UNIVERSITY OF SOUTH ALABAMA

IRB SOP 602
Protocol Deviations and Non-Compliance

Purpose

The purpose of this Standard Operating Procedure (SOP) is to provide guidance in the reporting requirements and responsibilities of the Investigator and the University of South Alabama Institutional Review Board (USA IRB) regarding protocol non-compliance and deviations.

Scope

This SOP applies to all research protocol non-compliance and deviations occurring at a USA research site, for a study in which USA IRB is the IRB of record.

USA IRB does not require reporting of deviations that occur at other research sites in multi-center trials. If the research was reviewed by an External IRB, the researcher should adhere to the policies and procedures of the External IRB.

Definitions

Continuing non-compliance: A pattern of repeated actions/omissions taken by an investigator or key research personnel that indicates a lack of ability and/or willingness to comply with federal regulations or USA IRB policies/guidelines. Repeated minor or major protocol deviations may constitute continuing non-compliance.

Non-compliance: Failure to comply with applicable Federal Regulations or USA IRB policies/guidelines

Serious non-compliance: An action or omission taken by an investigator or key research personnel that any other reasonable investigator would have foreseen as compromising the rights and/or welfare of the research participant. Examples include, but not limited to:

- Failure to adhere to federal regulations governing use of human subjects in research;
- Failure to obtain IRB approval prior to initiation of research activities
- Failure to notify the IRB of changes in approved procedures
- Failure to obtain and/or document informed consent
- IRB approval expires due to failure to renew
- Failure to notify the IRB of changes in the scope/intent of the study
- Failure to adhere to institutional policies where participant welfare has been adversely affected.

Protocol Deviation: Any change, divergence, or departure from the approved study design or procedures of an IRB approved research protocol. Protocol deviations may be categorized as Major, Minor, or Exceptions:

- **Major Protocol Deviations** (sometimes called protocol violations) include any deviation that have or may have the potential to negatively impact the rights, welfare, or safety of a research participant or substantially negatively impact the scientific integrity or validity of the study data.

- **Minor Protocol Deviations** include any deviation which *does not* meet the criteria outlined for major deviations. They are considered *minor* or administrative, and may involve no more than minimal risk to participants or others.

- **Protocol Exceptions** include any temporary, planned deviation to the currently approved protocol or study plan that has received IRB approval *prior* to its initiation. Protocol exceptions are typically granted for a single participant or a small group of participants, but are not a permanent revision to the protocol.=

Policy

Federal regulations require the IRB to review and approve proposed changes to research studies before initiation of these changes, except when changes are “necessary to eliminate apparent immediate hazards to the subject” [45 CFR 46.103(b)(4)(iii)]. Most proposed changes are reviewed through submission of amendments. Changes that have not been approved through the IRB amendment process are considered deviations.

Deviations include intentional (planned) or unintentional departures from the IRB approved protocol or study plan. Deviations may be categorized as Minor Deviations, Major Deviations (sometimes called Violations), or Protocol Exceptions. Major Deviations require reporting to the USA IRB and include those that have or may have the potential to negatively impact the rights, welfare, or safety of a research participant or substantially negatively impact the scientific integrity or validity of the study data. Planned major deviations may be granted Protocol Exception status if they are requested and approved prior to implementation.

It is the responsibility of the researcher to track all deviations from the approved study plan and report to the IRB, sponsor, or funding agency as applicable. Study teams are encouraged to maintain a deviation log for tracking and auditing purposes.

Procedures

The Principal Investigator (PI) or delegated study personnel must report Major Protocol Deviations (sometimes called Violations) and Protocol Exception requests to the IRB as outlined below. Minor protocol deviations do not require reporting to the IRB. If an investigator or study team is uncertain whether a deviation requires reporting, they are encouraged to seek guidance from the USA Office of Research Compliance and Assurance.

1.0 Minor Protocol Deviations

A Minor Protocol Deviation is considered a *minor* or administrative divergence from an IRB approved protocol or study plan when the deviation *does not* affect the participant's rights, safety, or welfare, and/or the completeness, accuracy and integrity of the study data. Minor Protocol Deviations do not require reporting to the USA IRB. Repeated minor deviations that indicate systemic or continuing non-compliance should be reported to the IRB as a Major Deviation.

Examples of minor protocol deviations include, but are not limited to the following:

- Implementation of minor changes to previously approved recruitment procedures or materials;
- Missing original signed and dated consent form or missing pages from executed consent form when a complete photocopy or scan is available;
- Use of incorrect consent form where changes are minor or administrative;
- Consent form missing the signature or date of the person obtaining consent;
- Consent form signed by the participant but missing printed name;
- Individual obtaining consent not listed on IRB approved application;
- Not reporting adverse events within the required window;
- Receiving incomplete questionnaires back from a participant;
- Study visit or procedure falls outside widow of time indicated by the protocol or

is not done per protocol, and there is no increased potential for risk to the participant or damage to the integrity or completeness of the data

2.0 Major Protocol Deviations

2.1 Reporting Procedures

Major Protocol Deviations are to be reported to the USA IRB within 7 calendar days of becoming aware of the event. Major Protocol Deviations are reported through IRBNet using a Deviation Reporting Form. This form should include a corrective action plan for IRB for review and approval. This corrective action plan will outline what steps the investigator has taken or will take to resolve the event and to prevent such events from occurring in the future.

Examples of Major Protocol Deviations include, but are not limited to the following:

- Participant met withdrawal criteria during the study but was not withdrawn;
- Participant received an excluded concomitant medication;
- Participant enrolled but does not meet the protocol's eligibility criteria;
- Failure to perform study procedures outlined in the protocol where participant safety or data integrity may be significantly and negatively impacted;
- Inadvertent loss of samples or data;
- Any medication error made by the site involving incorrect treatment, dose, administration, and/or preparation;
- Any medication error made by the participant which, in the opinion of the investigator, placed the participant at an increased risk than was previously identified
- Failure to obtain informed consent prior to initiation of study-related procedures;
- Falsifying research or medical records;
- Working under an expired professional license/certification, debarred, or disqualified status;
- Premature unblinding of research treatment or data
- Repeated minor deviations;
- Inadequate or improper informed consent procedure;
- Failure to follow federal and/or local regulations and policies;
- Any lapse in study approval where there is a continuation of research activities (i.e. recruitment, enrollment, procedures, data analysis);
- Use of an outdated informed consent form where there have been changes indicating an increased risk, requirements of the participant, costs to the participant
- Breach in confidentiality
- Any emergent deviation from the protocol made without prior IRB approval to eliminate apparent immediate hazard to a research participant

2.2 Review by the IRB Committee

Major Protocol Deviations are administratively reviewed by the Office of Research Compliance or IRB Office staff by adding reviewer comments to the submitted package in IRBNet, selecting a recommendation and checking the box confirming the review has been completed. This manner confirms the date of review. Information including deviation description, corrective action, risk to the participant or data, and other pertinent information is listed on the agenda for Full Board review.

Major Protocol Deviations will be forwarded to the IRB Chair for review if the deviation presents significant risk to the participant(s) or if the event is medically complex. The Chair's determination will be included on the agenda for the next Full Board meeting.

3.0 Protocol Exception

3.1 Reporting Procedures

The IRB *only* requires reporting of protocol exceptions that meet the criteria for a major deviation. Minor deviations, when known in advance, do not need to be reported to the IRB prior to implementation.

A protocol exception is a temporary, planned protocol deviation that is approved by the sponsor or funding agency, (and, if applicable, the FDA) and the IRB, *prior* to its implementation. Protocol exceptions are typically granted for a single participant or a small group of participants, but are not a permanent revision to the protocol.

Protocol exceptions must be submitted to the USA IRB and granted approval prior to implementation. Deviations planned to eliminate apparent immediate hazards to the participant should be implemented immediately, then submitted to the IRB as a Major Deviation as outlined above. Protocol exceptions should be requested using the Protocol Exception Request Form located in IRBNet. Repeated failure to obtain prospective IRB approval for protocol exceptions may be viewed as non-compliance.

Examples of exceptions include, but are not limited to the following:

- Waiver of one or more inclusion/exclusion criteria
- Failure to withdraw a participant meeting withdrawal criteria;
- Accommodations for a single participant
- Temporary changes to study procedures

3.2 Review by the IRB Committee

Protocol exceptions must be approved by the IRB prior to implementation. The IRB will, within IRB standard operating procedures, accommodate exception requests as quickly as possible. For time-sensitive requests, researchers are encouraged to reach out to the IRB to expedite this process.

Exceptions will be reviewed by the IRB Chair and a decision will be placed on the agenda for the next scheduled Full Board meeting. The Chair will consider the implications of the requested exception on the rights, welfare, or safety of a research participant and the impact on the scientific integrity or validity of the study data. When the same exception is requested more than once or the study team can anticipate the need for additional similar exceptions, a protocol amendment may be requested.

4.0 Serious or Continuing Non-Compliance

The IRB Office will review all submitted protocol deviations to determine if they meet the criteria for serious or continuing non-compliance. The Office will consider if there is a sufficient corrective action plan associated with non-compliance reports and if there is or is not a trend of similar non-compliance. The IRB may defer this determination to request additional information from the study team before a final determination is made.

If the investigator offers a timely and satisfactory explanation for the concern and a plan to eliminate future incidents of such noncompliance and the IRB accepts, the IRB may elect to terminate the noncompliance investigation process and report that the noncompliance issues were met with no further action.

If the corrective action plan calls for any changes to the previously approved research and the changes involves more than minor modifications, the modification must be reviewed by the convened IRB. Minor changes will be reviewed by expedited review.

If the Investigator does not provide adequate information or corrective action plan, the IRB may ask the investigator to meet with the chair or attend an IRB meeting to discuss the issue(s).

DHHS regulations at 45 CFR 46.103(a) and (b)(5) require unanticipated problems involving risks to participants, serious or continuing noncompliance, or suspension/termination of IRB approval conducted under an approved assurance be reported to OHRP.

4.1 Actions That May Be Taken During or After the Investigation of Non-Compliance

- No action
- Suspension: suspend enrollment and/or all research procedures for the specific research study in question

- Termination of the research
- Require a response from the investigator with a plan of corrective action
- Initiate audits of all or some part of the investigator's active protocols
- Modification of the research protocol
- Modification of the information disclosed during the consent process
- Additional information provided to past participants
- Modification of the annual review schedule
- Acquire additional information pending final outcome
- Requirements that current participants re-consent to participate (if applicable)
- Monitoring of the research and/or consent process

4.2 Continuity of Care of Research Participants when study is suspended

After the IRB has decided to suspend/terminate a research project, the IRB may make recommendations to investigators regarding ongoing care and treatment of the research participants. The IRB shall take into consideration the risk to the participants from withdrawal of any investigational drug, device, or social or behavioral interventions. Interventions may be permitted to continue by another qualified physician or social/behavioral scientists and need further supervision of the participant(s).

4.3 Final Outcome

If a finding of research noncompliance has been made, the IRB, IRB chair, or designee shall decide which corrective action(s) should be taken.

Corrective actions may include any of the following:

- suspension or termination of the investigator's research protocol(s);
- required training with respect to human subjects research and the regulatory requirements for the conduct of such research;
- imposition of changes in such research protocol(s) to further protect participants;
- a monitoring plan
- imposition of restrictions as a condition for the continuation of research by the investigator

Additional processes regarding non-compliance with USA IRB policies are detailed in IRB SOP 807: Research Procedures Conducted Without IRB Approval.

Regulated Documents

45 CFR 46.103, 109
21 CFR 56.108, 109

University Related Documents

Protocol Deviation Reporting Form (located in IRBNet forms and templates)
Protocol Exception Request Form (located in IRBNet forms and templates)
IRB SOP 807: Research Procedures Conducted Without IRB Approval

History:

Effective Date: March 2024
Revisions: October 2018, March 2024

Responsible Office:

Office of Research Compliance and Assurance

Protocol Deviation Infographic

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Any change, divergence, or departure from the approved study design or procedures of an IRB approved research protocol.

Major Protocol Deviation:	**Minor Protocol Deviation:**	**Protocol Exceptions:**
(Sometimes called Violations) A deviation that may negatively impact the rights, welfare, or safety of a research participant or substantially negatively impact the scientific integrity or validity of the study data.	A deviation which does not meet the criteria outline for major deviations. Considered minor or administrative and may involve no more than minimal risk.	A temporary, *planned* deviation that has received IRB approval prior to implementation. Typically granted for a single participant and are not a permanent revision to the protocol.
Report to USA IRB within 7 calendar days of awareness	**Do not require reporting to the USA IRB**	**Report to USA IRB prior to implementation *if* it is a major deviation**