>
<tr>
<td></td>
<td>2. May recommend an action plan to the IRB Chairperson.</td>
</tr>
</tbody>
</table>
Institutional Policy & Procedure

IRB Committee

1. Review the documents outlining the potential non-compliance.
2. Determine if action was non-compliance, serious non-compliance or continuing non-compliance.
3. Determine what action is needed to resolve findings of continuing non-compliance or serious non-compliance beyond any action the IRB Chairperson may have already taken.
4. The IRB committee may recommend actions as outlined in this policy.
5. If investigator proposed changes based on event prior to IRB review, the IRB will consider if the changes were consistent with the rights and welfare of participants.

Institutional Official

1. Report findings of continuing non-compliance and serious non-compliance to the appropriate officials including federal authorities.

Investigator

1. Provide Office of the IRB and IRB committee with requested information related to the review of protocol deviations and potential non-compliance, continuing non-compliance and serious non-compliance.
2. Follow all action plans as requested by the IRB.

CONCURRENT CONSENTS:

Institutional Official

[Signature]