

PARTNERS HUMAN RESEARCH COMMITTEE POLICIES AND PROCEDURES

Noncompliance Policy

1.0 PURPOSE

The purpose of this policy is to define the duty and responsibility of individuals to report to the Partners Human Research Committees (PHRC) observed or apparent noncompliance with federal, state and local laws and regulations or the requirements or determinations of the PHRC and the procedures the PHRC follows when reviewing reports of observed or apparent noncompliance.

This policy is established to comply in part with the regulatory requirement in 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)(2) requiring IRBs to have written procedures which the IRB will follow for ensuring prompt reporting to the IRB, appropriate institutional officials, Office for Human Research Protections, and, when applicable, the Food and Drug Administration (FDA), any serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB.

2.0 SCOPE

This policy applies to investigators and others employed by, on staff at, or otherwise affiliated with BWH and MGH who observe or otherwise become aware of apparent noncompliance in connection with human-subjects research and clinical investigations subject to review by the PHRC and to investigators who are the subject of a report of observed or apparent noncompliance.

3.0 DEFINITIONS

Human-subject research means activities that meet the DHHS definition of *research* and involve a *human subject* as defined by DHHS or meet the FDA definition of *clinical investigation* and involve a *human subject* or *subject* as defined by FDA. The DHHS definition for *research* and *human subject* and the FDA definition for *clinical investigation*, *human subject*, and *subject* are provided below:

Research as defined by DHHS means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. [45 CFR 46.102(d)]

Human subject as defined by DHHS means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable

private information. *Intervention* includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. *Interaction* includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects. [45 CFR 46.102(f)(1)(2)]

Clinical investigation as defined by FDA means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical studies. The terms *research*, *clinical research*, *clinical study*, *study*, and *clinical investigation* are deemed to be synonymous... [21 CFR 50.3(c) and 21 CFR 56.102(c)]

Human subject as defined by FDA means an individual who is or becomes a participant in research, either as a recipient of the *test article* or as a control. A subject may be either a healthy human or a patient. [21 CFR 50.3(g) and 21 CFR 56.102(g)]

Test article as defined by FDA means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

Subject as defined by FDA means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or have a medical condition or disease [21 CFR 812.3(p)].

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine

physical or psychological examinations or tests. [45 CFR 46.102(i)][21 CFR 56102(i)]

Noncompliance means any failure to comply with any applicable federal, state, or local laws and regulations or the requirements or determinations of the PHRC, which include PHRC and institutional policies related to human subject protection.

Minor noncompliance means any non-compliance that is not serious or continuing noncompliance. For example, minor noncompliance might include the following violations: (1) missing an original signed and dated research consent form; (2) missing pages of executed research consent forms; (3) inappropriate documentation of informed consent, e.g., missing one or more signatures or date; (4) obtaining informed consent using an invalid/outdated research consent form that contains all of the information required by the PHRC; (5) failure to submit continuing review forms/documents prior to expiration of IRB approval; (6) unplanned deviation from the approved protocol where the deviation does not impact the rights and welfare of subjects or the integrity of the research.

Serious noncompliance means any noncompliance that negatively impacts the rights and welfare of subjects or compromises the integrity of the study data. For example, serious noncompliance might include, but is not limited to, the following violations: (1) failure to obtain prospective PHRC approval; (2) failure to obtain informed consent of subject(s); (3) enrollment of subject(s) who do not meet all eligibility criteria; (4) obtaining informed consent using an invalid/outdated research consent form that is missing information that might affect the individual's willingness to participate or continue to participate in the research; (4) failure to perform follow-up as outlined in the protocol where the lack of follow-up places the subject at increased risk of harm; and (5) failure to report a serious unanticipated problem involving risks to subjects or others, including adverse events.

Continuing noncompliance means any noncompliance that occurs repeatedly after appropriate remedial education or corrective action has been instituted taking into consideration all relevant factors, including, for example: (1) whether the continuing noncompliance was intentional, or (2) whether the investigator collaborated in remedial activity and the continuing noncompliance was not intentional.

Scientific Misconduct means any fabrication, falsification, plagiarism, or other practice that seriously deviates from those that are commonly accepted within the scientific community for proposing, conducting, or reporting research. (See Partners Research Integrity Policy.)

4.0 POLICY

Brigham and Women's Hospital (BWH) and Massachusetts General Hospital (MGH) ("the Hospitals) provide and maintain a culture characterized by integrity, responsible

behavior and a commitment to the highest legal and ethical standards of human subject protection. Consistent with these principles, all human-subjects research and clinical investigations conducted by employees or agents of the Hospitals or under the auspices of the Hospitals shall be conducted in accordance with all applicable federal, state, and local laws and regulations and the highest ethical standards.

Any investigator or other individual employed by, on staff at, or otherwise affiliated with BWH and MGH who observes or otherwise becomes aware of apparent noncompliance with applicable federal, state, and local laws and regulations or the requirements or determinations of the PHRC in connection with human-subjects research and clinical investigations has the duty and responsibility to report the noncompliance to the PHRC.

The PHRC has the responsibility to: (1) fully investigate any reports of noncompliance; (2) have a process for determining appropriate actions for any findings of noncompliance; and (3) report any findings of serious or continuing noncompliance as required by DHHS and FDA regulations. When reviewing reports of noncompliance, the PHRC Chairpersons and members of the PHRC are subject to the *Partners Conflicts of Interest Policy for IRB Members*.

5.0 PROCEDURES

5.1 Reporting Observed or Apparent Noncompliance

The reporting party is responsible for reporting observed or apparent noncompliance in good faith, maintaining confidentiality, and cooperating with any internal inquiries. BWH and MGH intend to protect, to the extent possible, the privacy of an individual who in good faith reports noncompliance on the part of another individual.

Reports of noncompliance made in good faith will not reflect negatively on the individual reporting such noncompliance and, when applicable, will not affect his/her employment, in accordance with *Partners Non-Retaliation Policy*.

If an individual is unsure whether there are grounds to suspect noncompliance, s/he may call upon the Director and Chair of the PHRC or designee to discuss the situation informally.

Observed or apparent noncompliance should be reported to the Director and Chair of the PHRC as soon as possible after the noncompliance is observed or discovered. Reports of noncompliance should be made in writing; however, in some cases, reports of noncompliance may be made orally. When a report of noncompliance is received orally, the person receiving the report is responsible for creating a written account of the report.

Reports of noncompliance, whether written or oral, should include a complete description of the noncompliance, of the observed circumstances and, the names of the individuals involved, if known. Whenever, possible, the report should contain sufficient details to allow an assessment of noncompliance.

5.2 Investigating Reports of Noncompliance

5.2.1 Initial Fact Gathering Process

The Director and Chair of the PHRC or designee shall be responsible for gathering or causing to be gathered (through an audit or otherwise) further facts to better ascertain the nature and scope of noncompliance, if any. Such fact gathering shall be concluded within forty-five (45) days of receipt of the report. If additional time is needed to complete the fact gathering process, an extension beyond the 45-day time period may be granted by the Director of Human Research Affairs and shall be granted in writing. The fact gathering process shall include an interview with the affected investigator(s). Failure of the investigator(s) to cooperate with such a request or with any other inquiry or process described in this Policy shall itself be grounds for PHRC action.

5.3 Preliminary Written Report of Findings of Fact and PHRC Action

Within fifteen (15) days of the completion of the initial fact gathering process, the Director and Chair of the PHRC shall issue or cause to be issued a preliminary written report of findings of fact and one of the following determinations:

5.3.1 No noncompliance

When the Director and Chair/designee determines that the facts do not support a finding of noncompliance as defined in this Policy, the report of noncompliance will be dismissed and no further action will be taken under this Policy. The written report of findings of fact and determinations of the Director and Chair/designee shall be sent to the Principal Investigator and, when relevant, the affected investigator(s).

5.3.2 Minor noncompliance

When the Director and Chair/designee determines that the facts support a finding of minor noncompliance as defined in this Policy, the Director and Chair/designee will approve the research to continue with no further action required or require modifications that do not constitute more than a minor change in the research.

The written report of findings of fact and determinations of the Director and Chair/designee and corrective action, if any, shall be sent to the

Principal Investigator and, when relevant, the affected investigator(s). No further action will be taken under this Policy.

Modifications submitted by the investigator in response to the report shall be reviewed by the PHRC according to the policy on review of proposed minor changes in approved research using the expedited review procedure.

5.3.3 Serious or continuing noncompliance

When the Director and Chair/designee determines that the facts support a finding of serious or continuing noncompliance as defined in this Policy, the matter shall be referred to the PHRC for review as described in Section 5.7 of this Policy or, at the discretion of the Director and Chair/designee, the Director shall appoint a case-specific Committee on Research Compliance to make recommendations to the PHRC with respect to corrective action appropriate to the noncompliance, as described in Section 5.6 of this Policy.

The written report of findings of fact and determinations of the Director and Chair/designee shall be sent to the affected investigator(s).

The Director and Chair of the PHRC or designee shall be responsible for submitting a preliminary report of the serious or continuing noncompliance and, when applicable, suspension or termination of the research in accordance with the policy *Reporting to Regulatory Agencies and Institutional Officials*.

5.4 Referral to Other Institutional Officials

At any point during the initial fact gathering process or later, when the Director and Chair/designee determines that the facts raise issues apart from or in addition to noncompliance with applicable federal, state, and local laws and regulations or the requirements or determinations of the PHRC, the Director and Chair/designee shall notify or refer the matter or relevant aspects of the matter to other institutional officials for review or other remedial or correction action.

5.5 Temporary Suspension (Hold) or Termination of Research

5.5.1 Voluntary Hold Placed on Research by the Investigator

The Principal Investigator (PI) may voluntarily place the research on hold in whole or in part while the investigation into reports of noncompliance is being conducted. Such temporary holds are not subject to the reporting requirements in 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)(2).

5.5.2 Temporary Suspension or Termination of Research by the PHRC

At any point during the initial fact gathering process or later, the Director and Chair of the PHRC may temporarily suspend in whole or in part or terminate the research. Such suspensions or terminations will be reported in accordance with PHRC policy on *Suspension or Termination of Research*.

5.6 Committee on Research Compliance

The Committee on Research Compliance shall be a subcommittee of the PHRC that includes the Director and Chair and at least three (3) members.

The Committee shall meet within thirty (30) days of the issuance of the preliminary report of findings and determination of serious or continuing noncompliance. The Committee shall have available for its consideration the report of noncompliance, the preliminary report of findings and determinations. The affected investigator(s) and the individual who reported the noncompliance may also present a statement, which may be written or oral at the Committee's discretion.

At the sole discretion of the Committee, it may consider new or additional information, which shall be shared with investigator and the individual who reported the noncompliance, both of whom shall be given an opportunity to respond.

Within fifteen (15) days of the meeting of the Committee, the Committee shall send to the Institutional Official and the Director of Human Research Affairs its written findings and determinations as to whether the facts support a finding of noncompliance and, if so, whether the noncompliance is minor or serious or continuing noncompliance as defined in this Policy, as well as its recommendations for corrective action.

Findings and determinations of no noncompliance or minor noncompliance shall be referred back to the Director and Chair of the PHRC for action, as described in Section 5.3 of this Policy.

Findings and determinations of serious or continuing noncompliance shall be referred to the PHRC for action, as described in Section 5.7 of this Policy.

5.7 Review of Serious or Continuing Noncompliance at a Convened PHRC Meeting

The PHRC Chairperson and members shall receive a copy of the initial report of noncompliance, written reports of findings of fact and determinations and recommendations issued by the Director and Chair/designee and, when applicable, the Committee on Research Compliance, and any audit or other report generated as part of the initial fact gathering process. The entire protocol file

and/or minutes of meetings at which the protocol was discussed previously shall be made available to members, upon request. The Director and Chair of the PHRC or designee shall be responsible for presenting the report of serious or continuing noncompliance to the PHRC and the findings of fact and determinations and recommendations of the Committee on Research Compliance.

By majority vote of a quorum of the membership present at the convened meeting, the PHRC will make a determination as to the noncompliance and take one or more of the following actions with respect to the research:

- Approve the research to continue with no further action required;
- Defer action pending additional information;
- Require modifications in the research and/or consent form;
- Require that subjects who are still participating in the research be re-consented or notified in writing of the noncompliance;
- Require that subjects whose participation has ended be notified in writing of the noncompliance;
- Modify the continuing review schedule;
- Suspend the research;
- Terminate the research;
- Require periodic audits by the Partners Human Research Quality Improvement Program (QI Program); or
- Any other action the PHRC deems appropriate to the noncompliance.

By majority vote of a quorum of the membership present at the convened meeting, the PHRC may also take one or more of the following actions with respect to the affected investigator(s):

- Require remedial education;
- Require oversight by a senior investigator;
- Restrict the conduct of research; and/or
- Restrict research privileges.

The PHRC Administrative Chair is responsible for preparing a description of the noncompliance and recording the findings and actions of the PHRC in the Minutes.

The findings and actions of the PHRC shall be communicated in writing to the affected investigator(s).

5.8 Reporting Serious or Continuing Noncompliance and, When Applicable, Suspension or Termination of the Research

Within fifteen (15) days of the PHRC meeting, the Director and Chair of the PHRC or designee shall be responsible for submitting a final report of the serious or continuing noncompliance and, when applicable, suspension or termination of the research in accordance with the policy *Reporting to Regulatory Agencies and Institutional Officials*.

5.9 Recordkeeping

The records of the fact gathering process and review by the PHRC and associated findings of fact and determinations and recommendations shall be maintained in the Human Research Office with the protocol file.