NON-COMPLIANCE WITH THE REQUIREMENTS OF THE HUMAN RESEARCH PROTECTION PROGRAM

12/13/2022

In order to comply with 45 CFR 46.108(a)(4)(i) and 21 CFR 56.108(b)(2), DUHS IRB will promptly report to the Office for Human Research Protections (OHRP) and US Food and Drug Administration (FDA) all applicable events adversely affecting the rights, welfare, and/or safety of human research participants. The required reporting events include any serious and/or continuing non-compliance with federal policy or with determinations made by the IRB.

Definitions

(1) Allegation of non-compliance is an assertion or report of non-compliance.

(2) Documentation is any document, tangible item, or testimony offered or obtained during a non-compliance review that tends to prove or disprove the existence of an alleged fact.

(3) Non-compliance is the failure to follow federal, state, or local regulations governing human subject research, institutional policies related to human subject research, an IRB-approved research protocol, or the requirements or determinations of the IRB. This may pertain to the principal investigator, research staff, or any member or component of the Human Research Protection Program (HRPP).

(a) Serious Non-compliance:
Means actions or omissions by any members of the HRPP that are known or should be known to create an increase in risk to subjects, adversely affects the rights, welfare and safety of the research subjects, or adversely affects the scientific integrity of the study. Willful violation of policies and/or federal regulations may also constitute serious non-compliance.

(b) Continuing Non-compliance:
Means a pattern of repeated actions or omissions by any member of the HRPP that are known or should be known to create an increase in risk to subjects, adversely affect the rights, welfare and safety of research subjects, or adversely affect the scientific integrity of the study.

(4) Preponderance of Documentation
Means proof of information that, when compared to the information opposing it, leads to the conclusion that the fact at issue is more probably true than not.

Examples of non-compliance

The actions of anyone or any organization within the HRPP may result in non-compliance. Examples of non-compliance include, but are not limited to:

- Conducting human subject research without first obtaining IRB and institutional approval or an IRB declaration of exemption
- Deviating from or violating the provisions of an IRB-approved protocol
- Failing to secure IRB approval of a protocol due for periodic continuing review prior to its expiration date
- Permitting a protocol's IRB approval to lapse without stopping all research-related activities and submitting a Final Progress Report to the IRB, or in the event of an overriding safety concern or ethical issue such that it would be in the individual subject's best interest to continue study participation, not arranging with the IRB to continue those activities
- Deviating from written Duke University Health System policies and procedures governing research with human subjects
- Failure of any organization with a defined responsibility for oversight of any part of the HRPP to fulfill its obligations

Requirements for reporting allegations of non-compliance

Investigators, research staff and any other member of the HRPP are required to report any potential, observed, suspected, or apparent non-compliance to the IRB. This refers to all non-compliance, whether or not it may be serious and/or continuing non-compliance. All institutional members, research participants and others are encouraged to report any potential, observed, suspected, or apparent non-compliance. Reports of non-compliance may also arise from: (i) calls to the Integrity Line, the confidential institutional hotline for reporting compliance concerns; or (ii) as a result of internal or external audits; or (iii) through direct communication to the IRB. Regardless of how reports arise, all allegations of non-compliance related to research with human participants must be referred to the IRB. The allegation may be referred to other institutional offices for evaluation and management as appropriate.

Reports of non-compliance must contain enough information to determine whether the report is sufficiently credible and specific so that potential documentation of non-compliance may be identified and acted upon.

Handling allegations of non-compliance

Any **allegation** of non-compliance will be referred to the Executive Director of the IRB or designee. In most instances, the Executive Director or designee will submit a written inquiry to the related Principal Investigator (PI) for the research study in question. However, in cases where the identity of the complainant must be protected or otherwise warranted, the Executive Director may submit a written request to the Duke University Office of Audit, Risk and Compliance (OARC) to conduct a directed audit in response to the allegation. Once either the response from the PI or the audit report from OARC has been received, the Executive Director, in conjunction with the Lead IRB Chair, may conclude that the allegations have a basis in fact. In such cases, the process under "Handling non-compliance" will be followed. Otherwise, no further action is taken under this policy and the PI is informed that the IRB considers the issue to be resolved. The allegation may be referred to other institutional entities for evaluation and management as appropriate.

Handling non-compliance
If the Executive Director of the IRB or designee determines the non-compliance is neither serious nor continuing, the process under "**Non-compliance that is determined to be neither serious nor continuing**" is followed.

If the Executive Director of the IRB or designee assesses the non-compliance to potentially be serious and/or continuing, the process under "**Non-compliance that is determined to potentially be serious and/or continuing**" is followed.

Non-compliance that is determined to be neither serious nor continuing
If the non-compliance is considered to be neither serious nor continuing non-compliance, the Executive Director of the IRB or designee will determine whether any corrective actions are needed, and if so communicate those to the involved individual(s) and ensure all corrective actions are completed. The Executive Director or designee will work with the involved individuals to implement the corrective action plan and will monitor the completion of all required corrective actions. If the Executive Director or designee are unable to work with the involved individuals to implement the corrective action plan, the allegation will be considered to be continuing non-compliance and the procedures in **"Non-compliance that is determined to potentially be serious or continuing"** will be followed.

Non-compliance that is assessed to be serious and/or continuing
The Executive Director of the IRB or designee may use any of the following mechanisms to investigate the allegation(s) or non-compliance event:

(1) communicate directly with the PI and/or relevant study team,
(2) communicate with the complainant(s),
(3) contact the Office of Audit, Risk and Compliance, and any other relevant internal departments at Duke.

If the non-compliance is initially assessed to represent serious and/or continuing non-compliance, the Executive Director of the IRB or designee will refer the non-compliance event or allegation to IRB #9, the DUHS IRB's dedicated non-compliance board, for formal review and recommendation. Prior to the IRB #9 meeting, communication will be sent to the PI and study team, apprising them of the investigation and review by the convened IRB. This communication will request any additional information or a written response that the PI/study team would like to provide for the board's consideration. Any additional information must be submitted no later than 5 business days prior to the IRB #9 meeting to allow adequate time for IRB #9 members to review submitted information prior to the board meeting.

Information provided to the IRB for review of serious or continuing non-compliance
A primary reviewer will be assigned to present non-compliance allegations that are referred to IRB #9 for review and action. The primary reviewer will have access to all evidence gathered during the review. All evidence will be provided to all members attending the IRB meeting. In addition, all attending members will have access to the

entire study record in the IRB's software, including study documents, audit reports, other submissions, safety events, and correspondence throughout the history of the study. All attending members will be expected to review these materials. The IRB may, in its discretion, request an in-person or virtual presentation from any individuals involved in the non-compliance or the review of the non-compliance allegation. The IRB may also, in its discretion, allow the PI/study team member to appear before the IRB if they request to do so. In making/granting such a request, the IRB will ensure it obtains sufficient input, to establish an accurate understanding of the event at issue.

Actions of the convened IRB

The convened IRB will confirm by vote whether there is a recommendation of serious and/or continuing non-compliance for the Institutional Official's (IO's) final determination. If the IRB does not find the non-compliance to be serious and/or continuing, the process for "Non-compliance that is determined to be neither serious nor continuing" is followed.

If the convened IRB finds that the non-compliance is serious and/or continuing, it may immediately suspend the research if it finds that doing so is necessary to eliminate apparent immediate hazards to the research subject. The IRB will specify any required corrective actions, which may include, but are not limited to:

- Suspension of the research
- Termination of the research
- Notification of current participants (required when such information might relate to participants' willingness to continue to take part in the research)
- Modification of the research protocol
- Modification of the information disclosed during the consent process
- Additional information provided to past participants
- Requirement that current participants re-consent to participation
- Modification of the continuing review schedule
- Monitoring of the research
- Monitoring of the consent
- Additional training for the PI and study team
- Obtaining more information pending a final decision
- Referral to other organizational entities such as legal counsel, risk management, human resources, the privacy office or the IO
- Providing additional recommendations to the IO
- Other actions appropriate for the local context

If the convened IRB concludes that a limited number of individuals involved with the study were responsible for the serious or continuing non-compliance, then it may require corrective actions from only those individuals. It may also suspend or terminate research privileges for those individuals.

Final Authority

The IO has the final authority to confirm the IRB's recommendation of serious and/or continuing non-compliance. The IO may establish additional investigative groups with

members drawn from appropriate divisions across the Health System, University, School of Medicine and/or School of Nursing to further consider the non-compliance. This group will report its findings to the IO in a timeframe prescribed by the IO.

Reporting
The Principal Investigator of the affected research study will be apprised of the convened IRB's recommendation in the post-meeting modifications letter. This letter will also contain any corrective actions required by the IRB.

The Executive Director or designee and appropriate Clinical Research Unit (CRU) administrators will work with the individuals involved in the non-compliance to implement the corrective action plan and will monitor the completion of all required corrective actions. The Vice Dean for Scientific Integrity and the Vice Dean for Clinical Research for the School of Medicine will be notified of the board's decision. The Principal Investigator will be notified that they may respond with any concerns within 5 business days of receiving the board's decision.

Once the IO has made its decision, a notice of the IO determination will be sent to the PI, study coordinator, and regulatory coordinator.

The IO or designee will report the institution's determination and findings to all appropriate offices within DUHS, the University, and to relevant regulatory agencies, as described in the policy titled "Reporting of IRB Findings to Institutional Officials and Federal Regulatory Agencies."

Previous Version Date(s): 6/20/2008, 1/7/2009, 2/10/2011, 4/22/2011, 2/19/2016, 6/23/2020, 3/25/2021.

Attachment I

NOTICE FROM THE DUHS IRB
REGARDING AN EVENT TO BE PRESENTED AT IRB #9 (BOARD FOR SERIOUS AND/OR CONTINUING NON-COMPLIANCE CONCERNS)
[to be sent via email to PI along with cc: to study coordinator, regulatory coordinator, CRU director and research practice manager (RPM)]

The DUHS IRB has received a report of alleged non-compliance related to a research study involving human subjects with which you are associated. Please refer to the definitions at the end of this document or to the DUHS IRB policy titled "NON-COMPLIANCE WITH THE REQUIREMENTS OF THE HUMAN RESEARCH PROTECTION PROGRAM."

As part of its review, the IRB is requesting your response. Please complete the following fields, and return this form to **(list name and email)** in the IRB office no later than **5 business days prior to the IRB #9 meeting**. Your responses will be included in the discussion of this alleged non-compliance at the meeting of IRB #9 on XX/XX/XXXX.

PI: (prepopulated by IRB)

Name of person completing this form (if different from PI):

PRO #: (prepopulated by IRB)

Study Title: (prepopulated by IRB)

Description of Event/Complaint: (prepopulated by IRB). Please provide a response to each separate issue, detailed below:

If appropriate, please provide any additional information that you believe the IRB should have in order to make a determination regarding this alleged non-compliance. You may also attach separate documents to support your statements.

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