

BROOKHAVEN NATIONAL LABORATORY CLINICAL RESEARCH CENTER POLICY	CRC POLICY 2.4	PAGE 1 OF 4
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SUBJECT: Protocol Adherence	REVIEWED BY: A. Baumann	
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1.0 POLICY

Research investigators can only conduct research involving human subjects under an IRB approved protocol. Research investigators must implement research under an IRB approved protocol following the exact research plan defined in the protocol. Research investigators shall not implement any change to an IRB approved protocol without first receiving IRB approval of the addendum to the protocol, except where a protocol change is necessary to eliminate an immediate hazard to a study subject.

2.0 PROTOCOL DEVIATION IDENTIFICATION:

- 2.1 Any individual noting an actual or potential deviation from an IRB approved protocol shall report such to the Clinical Research Manager (CRC) and the Principal Investigator for that protocol.
- 2.2 The PI should review the protocol and relevant documentation and notify the CRC Manager of the findings.
- 2.3 The CRC Manager, with assistance from the appropriate staff, will evaluate the significance of the deviation and categorize the event based on the criteria below. He will notify the Medical Department Chair, QA Physician, and Institutional Official, as appropriate.

3.0 CATEGORIZATION OF A PROTOCOL DEVIATION:

- 3.1 A protocol violation is any deviation that results in actual or potential harm to the subject and is reportable to external regulatory agencies. An adverse event report may also be required (see CRC Policy 4.6).
- 3.2 A less serious protocol deviation is classified as a protocol nonconformance. A protocol nonconformance does not harm or potentially harm a subject and does not require a report outside of the Lab. It is generally associated with administrative inconsistencies or minor errors in the implementation of the protocol.
- 3.3 The Medical Department Chair may alter the categorization of a protocol deviation or violation following review. The CRC Manager and QA Physician will evaluate the need to modify the corrective actions if this occurs.

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4.0 DOCUMENTATION AND FOLLOWUP OF PROTOCOL DEVIATIONS:

- 4.1 The Principal Investigator is responsible for developing a corrective action plan for a protocol violation. The corrective action plan should be submitted to the CRC Manager for review and approval within 7 working days and should consider training or other means to prevent reoccurrence. The Protocol may be suspended by the CRC Manager, Medical Department Chair, QA Physician or IRB and remain suspended until the corrective action plan is reviewed and approved.
- 4.2 If a Protocol Deviation is not considered serious and is classified as a nonconformance, the PI may still be requested to submit a corrective action plan to ensure that the deviation is corrected and does not reoccur.
- 4.3 The CRC Manager will work with the QA Physician and Medical Department Chair to periodically evaluate the effectiveness of corrective actions. A pattern of continued deviations - or a serious protocol violation- will result in suspension of the protocol and possible disciplinary action by the Department Chair. Guidance for the appropriate disciplinary action is provided in Attachment 1 to this procedure.

5.0 REGULATORY REQUIREMENTS AND GUIDANCE:

- 5.1 45 CFR 46.113 authorizes the IRB 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 or serious harm to subjects.
- 5.2 45 CFR 46.103.b.5 mandates the IRB to report any unanticipated problems involving risks to subjects or other or any serious or continuing noncompliance with 45 CFR 46 or the requirements or determinations of the IRB; and any suspension or termination of IRB approval.
- 5.3 ICH Guideline 4.5 states that the investigator should not implement any deviation from or changes of the protocol without prior review and documented approval from the IRB except where it is necessary to eliminate an immediate hazard(s) to a study subject or when the change(s) involve only logistical or administrative aspects of the study.
- 5.4 If a change to a protocol is made for emergency reasons, the change should be written out and signed by the subject, if possible, as documentation that the subject consented.

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Attachment 1: Disciplinary Action Guidance

Introduction

When considering protocol deviations, procedural infractions or employee misconduct in **the performance of human subject research**, the Medical Department Chair and CRC Manager, in consultation with the QA Physician, Human Resources, and others, should use the following process and guidelines to determine the appropriate disciplinary action.

Guidelines for assessing responsible person(s)

The Principal Investigator (PI) is ultimately responsible for the proper conduct of each of his/her protocols. The PI will be held accountable for actions taken by other members of the team in the implementation of the protocol. Consequently, the PI's staff privileges may be affected as part of the response to instances of misconduct by members of his/her research team in the implementation of the protocol.

Responsibility for Recommending and Implementing Disciplinary Action

The Medical Department Chair, in consultation with the CRC Manager, QA Physician, and Institutional Official as necessary, has the authority and responsibility for categorization of the incident severity and for recommending and administering the disciplinary action associated with the conduct of human subjects research. The Medical Department Chair is also responsible for notifying the supervisor of the PI or individual responsible for the protocol deviation or misconduct so that consideration can be given to employment related disciplinary action.

Categorization of Incident Severity

Due to the nature of the work involved in human subject research, protocol deviations or misconduct may be reported in at least three possible contexts. Any incident may be considered in the context of one, two or all of these categories.

1. The actions of an individual.
2. The aggregate actions of members of a team working on a particular protocol.
3. The accountability of the Principal Investigator who is responsible for both contexts mentioned above.

The following are the three severity categories used in assessing appropriate disciplinary action:

SIGNIFICANT: is a procedural violation or instance of misconduct that **immediately** jeopardizes the actual physical, ethical, or emotional safety and welfare of a subject. This category includes actions that are considered serious and are reportable to DOE, OHRP and other government and funding agencies.

Examples: A physical safety issue might involve exposing a subject to excess radiation or medication dosages well beyond protocol limits that are likely to have damaging effects.

A **significant** ethical/emotional violation would be the participation of a subject in a study procedure without having obtained a signed informed consent.

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MAJOR: is a procedural violation or instance of misconduct that creates a **potential** to jeopardize the actual physical, ethical, or emotional safety of a subject. This is a threat that is not immediate in nature.

Examples: A potential physical threat would result from the lack of physician coverage in a situation where one is required by the protocol. A potential ethical/emotional threat could be a breach of confidentiality involving disclosure of medical information without the subject's permission. A similar violation would occur if a member of the study team were to be disrespectful to a subject's physical/emotional needs in a way that would lead to embarrassment.

The BNL policy on conflict in the workplace would also be applicable. Acts or threats of violence, verbal abuse, and any other behavior meant to intimidate others directed at the subject or enacted in the subject's presence are examples of prohibited actions.

MINOR: is a procedural violation or instance of misconduct that does not involve an actual threat to the physical, ethical, or emotional safety of a subject. This category demonstrates a carelessness or indifference to proper protocol implementation or to adherence to appropriate guidelines or procedures concerning the conduct of clinical research.

Example: Failure to consistently complete a subject chart or case report form paperwork in accordance with CRC procedures through either repetitive errors or lack of timeliness.

Disciplinary Action:

Disciplinary Actions instituted by the Medical Chair may range from a request for corrective action to the suspension of the study and/or termination of staff privileges, depending on the seriousness of the violation and the frequency of its occurrence. In determining the specific disciplinary action, the following guidelines will be employed:

- ◆ Willful violation of a subject's rights or welfare, fraud (including intentional use or omission of data to manipulate statistical results), or willful misconduct will result in termination of the protocol and/or termination of staff privileges, and will automatically be reported to the Director and Independent Oversight Office to consider appropriate employment related disciplinary action.
- ◆ Unintentional violation of the above requires a written corrective action plan by the PI and could result in suspension of the protocol for up to 30 days.
- ◆ Minor violations require protocol revision and/or a written corrective action plan. Repeated minor violations will result in the suspension of the protocol pending corrective action.

Those violations, which could result in the suspension of a protocol or the suspension or termination of staff privileges, will be reviewed with the Human Resources Division.

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