7. UNANTICIPATED PROBLEMS INVOLVING RISKS TO PARTICIPANTS AND OTHERS, COMPLAINTS, NONCOMPLIANCE AND SUSPENSION OR TERMINATION OF IRBAPPROVAL OF RESEARCH

7.1 UNANTICIPATED PROBLEMS

Federal regulations require organizations to have written policies and procedures to ensure the prompt reporting of unanticipated problems involving risks to subjects or others to the IRB, appropriate institutional officials, and regulatory agencies and departments.

Not all unanticipated problems involve direct harm to subjects. Events can occur which are unexpected and result in new circumstances that increased the risk of harm to subjects without directly harming them. In addition, the event may have presented unanticipated risks to others (e.g., the sexual partners of the subjects, individuals the subject may come in contact with, family members, research personnel, etc.) in addition to the subjects. In each case, while the event may not have caused any detectable harm or adverse effect to subjects or others, they nevertheless represent unanticipated problems and should be promptly reported.

7.1.2 DEFINITIONS

Unanticipated Problem Involving Risks to Participants or Others (Unanticipated Problem):

Any incident, experience, or outcome that meets **all** the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. related or possibly related to participation in the research (*related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Adverse Event

Any physical, psychological, or social harm to subjects during the course of research. An adverse event can be any unfavorable or unintended event.

7.1.3 REPORTING

Principal investigators must report via an incident report to the IRB as soon as possible any:

- an unanticipated event related to the research that exposes research participants or individuals other than the research participants (e.g., investigators, research assistants, students, the public, etc.) to potential risk
- information that indicates a change to the risks or potential benefits of the research.
- a breach of confidentiality, including the loss of digital storage devices
- change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant
- complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team
- protocol violation (meaning an accidental or intentional change to the IRB approved protocol) that harmed participants or others or that indicates participants or others may be at increased risk of harm
- event that requires prompt reporting to the sponsor
- sponsor imposed suspension for risk

7.1.4 IRB REVIEW

Upon receipt of an Incident Report from a Principal Investigator, the HRCD or designee checks the form for completeness. If any applicable sections of the form are incomplete or have been answered unsatisfactorily, the HRCD or designee will contact the investigator to obtain additional information. Corrections are documented in the IRB file.

The IRB Administrator assigns the report provided by the investigator to the Chair for review.

Based on the information received from the Principal Investigator and upon the advice of the Administrator or other reviewers, the IRB Chair may suspend research to ensure protection of the rights and welfare of participants. In making a determination whether to direct suspension, the Chair may consider whether the PI has voluntarily put the research on hold. Suspension directives made by the IRB Chair must be reported to a meeting of the convened IRB.

The Chair (or their designee) or the convened IRB determines whether additional information is necessary, including information from individuals other than the principal

investigator (e.g., other research staff, research participants, site administrators). The IRB may conduct the investigation itself or request assistance from others (e.g., post approval monitors).

The Chair determines whether the report should be reviewed by the convened IRB or whether it can be reviewed under expedited procedures. If reviewed under expedited procedures, then the Chair or their designee may make requested changes to the protocol but may not terminate the study or make a finding of an unanticipated problem involving risk to subjects or others, serious noncompliance, or continuing noncompliance.

If referred to the convened IRB, then it may make all applicable determinations, including a finding of unanticipated problems involving risks to subjects or others, serious noncompliance, or continuing noncompliance. The results of the convened IRB review are recorded in the IRB minutes, protocol record, communicated to the investigator and referred to the HRCO to be handled according to the reporting procedures.

7.2 COMPLAINTS

As part of its commitment to protecting the rights and welfare of human subjects in research, the IRB reviews all complaints and allegations of noncompliance and takes any necessary action to ensure the ethical conduct of research.

Complaints reported to the IRB will be evaluated as possible unanticipated problems involving risks to participants or others.

The Chair of the IRB (or designee) will investigate all complaints, concerns, and appeals received by the IRB. This includes complaints, concerns, and appeals from investigators, research participants, and others.

All complaints, written or verbal (including telephone complaints), and regardless of point of origin, are recorded and forwarded to the IRB Chair and HRC Director.

Upon receipt of the complaint, the Chair will make a preliminary assessment whether the complaint warrants immediate suspension of the research project. If a suspension is warranted, the procedures in suspension will be followed.

If the complaint meets the definition of noncompliance, it will be considered an allegation of noncompliance according to noncompliance.

If the complaint meets the definition of an unanticipated problem involving risk to subjects or others, it will be handled according to Unanticipated Problems.

Upon receipt of the complaint, the IRB Chair and/or HRC Director shall generate a letter to acknowledge that the complaint has been received and is being investigated, providing a follow-up contact name.

7.3 NONCOMPLIANCE

All members of the NYU community involved in human subject research are expected to comply with the highest standards of ethical and professional conduct in accordance with federal and local regulations and institutional and IRB policies governing the conduct of research involving human subjects.

Investigators and their study staff are required to report instances of possible noncompliance. The Principal Investigator is responsible for reporting any possible noncompliance by study personnel to the IRB. Common reports to the IRB that are not serious or continuing are typically viewed as protocol violations and do not have to be reported to OHRP when federally funded, unless they result in the IRB suspending or terminating its approval. Any individual or employee may report observed or apparent instances of noncompliance to the IRB. In such cases, the reporting party is responsible for making these reports in good faith, maintaining confidentiality, and cooperating with any IRB and institutional review of these reports.

If an individual, whether Investigator, study staff or other, is uncertain whether there is cause to report noncompliance, he or she may contact the IRB Chair or HRCO directly to discuss the situation informally.

Reports of noncompliance should be submitted to the IRB promptly. The report must include a complete description of the noncompliance, the personnel involved and a description of the noncompliance.

Complainants may choose to remain anonymous.

7.3.1 DEFINITIONS

Noncompliance is a failure to comply with any of the regulations and policies described in this document and failure to follow the determinations of the IRB. Noncompliance may be minor, sporadic, or it may be serious or continuing.

Serious Noncompliance is a failure to follow any of the regulations and policies described in this document or failure to follow the determinations of the IRB and which, in the judgment of the convened IRB, increases risks to participants, decreases potential benefits, or compromises the integrity of the human research protection program. Research being conducted without prior IRB approval or participation of

subjects in research activities without their prior consent (in studies where consent was not explicitly waived by the IRB) is considered serious noncompliance.

Continuing Noncompliance is a pattern of noncompliance that, in the judgment of the convened IRB, suggests a likelihood that instances of noncompliance will continue without intervention. Continuing noncompliance also includes failure to respond to a request to resolve an episode of noncompliance.

An Allegation of Noncompliance is an unproved assertion of noncompliance.

A Finding of Noncompliance is an allegation of noncompliance that is proven true or a report of noncompliance that is true. (For example, a finding on an audit of an unsigned consent document, or an admission of an investigator that the protocol was willfully not followed would represent reports of noncompliance that would require no further action to determine their truth and would, therefore, represent findings of noncompliance.) Once a finding of noncompliance is proven, it must be categorized as serious and/or continuing, or neither serious nor continuing.

7.3.2 IRB REVIEW OF ALLEGATIONS OF NON-COMPLIANCE

The IRB Chair, or designee, will review all allegations of noncompliance, and will exam all pertinent materials, such as:

- all documents relevant to the allegation
- the last approval letter from the IRB
- the last approved IRB protocol
- the last approved consent document
- the grant (if applicable)
- any other pertinent information (e.g., questionnaires, etc.)

The HRCO will provide the Investigator with notice of the allegation along with a list of the charges/allegations.

The individual has 10 days to respond in writing to the HRCO.

The IRB Chair or designee will make a determination as to the truthfulness of the allegation and the response. They may request additional information from either party or an audit of the research in question.

When there is a determination that noncompliance did not occur because the incident was within the limits of an approved protocol for the research involved, the determination is reported in writing to the Principal Investigator and, if applicable, the

reporting party. The Chair or designee may also determine that the letter be copied to the Institutional Official and other relevant officials.

If the reported allegation of noncompliance is determined to be not true, no further action will be taken. If the reported allegation of is determined to be accurate, the noncompliance will be processed according to Review of Findings of Noncompliance.

If, in the judgment of the IRB Chair, any allegation or findings of noncompliance warrants suspension of the research before completion of any review or investigation to ensure the protection of the rights and welfare of participants, the IRB Chair may suspend the research as described in below in with subsequent review by the convened IRB.

The Chair may determine that additional expertise or assistance is required to make these determinations and may form an ad hoc committee to assist with the review and fact-gathering process. When an ad hoc committee assists in the review process, the Chair is responsible for assuring that minutes of the meeting are generated and kept to support any determinations or findings made by the ad hoc committee.

7.3.3 REVIEW OF FINDINGS OF NONCOMPLIANCE

If, in the judgment of the IRB Chair, the reported finding of noncompliance is not serious, not continuing, and the proposed corrective action plan seems adequate, no further action is required, and the IRB is informed at the next convened meeting. Otherwise, the matter will be presented to the IRB at a convened meeting with a recommendation that a formal inquiry (described below) will be held.

If an allegation of noncompliance is referred to the convened IRB, then IRB members will receive all pertinent materials/information, such as:

- all documents relevant to the allegation
- all documents relevant to the response
- the last approval letter from the IRB
- the last approved IRB protocol
- the last approved consent document
- At this stage, the IRB may:

- find that there is no issue of noncompliance
- find that there is noncompliance that is neither serious nor continuing and an adequate corrective action plan is in place
- find that there may be serious or continuing noncompliance and direct that a formal inquiry (described below) be held

- request additional information
- find that there is serious or continuing noncompliance
- suspend or terminate IRB approval

7.3.4 INQUIRY PROCEDURES

A determination may be made by the IRB that an inquiry is necessary based on several issues that may include but are not limited to:

- subject's complaint(s) that rights were violated
- report(s) that Investigator is not following the protocol as approved by the IRB;
- unusual and/or unexplained adverse events in a study
- repeated failure of Investigator to report required information to the IRB

7.3.5 FINDINGS OF SERIOUS OR CONTINUING NONCOMPLIANCE

If the results of the inquiry substantiate a finding of serious or continuing noncompliance, the IRB's possible actions could include, but are not limited to:

- request a correction action plan from the Investigator
- verification that participant selection is appropriate and observation of the actual informed consent
- require an increase in data and safety monitoring of the research activity
- request a directed audit of targeted areas of concern
- request a status report after each participant receives an intervention
- modify the continuing review cycle
- request additional Investigator and staff education
- require notification of current subjects if the information about the noncompliance might affect their willingness to continue participation
- request modifications to the protocol
- request modifications to the information disclosed during the consent process
- require current participants to re-consent to participation
- suspend IRB approval (see below)
- terminate IRB approval (see below)

In cases where the IRB determines that the event of noncompliance also meets the definition of an unanticipated problem involving risks to subjects or others, the policy and procedure for review of such events will also be followed.

The Investigator is informed of the IRB determination and the basis for the determination in writing and is given a chance to respond. If the IRB determines that

the noncompliance was serious or continuing the results of the final review will be reported as described below in Reporting.

7.3.6 ADDITIONAL ACTIONS

A finding of serious or continuing noncompliance may also result in the following sanctions, among others:

- suspension or termination of IRB approval of specific research protocols or of all research involving human subjects in which the Investigator participates
- the IRB may impose additional requirements on the Investigator or other personnel involved in a study, according to IRB policies and procedures.

Failure to secure necessary NYU IRB approval before commencing may result in disciplinary action from the University.

Investigators should also be aware that, in general, NYU indemnifies them from liability for adverse events that may occur in NYU studies approved by the NYU IRB. Failure to follow approved procedures may compromise this indemnification and make the Investigator personally liable in such cases.

7.3.7 SUSPENSION OR TERMINATION

An IRB has the authority 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 serious harm to subjects. Suspension of IRB approval is a directive of the convened IRB or IRB Chair to stop temporarily, or permanently, some or all previously approved research activities. Suspended protocols remain open and require continuing review. Termination of IRB approval is a directive of the convened IRB to stop all activities permanently in a previously approved research protocol. Terminated protocols are considered closed and no longer require continuing review.

The IRB Chair may suspend research to ensure the protection of the rights and welfare of participants. Suspension directives made by the IRB Chair must be reported to a meeting of the convened IRB. The convened IRB determines if the suspension should continue.

Research may only be terminated by the convened IRB. Terminations of protocols approved under expedited review must be made by the convened IRB.

After review of the allegation and possible response from the Investigator, the IRB shall notify the Principal Investigator in writing of such suspensions or terminations and shall

include a statement of the reasons for the IRB's actions. The terms and conditions of the suspension must be explicit. The Investigator shall be provided with an opportunity to respond in person and in writing.

The convened IRB or individual ordering the suspension or termination of a study will consider whether procedures for withdrawal of enrolled subjects are necessary to protect the rights and welfare of the subjects, such as:

- transferring participants to another investigator;
- making arrangements for care or follow-up outside the research;
- allowing continuation of some research activities under the supervision of an independent monitor; or
- requiring or permitting follow-up of participants for safety reasons.

If follow-up of subjects for safety reasons is permitted/required by the convened IRB or individual ordering the suspension, the convened IRB or individual ordering the suspension will require that the subjects should be so informed and that any adverse events/outcomes be reported to the IRB and the sponsor.

Investigators must continue to provide reports on unanticipated problems and noncompliance to both the IRB and sponsor, as needed, just as if there had never been a suspension (i.e., all events that need to be reported during a study need to continue to be reported during the suspension period.)

7.3.8 REPORTING

Serious or continuing noncompliance with regulations or the requirements or determinations of the IRB, suspensions or terminations of IRB approval, and findings of unanticipated problems involving risks to subjects or others will be reported to the appropriate regulatory agencies and institutional officials according to the procedures below.

7.3.9 REPORTING TO REGULATORY AGENCIES AND INSTITUTIONAL OFFICIALS

Federal regulations require prompt reporting to appropriate institutional officials, OHRP, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others; (ii) any serious or continuing noncompliance of federal regulations or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval. The IRB will comply with this requirement, and the following procedures describe how these reports are handled.

The HRCO will initiate these procedures when the IRB takes any of the following actions:

- Determines that an event may be considered an unanticipated problem involving risks to participants or others
- Determines that noncompliance was serious or continuing
- Suspends or terminates approval of research

The Human Research Compliance Director or designee prepares a letter about the finding that may contain the following information:

- the nature of the event (unanticipated problem involving risks to participants or others, serious or continuing noncompliance, suspension or termination of approval of research)
- name of the institution conducting the research
- title of the research project and/or grant proposal in which the problem occurred
- name of the principal investigator on the protocol
- number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement)
- a detailed description of the problem including the findings of the organization and the reasons for the IRB's decision
- actions the institution is taking or plans to take to address the problem (e.g., revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.)
- plans, if any, to send a follow-up or final report by the earlier of specific date when an investigation has been completed or a corrective action plan has been implemented

The IRB Chair and the Institutional Official review the letter and modify the letter as needed. The Institutional Official signs the letter and returns it to the HRC Director or designee

The HRC Director or designee sends a copy of the report to:

- the IRB by including the letter in the next agenda as an information item
- the Institutional Official
- Principal Investigator
- department or agency head, if the study is funded by a Common Rule department or agency
- OHRP, if the study is funded by a Common Rule department or agency.

The Institutional Official and/or IRB may determine that a copy of the report be sent to others, such as:

- chairman or supervisor of the principal investigator or student investigator
- other sites engaged in the research

- sponsor, if funded by an entity other than a Common Rule agency.

The HRC Director ensures that all steps of this policy are completed promptly after the initiating action. For more serious actions, the HRC Director will expedite reporting.

The above reporting is not required if the event occurred at a site that was not subject to the direct oversight of NYU IRB.

8. VULNERABLE POPULATIONS

When some or all of the participants in a protocol are likely to be vulnerable to coercion or undue influence or to specific risks, the IRB should include additional safeguards to protect the rights and welfare of these participants. Some of the vulnerable populations that might be involved in research studies include children, pregnant women, fetuses, prisoners, persons with impaired decision-making capacity, or economically or educationally disadvantaged persons.

If the IRB reviews research that involves categories of vulnerable participants, the review process will include one or more individuals who are knowledgeable about or experienced in working with these participants.

The subparts within 45 CFR Part 46 provide extra protections for specific vulnerable populations. These populations have additional review requirements for IRBs. For research funded by DHHS agencies, there are also other reporting requirements.

Subpart B: Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

Subpart C: Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Subpart D: Additional Protections for Children Involved as Subjects in Research

Researchers conducting human subject research must check with the IRB to determine the applicability of and how to apply the subparts.

NYU recognizes individuals who have a unique relationship with investigators or cooperating sites, such as students and employees, as vulnerable due to the potential for undue influence and coercion in certain conditions.

8.1 PI RESPONSIBILITIES

The Principal Investigator is responsible for identifying the potential for enrolling vulnerable subjects in the research protocol and for adherence to the additional