COLUMBIA UNIVERSITY INSTITUTIONAL REVIEW BOARD POLICY

NONCOMPLIANCE IN HUMAN SUBJECTS RESEARCH

I. BACKGROUND

Columbia University (**Columbia** or the **University**) is responsible for protecting the safety and welfare of human subjects participating in research conducted at the University. This includes the University responding to potential noncompliance with (a) federal, state or local laws or regulations or institutional policies governing the protection of human subjects in research and (b) requirements or determinations of the Columbia University Institutional Review Boards or the external Institutional Review Board to which the responsibility for review has been ceded. This Policy applies to all individuals, including Officers of Instruction, Officers of Research, other staff and students, who may be involved in human subjects research conducted under the auspices of the University and all human subjects research conducted by such individuals.

This Policy does not apply to research misconduct involving fabrication, falsification or plagiarism of research or research results, which is covered by the Columbia University Policy on Misconduct in Research.

II. EFFECTIVE DATE

The Effective Date of this Policy is April 2, 2025 and supersedes the Columbia University Institutional Review Board Policy: Noncompliance with Human Subject Research, dated July 23, 2013 and revised as of March 1, 2016.

III. DEFINITIONS

For purposes of this Policy, certain terms are defined as follows:

Allegation: any concern about possible Noncompliance raised by a HRPO Officer, a member of the IRB, a subject or any other person, including any self-reported concern raised by a PI or other member of a study team about possible Noncompliance in a study in which such PI or member is involved.

Audit: an inspection of study records conducted by the COT to assess compliance of the selected study with the terms of the IRB-approved study protocol, applicable federal, state, and local regulatory statutes, and University policies and procedures governing the protection of human subjects in research.

AVP-HRP: the Associate Vice President for Human Research Protection of the University.

Continuing Noncompliance: a pattern of the same or similar Noncompliance in a non-exempt study or studies that increases the risks to subjects, compromises the rights and/or welfare of subjects or compromises the integrity of the research data, despite the implementation of an

appropriate CAPA Plan or due to the failure to institute appropriate corrective and preventive actions.

CAPA Plan: a corrective and preventive action plan.

Convened IRB: an IRB meeting where a quorum of IRB members is present.

COT: the Compliance Oversight Team of the HRPO.

CTO: the University's Clinical Trials Office.

CUIMC: Columbia University Irving Medical Center.

DCO: the Director for Compliance Oversight of the HRPO.

EVPR: the Executive Vice President for Research of the University.

Follow-up Audit: an Audit that is conducted by the COT after an initial Audit or Investigation. The scope of a Follow-up Audit is generally tailored to the findings from the initial Audit or Investigation**.**

For Cause Audit: an Audit that is conducted by the COT as part of its Investigation into an Allegation of Noncompliance.

FDA: the U.S. Food and Drug Administration.

HRPO: the Human Research Protection Office of the University.

HRPO Officer: any officer-level member of the HRPO staff, including members of the COT.

ICF: an informed consent form.

IEC: the IRB Executive Committee, comprised of the Chairs and Vice Chairs of the IRB, the VPROP, the HRPO Directors and the AVP-HRP.

Inquiry: the gathering of preliminary information and fact-finding to assess whether an Allegation has substance and if so, whether an Investigation is warranted.

Investigation: following an Inquiry, the further investigation of facts with respect to whether Noncompliance has occurred.

IO: the Institutional Official who is the signatory on the Federalwide Assurance for either CUIMC or Morningside.

IRB: any of the University's Institutional Review Boards or all of the University's Institutional Review Boards collectively, as the context requires.

IRB Chair: with respect to any Allegation, the Chair of the IRB that reviewed the research to which such Allegation relates.

IRB Noncompliance: Noncompliance by any member of the IRB or HRPO staff in their capacity as such.

Morningside: collectively, the University's Morningside Heights and Manhattanville campuses.

Near Miss Situation: With respect to any research study, a situation in which the potential for harm to subjects is materially increased, although no actual harm occurred.

Need to Know Individuals: (a) with respect to any COT report of an Investigation or Audit involving Research Noncompliance, the Respondent, the Chair and, if applicable, the Research Vice Chair of the Respondent's department, the applicable IO, the EVPR, the VPROP, the Office of the General Counsel, the AVP-HRP and, if externally funded, the CTO or SPA, as applicable, and (b) with respect to any Allegation of IRB Noncompliance, the AVP-HRP, the members of the IEC, the applicable IO, the EVPR and the VPROP.

Noncompliance: any failure to comply with (a) federal, state or local laws or regulations or institutional policies governing the protection of human subjects in research or (b) the requirements or determinations of the reviewing IRB.

Non-federally Reportable Noncompliance: any Noncompliance other than Serious Noncompliance or Continuing Noncompliance.

Not for Cause Audit: an audit that is conducted by the COT to review, inspect and assess the ethical conduct of human subjects research, the integrity of previously reported data, and adherence to the study protocol, IRB determinations or requirements, and applicable institutional, state and federal regulations and guidance, and that is not based on any Allegation of Noncompliance.

OHRP: the Office for Human Research Protections in the U.S. Department of Health and Human Services.

Outcome: following an Investigation, the determination as to whether Noncompliance has occurred and the corrective and preventive actions, if any, that are required.

PI: the principal investigator of the research study to which an Allegation relates.

Research Noncompliance: Noncompliance by any person other than a member of the IRB or the HRPO staff in their capacity as such. Protocol violations are not considered Research Noncompliance if the violations are not due to action or inaction of a research team member. For example, a missed or cancelled study visit due to inclement weather, a federal or state holiday, or other circumstances beyond the control of the study team is considered a protocol violation but not Research Noncompliance.

Respondent: the person, including a PI, who is the subject of an Allegation of Noncompliance.

Serious Noncompliance: any Noncompliance in a non-exempt study that materially (i.e., in a substantial or considerable way) increases the risks or materially compromises the rights and/or welfare of subjects or the integrity of the research data. Serious Noncompliance includes Near Miss Situations.

Serious Noncompliance may include, but is not limited to, the following examples, if the definition of Serious Noncompliance is met:

- Misadministration of an investigational drug (i.e., the drug, whether or not it is FDA-approved, that is the focus of a clinical investigation);
- Failure to obtain prospective IRB approval of a research study;
- Failure to obtain informed consent from subjects;
- Enrollment of a subject who does not meet all eligibility criteria without obtaining prospective IRB and, if applicable, sponsor approval to be enrolled;
- Obtaining informed consent using an invalid or outdated ICF that does not contain all of the information that might affect an individual's willingness to participate in the research study;
- Failure to perform follow up procedures required in the research protocol when the lack of follow up places the subjects at increased risk of harm;
- Failure to report an unanticipated problem that involves risk to subjects or others to the IRB, as defined by the Columbia University IRB Policy on Reporting to the IRB of Unanticipated Problems Involving Risks; and
- Failure to obtain prospective IRB approval of a substantive change in the conduct of the research except when the implementation of such change is required to avoid imminent harm to subjects.

SPA: the Office of Sponsored Projects Administration of the University.

Suspension: a directive of the IRB, IRB Chair, IEC or AVP-HRP to temporarily remove IRB approval for some or all activities for a previously approved research protocol or, in the case of research activities being conducted without IRB approval, to require such activities to stop.

Termination: a directive of the IRB, IEC or AVP-HRP to permanently stop all activities for a previously approved research protocol.

VP&S: Columbia University Vagelos College of Physicians and Surgeons.

VPROP: the Vice President for Research Operations and Policy of the University.

IV. RESEARCH NONCOMPLIANCE

A. ALLEGATION

Any Allegation received by the HRPO shall be forwarded to a HRPO Officer or the COT for an initial assessment. If the recipient of the Allegation believes that all of the information needed for the IRB to make a determination as to whether a finding of Noncompliance should be made, such information shall be forwarded to the IRB Chair and/or the Convened IRB to make such determination. The IRB Chair or the Convened IRB, assisted by the COT if necessary, may determine that (1) no further action is needed, (2) an Inquiry should proceed pursuant to Section B below or (3) a final determination should be made by the IRB Chair or the Convened IRB as to whether Noncompliance has occurred and if so the level of Noncompliance and the further determinations to be undertaken (e.g., whether (a) the proposed CAPA Plan is acceptable, (b) the data collected out of compliance can be used, (c) there are human subject safety concerns, and (d) subjects should be notified, etc.), provided that if the IRB Chair or the Convened IRB concludes that the level of Noncompliance is Serious or Continuing, the COT must initiate an Inquiry prior to a final determination being made.

B. INQUIRY

If determined pursuant to Section A above, an Inquiry with respect to an Allegation will be conducted by the COT to determine whether there is sufficient evidence to undertake an Investigation. If an Investigation is not warranted, the COT shall so notify the person who raised the initial concern and such other individuals that the COT deems necessary.

C. INVESTIGATION

If the COT determines that an Investigation is warranted, the Investigation will be undertaken promptly. The Investigation will cover such matters as the COT shall determine, including a review of the research records and interviews with the Respondent and other individuals who may have knowledge of the matters at hand.

The COT shall complete the Investigation promptly and, at its conclusion, shall send the findings to the Respondent for verification of the facts. Whether or not a response to the COT's findings is received, the COT shall prepare and submit an initial written report (the **COT Preliminary Report)** to the IRB Chair.

The IRB Chair will review the Report and make the required determinations or route the Report to the Convened IRB for review.

If the Investigation involves multiple protocols for which there are multiple reviewing IRBs, or a Respondent who is a member of the reviewing IRB, the COT Preliminary Report will be routed to the IEC. If the Investigation involves a protocol that is reviewed by expedited review, the COT Preliminary Report may be routed to the IEC prior to the IRB Chair, depending on the seriousness of the Allegations or Noncompliance.

The COT Preliminary Report shall include the COT's recommendations as to (a) whether a finding of Noncompliance should be made, (b) if so, the level of Noncompliance, and (c) a CAPA Plan, if applicable.

Corrective and preventive actions may include, but are not limited to, any of the following:

- Changes in the research protocol(s) and/or ICF to further protect human subjects;
- Required training with respect to human subjects research and the regulatory requirements for the conduct of such research;
- Restrictions as a condition for the continuation of research by the Respondent;
- Notification to the subjects;
- Destruction of data collected during the period of Noncompliance;
- Disallowance of the publication of data collected during the period of Noncompliance;
- Oversight monitoring by the COT;
- Suspension or Termination of the Respondent's research protocol(s); or
- Any other appropriate action.

The IRB Chair or the Convened IRB may accept, reject or modify the conclusions and recommendations in the COT Preliminary Report and shall determine whether Noncompliance has occurred and if so, whether such Noncompliance constitutes Non-federally Reportable, Serious or Continuing Noncompliance, what corrective and preventive actions are necessary and such other determinations as appropriate. After the IRB Chair or Convened IRB determinations have been made, the COT will undertake the necessary actions to address the requests of the IRB Chair or the Convened IRB, and when completed, a COT Final Report will be prepared and issued to the Respondent. The COT Final Report will reflect the final determinations of the IRB, and recommendations or requirements, if any, for the Respondent. If a determination of Noncompliance has been made, the Need to Know Individuals will receive a copy of the COT Final Report. If Noncompliance is not found, the COT Final Report will be issued to the Respondent only.

The Outcome phase of an Investigation will consist of the following:

- If the Respondent accepts the COT Final Report and the finding of Noncompliance, or the final decision of the IRB Chair or the Convened IRB, the COT will close the case when it has been confirmed that the CAPA Plan has been implemented.
- If the Respondent disagrees with the finding(s) of Noncompliance or IRB determinations described in the COT Final Report, they may so notify the COT and the IRB Chair, with copies to the Chair of the Respondent's Department and the applicable IO, citing the reasons for such disagreement within 30 days of receipt of the COT Final Report. The IRB Chair or the Convened IRB will make a final decision as to the finding of Noncompliance and the CAPA Plan, and the COT shall so notify the Need to Know Individuals. Such decision shall be final in all respects and the Respondent shall have no further right to appeal the decision.
- Notice of closure shall be sent to the Respondent and may, at the discretion of the DCO, be sent to the Need to Know Individuals.
- For determinations of Serious or Continuing Noncompliance, the COT will prepare the federal reporting letter(s) and implement a plan for follow-up monitoring within six months of the closure of the Inquiry or Investigation, which may or may not include a Follow-up Audit.

D. COT CONSULT

A COT consult may be requested to assist with the review or processing of an Allegation of Noncompliance, including but not limited to: (a) obtaining additional information and providing a recommendation about alleged Noncompliance so it can be reviewed by the IRB; (b) development of a CAPA Plan; (c) response to a federal agency or sponsor; (d) response to an audit/inspection that was not conducted by the COT; and (e) a root cause analysis.

The consult shall be completed promptly and, at its conclusion, result in feedback to stakeholders, e.g., HRPO staff, IRB Chair or Convened IRB, and PI.

A consult may result in the need for an Inquiry or Investigation.

E. NOT FOR CAUSE AUDITS

If possible Noncompliance is identified during a COT Not For Cause Audit, the COT shall follow the same steps set forth in Sections IV.A, IV.B, and IV.C above with respect to an Inquiry, Investigation and the Outcome phase.

F. SUSPENSION OR TERMINATION OF IRB APPROVAL

1. AUTHORITY TO SUSPEND OR TERMINATE IRB APPROVAL

Each of a Convened IRB, an IRB Chair or the AVP-HRP has the authority to suspend or terminate the approval of research (a) for which there has been a determination that it is not being conducted in accordance with federal regulations or stipulations imposed on the research activity by the IRB, or (b) if an Allegation is received by the IRB that requires immediate action for the protection of human subjects or to address a concern regarding potential Noncompliance. In the event that none of the Convened IRB, an IRB Chair or the AVP-HRP has taken the above actions, the IO may suspend or terminate the approval of such research. This may occur at any time after initial approval of the research.

The IEC may suspend or terminate IRB approval for activities that affect more than one Board or are assigned to the Expedited IRB or Administrative Review Committee. Suspensions and terminations by a person or entity other than the IRB must be reported to the assigned IRB.

2. FOLLOW UP ACTIONS

When study approval is suspended or terminated, the IRB, the IEC or the individual making the determination must consider the following:

- Actions to protect the rights and welfare of currently enrolled subjects;
- Whether any pertinent adverse events or outcomes have been reported to the IRB;
- Whether current subjects must be informed of the Termination or Suspension, and if so, in what manner;
- Whether data collected from subjects can be used for the research; and

- Whether safety procedures are required for paused participation or withdrawal of enrolled subjects (e.g., making arrangements for medical care outside of a research study, transfer to another investigator, or continuation in the research under independent monitoring).

3. NOTIFICATION

The PI must be promptly notified in writing of actions to suspend or terminate IRB approval. Reporting to applicable federal agencies will occur as described in Section VI of this Policy.

4. APPEAL

Although there is no regulatory authority for appeal of decisions to suspend or terminate IRB approval of research, the PI may submit an appeal in writing to the DCO and have the response considered by, as applicable, the AVP-HRP, the convened IRB or the IEC. In all cases, the decision by the AVP-HRP, the convened IRB or the IEC is final.

V. IRB NONCOMPLIANCE

A. ALLEGATION AND INQUIRY

The general Allegation, Inquiry and Investigation steps described in Sections IV.A, IV.B, and V.B shall be followed with respect to any concern about possible IRB Noncompliance that may constitute Serious or Continuing Noncompliance, provided that if any of the members of the IRB may be considered to be complicit in the IRB Noncompliance, the AVP-HRP shall make the determinations required by such Sections, unless they are a Respondent, in which case the reports will be reviewed by the IEC or the EVPR. The COT, senior HRPO staff or others, as designated by the AVP-HRP, may conduct the Allegation, Inquiry and Investigation processes.

For IRB Noncompliance that is not Serious or Continuing, senior HRPO staff or others, as designated by the AVP-HRP, may review the Noncompliance and confirm implementation of the appropriate CAPA Plan.

B. INVESTIGATION

If the DCO determines that an Investigation is warranted, they shall direct the COT to proceed with such Investigation. The Investigation will cover only the specific Allegation unless findings indicate that the Investigation should be expanded. If any facts are at issue, the COT may contact the Respondent or any other appropriate persons for verification of such facts.

The COT shall complete the Investigation promptly and, at its conclusion, shall submit a COT Preliminary Report to the AVP-HRP, IEC or EVPR for review, depending on the role of the Respondent. The COT Preliminary Report shall include the COT's recommendations as to (a) whether a finding of Noncompliance should be made, and, as applicable, (b) level of Noncompliance and (c) a CAPA Plan.

The AVP-HRP, IEC or the EVPR, as the case may be, may accept, reject or modify the conclusions and recommendations of the COT in the COT Preliminary Report and, if applicable, shall make the determination as to whether Noncompliance has occurred and if so, whether such Noncompliance constitutes Non-federally Reportable, Serious or Continuing Noncompliance and what corrective and preventive actions are necessary.

Corrective and preventive action(s) may include, but are not limited to, any of the following:

- Required training with respect to human subjects research and the regulatory requirements relating to such research;
- If the Respondent is a HRPO staff member, suspension or termination of employment;
- If the Respondent is a member of the IRB, suspension or termination of their appointment to the IRB; or
- Any other appropriate action.

If the COT Preliminary Report is not accepted, the COT shall undertake the necessary actions to address the AVP-HRP, IEC or the EVPR requests, and when completed, shall generate a COT Final Report. The COT Final Report will reflect the final determinations of the AVP-HRP, IEC or the EVPR, and recommendations or requirements, if any, for the Respondent. If a determination of Noncompliance has been made, the Report will subsequently be forwarded to the Need to Know Individuals. If Noncompliance is not found, the Report will be provided to the Respondent only.

The Outcome phase of the Investigation will consist of the following:

- If the Respondent does not appeal the COT Final Report, the COT will close the case when it has been confirmed that the CAPA Plan has been implemented. Notice of closure will be sent to the Respondent, and may, at the discretion of the COT, IEC or the EVPR, be sent to the Need to Know Individuals.
- If the Respondent disagrees with the finding(s) of Noncompliance, they may so notify the AVP-HRP, IEC or the EVPR, as applicable, citing the reasons for such disagreement. The AVP-HRP, IEC or the EVPR will make a final decision as to the finding of Noncompliance and the CAPA Plan and may, at their or its discretion, notify the Need to Know Individuals. Such decision shall be final in all respects and the Respondent shall have no further right to appeal the decision.

VI. REPORTING TO REGULATORY AGENCIES OR SPONSORS

The DCO shall report a finding of Serious or Continuing Noncompliance, and any Suspension or Termination of IRB approval, to the appropriate regulatory agency as required by applicable law or regulations, or the sponsor's grant or contract. The DCO will work with SPA or the CTO to facilitate sponsor notification when it is required.

Allegations that fall outside of the mandatory reporting requirements shall be reported to the regulatory agency, the sponsor, or any other relevant person(s) involved in the research project at the discretion of the AVP-HRP or the EVPR.

The Need to Know Individuals and the AVP-HRP will be copied on notifications from the HRPO to regulatory agencies or sponsors of Serious or Continuing Noncompliance, and Suspension or Termination of IRB approval.