UMKC
Office of Research Services

9. Protocol Violations

9.1. Policy

Federal regulations require the IRB to review proposed changes in any research activity and to ensure the investigator does not initiate such changes in approved research without IRB review and approval except when necessary to eliminate apparent immediate hazards/risks to the subject [45CFR46.108(a)(3)(iii) and 21CFR56.108(a)(4)]. Research activity includes all aspects of the conduct of the research study (e.g., recruitment methods, consent process, procedures used to protect privacy and confidentiality, etc.) And all of the information outlined in the IRB application/protocol reviewed and approved by the IRB.

9.2. Definitions

The following definitions apply throughout this Guidance document:

Protocol deviation: any alteration/modification in the IRB-approved protocol that has not been approved by the IRB in an amendment. The protocol includes the detailed protocol, protocol summary, consent form, recruitment materials, questionnaires, and any other information relating to the research study.

Protocol exception: any temporary protocol deviation that is approved by the IRB prior to its implementation, e.g., enrollment of a subject who does not meet the eligibility criteria.
Note: any permanent change to the protocol constitutes an amendment that must be submitted to the IRB for approval prior to initiation.

Protocol violation: any protocol deviation that is not approved by the IRB prior to its initiation or implementation.

- **Reportable violation**: a violation that may impact subject safety, affect the integrity of study data and/or affect subject's willingness to participate in the study.
    - All *reportable protocol violations* must be reported to the IRB within ten (10) days of discovery.

- **Non-reportable violation**: a violation that does not impact subject safety, compromise the integrity of study data and/or affect subject's willingness to participate in the study.

Some protocol violations, regardless of other reporting requirements, may also meet the definition of an Adverse Event according to FDA or an Unanticipated Problem according to OHRP. If the protocol violation is also an Adverse Event or Unanticipated Problem, UMKC Adverse Event reporting requirements (see SOP 8) should be followed when determining when and how to report the violation. In the case of an Unanticipated Problem, additional reporting to OHRP is required.

If the PI is unsure of whether a violation is reportable, the PI is urged to contact the IRB office for assistance. When applicable, reports of protocol violations should also be submitted to the sponsor as outlined in the sponsor's protocol or other instructions to the PI.

> ***Note: whether a protocol violation qualifies as "reportable" or "non-reportable" depends heavily on the specific facts of the violation. The examples provided below are not intended as exhaustive lists and there may be overlap between the examples. The key to whether a given example will qualify as "reportable" vs. "non-reportable" depends on whether, under the specific circumstances, the violation may impact subject safety, affect the integrity of study data, and/or affect subjects' willingness to participate in the study.***

9.3. Planned Changes to Research Protocol

Most planned changes to a research protocol must be approved by the IRB through the submission of an amendment. Examples of these planned changes include an increase in subject number, changes in investigators or key personnel, a change to the funding source, changes in procedures, and revised consent documents. In these cases, planned changes are not protocol deviations themselves (although they may result from a protocol deviation).

Another type of planned change to the research protocol is called a protocol exception, which is made for a single subject or a small group of subjects, but is not a permanent revision to the research protocol. Protocol exceptions are a subset of protocol deviations. Similar to an amendment, a protocol exception must be IRB approved prior to its implementation. If the research involves an investigational agent (e.g., drug, device, or biologic), except in an emergency situation to eliminate immediate harm, prior approval by the sponsor also is required. Additionally, when research involves an investigational device and the changes or deviations may affect the scientific soundness of the research plan or rights, safety, or welfare of subjects, FDA and IRB pre-approval is required [21 CFR §812.150(4)]. Although a protocol exception must be prospectively approved by IRB, because the change does not involve a ***permanent*** change to the research protocol, the FDA considers it to represent a protocol deviation.

9.4. Unplanned Changes to Research Protocol

The next category involves unplanned changes to a research protocol not otherwise approved by the IRB. Such unplanned changes are protocol violations.

9.5. Protocol Deviations

A protocol deviation is any change from the procedures stated in the IRB- approved study protocol, consent document, recruitment process, or study materials (e.g. Questionnaires) that has not itself been IRB-approved. Protocol deviation is a general term and includes, protocol exceptions, changes made to avoid immediate harm to subjects, and protocol violations. [45 CFR 46.103 (b) (4) (III), 21 CFR 56.108 (a) (4)]. Repeated failure by a PI to not report protocol deviations may be viewed as Non-Compliance with the Federal regulations, the guidelines that govern ethical conduct of research, and UMKC's HRPP.

9.5.1. Protocol Violation

A protocol violation is a subset of protocol deviation. It is any change from the IRB approved study protocol, consent document, recruitment process, or study materials that was not approved by the IRB prior to implementation. Generally, protocol violations occur after the subject is enrolled in the research. However, some protocol violations, such as deviations from the approved consent process, can occur before the subject is enrolled in the research. Protocol violations may be either reportable protocol violations or non-reportable protocol violations, based on their relative severity.

9.5.1.1. Reportable Protocol Violation

A reportable protocol violation is a deviation that has an impact on subject safety, may substantially alter risks to subjects, may have an effect on the integrity of the study data, or may affect the subject's willingness to participate in the study. Reportable protocol violations can vary in the degree of seriousness according to how the changes impact subject safety, the degree of Non-Compliance with Federal regulations, state laws, UMKC policies or procedures, and the degree of foreknowledge of the event.

All reportable protocol violations must be reported by the PI to the IRB within ten (10) days of learning of the violation. If it is necessary to make a permanent change to the study procedures in order to avoid harm to other subjects, then a protocol amendment should be submitted, by the PI, as soon as possible. If appropriate to maintain safety of the subjects, new subject enrollment should be temporarily stopped by the PI until the amendment is approved.

No matter who discovers a reportable protocol violation (e.g., sponsor or their agent during a monitoring visit), the PI is responsible for reporting it to the IRB.

Examples of reportable protocol violations (this list is intended as a guide and is not all-inclusive):

- Implementation of unapproved recruitment procedures that, in the opinion of the PI, may affect subjects' willingness to participate in the study.
- Failure to obtain consent or document the consent process (e.g., there is no documentation of consent for a particular subject).
- Failure to provide a copy of the signed consent form to the research subject
- Consent is obtained after initiation of study procedures.
- Consent is obtained using an outdated or expired consent form where there is a material difference that, in the opinion of the PI, may affect subjects' willingness to participate in the study).
- Consent for greater than minimal risk studies obtained by someone other than Individuals authorized by the IRB to obtain consent.
- Enrollment of a subject beyond screening who did not meet all inclusion and exclusion criteria.

- Performing study procedures not approved by the IRB (including changes in the frequency of approved procedures or the dosage or route of administration for approved drugs that were not approved by the IRB).
- Consenting subjects or performing study procedures after IRB approval for the study has lapsed.
- Failure to report a serious Adverse Event or Unanticipated Problem involving risks to subjects or others to the IRB and/or sponsor as required by applicable policies, regulations and/or sponsor requirements.
- Failure to perform a required lab test that, in the opinion of the PI, may affect subject safety or data integrity.
- Study medication dispensing or dosing error.
- Study visit conducted outside of the required timeframe that, in the opinion of the PI, may affect subject safety.
- Failure to follow the safety monitoring plan.
- For all non-exempt research, significant over-enrollment (such that it triggers safety or data integrity concerns).
- Recruiting or consenting subjects without a current IRB approval
- Use of recruitment procedures that have not been approved by the IRB.
- Any deviations from the investigational plan for an investigational device taken to protect the life or physical well-being of a participant in an emergency.
- Any emergency use of an FDA-regulated test article or humanitarian use device (HUD) prior to IRB approval.
- Sponsor-imposed suspension for risk.
- Breaches in subject confidentiality or privacy that could pose an increased risk to subjects or others.
- Loss of laptop computer that contained identifiable, private information about subjects.

9.5.1.2. Non-Reportable Protocol Violations

A non-reportable protocol violation is one that does not impact subject safety, compromise the integrity of the study data, or affect the subject's willingness to participate in the study. Non-reportable protocol violations do not require reporting to the IRB.

Examples of non-reportable protocol violations (this list is intended as a guide and is not all-inclusive):

- Missing original signed and dated consent form (only a photocopy is available).
- Inappropriate documentation of consent, such as:
    - Missing investigator signature;
    - Someone other than the subject dated the consent form; or
    - The date the authorized person obtaining consent signed the form does not match the date the subject signed the form.

    - *These must be singular instances. Inappropriate documentation on a consistent level is a reportable violation and may constitute Non-Compliance.*
- Failure to follow an approved study procedure that, in the opinion of the PI, does not affect subject safety or data integrity, such as: study procedure conducted out of sequence; or study visit conducted outside of the required time frame.
- Failure of subject to return study medication.
- Research study visits occurring outside of study window not impacting subject safety or research data.
- A rescheduled study visit.
- Incarceration of a participant enrolled in a protocol not approved to enroll prisoners.
- Study participant non-adherence.
- The sponsor may require the violation to be reported to the IRB or the study team may feel more comfortable reporting all violations.

9.5.2. Protocol Exception

A protocol exception is a temporary protocol deviation that is approved by the sponsor or funding agency, (and, if applicable, the FDA for investigational device studies) and the IRB, prior to its implementation. Protocol exceptions are generally for a single subject or, occasionally, a small group of subjects.

Protocol exceptions must be submitted to the IRB and granted approval prior to subject enrollment and implementation, except where necessary to eliminate apparent immediate hazards to the human subjects. [DHHS 45 CFR 46.103(b)(4); FDA 21 CFR 56.108(a)(4); ICH 3.3.7].

The protocol exception is usually evaluated by both the sponsor or funding agency (and the FDA, if applicable) and the IRB in order to determine that it does not increase the risk to the subject(s), or jeopardize the integrity of the research data. Documentation of sponsor (or FDA) pre-approval and IRB approval of the exception should be maintained in the PI's research records.

The PI has ultimate responsibility for obtaining prior IRB approval for protocol exceptions. Repeated failure to obtain prospective IRB approval for protocol exceptions may be viewed as Non-Compliance with the Federal regulations, the guidelines that govern ethical conduct of research, and UMKC's HRPP.

Example of protocol exceptions:

- Enrollment of a research subject who fails to meet all of the protocol eligibility criteria (e.g., the subject may have been evaluated for all other parameters, and it was determined that not meeting this inclusion criteria or laboratory screening value would not cause harm to the subject or alter the validity of the study).

9.6. IRB Review Process

The IRB Chair or designee will review the violation and determine whether it should have an expedited review or requires convened IRB review. All major protocol violations that occurred since the initial or most recent continuing review should be summarized in the appropriate section of the continuing review form. 9.9.2 Reportable protocol violations

Each protocol violation report should discuss what measures have been put in place to prevent future re-occurrences of the same event. The PI should also evaluate protocol violations for any trends or patterns that would require additional corrective actions or submission of a protocol amendment to prevent future violations. Repeated violations of a similar nature may be a clear Indication that a permanent change (i.e. an amendment) to the study procedures is necessary.

The possible determinations the IRB reviewer may make about the event through expedited review are as follows:

- Acknowledged - no further information or action required;
- Modifications or additional information required additional information is needed in order to appropriately evaluate the event or changes to the research that are minor in nature;
- Refer for convened review –The IRB member determines the event is not eligible for expedited review and prefers the proposal be reviewed by the convened IRB. Additional information or materials may also be requested.

For protocol violations that require fully convened IRB review, the potential determinations are as follows:

- Acknowledged - no further information or action required;
- Modifications or additional information required – additional information needed in order to appropriately evaluate the event or changes to the research that are minor in nature is required based upon the event.

If there are safety issues or concerns related to the event the IRB may make additional determinations that include, but are not limited to, the following:

- Require substantive changes of the research protocol and/or consent document including the re-consenting of previously enrolled subjects;
- Implement additional safeguards, such as additional safety monitoring or more frequent safety monitoring;
- Increase the continuing review frequency (i.e. 6 months or 3 months);
- Suspend or place a temporary hold on the research and recommend revisions to the research that must be made before the suspension can be lifted (suspensions must be reported to the appropriate federal agencies);

- Suspend or place a temporary hold on enrollment of new subjects, either temporarily or permanently (suspensions must be reported to the appropriate federal agencies);
- Discontinue the participation of currently enrolled subjects;
- Terminate the research.

For Federal reporting purposes the IRB will need to determine whether the protocol violation constitutes an instance of serious or continuing Non-Compliance. If the violation is an event involving a change in the protocol to eliminate immediate hazard or harm to subjects, the IRB should ensure that the event was reported in the required period. Also, the IRB should make certain the PI implemented appropriate measures to alleviate or eliminate the harm to current and future subjects in the research.

The fully convened IRB discusses the event at the convened meeting and the IRB meeting minutes document the discussion and final determination of the convened IRB regarding the protocol violation. The documentation of review is maintained. Once a determination is made by the IRB, the PI will receive notification from the IRB. If there are no issues with the protocol violations, the PI will receive an acknowledgement of protocol violation.

9.6.1. Non-Reportable Protocol Violations

Non-reportable protocol violations do not require reporting to the IRB. All protocol violations should be reported to the research sponsor or funding agency in a timely fashion and according to that company's or agency's policy. All protocol violations should be documented in the investigator's research study files.

The study file should include documentation of the measures that have been put in place to prevent future re-occurrences of the same event. The PI should also evaluate protocol violations for any trends or patterns that would require additional corrective actions or submission of a protocol amendment to prevent future violations. Repeated violations of a similar nature may be a clear Indication that a permanent change (i.e. an amendment) to the study procedures is necessary.

UMKC investigators are not required to report protocol violations to UMKC's IRB that occur at other research sites in multi-center research trials. The investigator may have other reporting requirements such as reporting to an institutional biosafety committee, and/or other appropriate institutional entities that are not covered in this policy.

It is highly recommended that the investigator keep a log of protocol violations for each research study. The log should include the subject study identifier, the date of the violation, an indication of whether the violation was a reportable or non-reportable violation, a description of the violation, the date of the IRB submission, date of notification from the IRB, date of sponsor notification, and the date of sponsor notification of receipt. Copies of the report sent to the IRB should also be maintained in the research files.

9.6.2. Protocol Exceptions

Once the submission is entered by the PI as a protocol deviation, the RCO Director, or a Research Compliance Officer/specialist for the IRB will screen the submission for completeness and make an initial determination of the level of review required.

Protocol exceptions can be reviewed either through expedited or convened procedures depending upon the type of research and nature of the exception request. If the exception requires fully convened IRB review, the compliance staff will schedule the protocol exception for an IRB meeting agenda. The screening and any subsequent IRB member review is documented. The IRB members reviewing the protocol exception will have access to the full protocol file, which includes the current version of the research protocol. The possible determinations IRB members can make regarding exceptions include:

- Exception approved – no issues;
- Expedited review (as determined by IRB Chair (or designee));
- Modifications required;
- Referred for fully convened IRB review;
- Disapproval (use only for fully convened IRB review);
- Deferral- further justification or information required (use only for fully convened IRB review).

For protocol exceptions reviewed via expedited review, the IRB reviewer documents their determination. If the protocol exceptions are reviewed at a convened IRB meeting, the IRB members document their initial determinations regarding the protocol exceptions. The fully convened IRB discusses the event at the convened meeting and the IRB meeting minutes document the discussion and final determination of the fully convened IRB regarding the protocol exceptions. The documentation of review is maintained.

Once a determination is made by the IRB, the PI will receive notification from the IRB.

Regulations & Guidelines: DHHS 45 CFR 46.103(b)(4)(III); FDA 21 CFR 56.108(a)(4); 21 CFR 56.108(b); 21 CFR 812.150.

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