I. Purpose of this SOP

The purpose of this SOP is to set forth the procedures to be followed for the reporting of unanticipated problems, any serious or continuing noncompliance, and any suspension or termination of IRB approval of human subjects research conducted under the auspices of Brandeis University.

II. Scope of this SOP

This SOP applies to human subjects research projects conducted under the auspices of Brandeis University.

III. Key Definitions

Unanticipated Problem refers to any incident, experience, or outcome that meets all of the following three criteria:

1) Unexpected (in terms of nature, severity, or frequency) given the following two criteria:
   a) The research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document.
   b) The characteristics of the subject population being studied.
2) Related or possibly related to participation in the research (where there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
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 refers to any untoward or unfavorable occurrence (either physical or psychological) in a human subject, including any abnormal sign, symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research.

Serious Adverse Event refers to any adverse event that:
1) Results in death
2) Places the subject at immediate risk of death
3) Results in inpatient hospitalization or prolongation of existing hospitalization
4) Results in persistent or significant disability/incapacity
5) Results in congenital anomaly/birth defect
6) Based upon appropriate medical judgment may jeopardize the subject’s health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

Unexpected Adverse Event refers to an event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is not consistent with either:
1) The known or foreseeable risk of adverse events associated with the procedures involved in the research as described in either of the two following:
   a) The protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document.
   b) Other relevant sources of information, such as product labeling and package inserts.
2) The expected natural progression of any underlying disease, disorder, or condition of the subject experiencing the adverse event and the subject’s predisposing risk factor profile for the adverse event.

Noncompliance refers to the failure to fully comply with all laws and regulations governing human subject research activities, as well as the policies, procedures, or determinations of the Brandeis University IRB, or its designee. Noncompliance may be serious or non-serious, continuing or sporadic. Examples of noncompliance include, but are not limited to:
- Lapses in continuing IRB approval
- Changing study personnel without notifying the IRB
- Implementing wording changes in study instruments without obtaining IRB approval
- Failure to obtain exempt determination before exempt research involving human subjects is conducted
- Changes in or deviations from an approved protocol
- Administrative errors
- Continuing non-exempt human subjects research without IRB approval
- Lack of legally effective informed consent from research participants
- Failure to retain copies of informed consent forms
- Failure to report or review serious adverse events, unanticipated problems, or substantive changes in research
- Inappropriate oversight of the research to ensure the safety of human subjects and the integrity of the research/data

Serious Noncompliance refers to noncompliance that has the potential to increase risk to research participants, compromise participants’ rights or welfare, or affect the integrity of the research/data.

Non-serious Noncompliance refers to noncompliance that does not increase risk or decrease the benefits to research participants, compromise participants’ rights or welfare, or affect the integrity of the research/data.

Continuing Noncompliance refers to noncompliance that has been previously reported, or a pattern of ongoing activities that indicate a lack of understanding of human subjects protection requirements that may affect research participants or the validity of the research and suggest the potential for future noncompliance without intervention. Examples of continuing noncompliance include, but are not limited to:
- A pattern of deviating from the approved protocol
- Repeated failures to provide continuation or modification requests resulting in lapses of IRB approval
- Inadequate oversight of ongoing research
- Failure to respond to or resolve previous allegations or findings of noncompliance
Non-continuing Noncompliance refers to noncompliance that is a single event and that has not previously been reported.

IV. Statement of SOP

It is the standard operating procedure of Brandeis University that it require the timely reporting and review of adverse events and other unanticipated problems and/or non-compliance in all human subjects research conducted under its auspices.

V. Procedures

Unanticipated Problems and Adverse Events
If an investigator believes an unanticipated problem or adverse event has occurred, s/he must report it to the IRB.

Unanticipated problems that are serious adverse events must be reported within one week of the investigator becoming aware of the event.

Unanticipated problems that are non-serious adverse events must be reported within two weeks of the investigator becoming aware of the event.

Included in this report must be:

1) The appropriate identifying information for the research protocol, such as the title, investigator's name, and IRB project number.
2) A detailed description of the adverse event, incident, experience, or outcome.
3) An explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem.
4) A description of any changes to the protocol or other corrective actions that have been taken – if it is determined by the principal investigator that such corrective actions are in the best interest of individual subjects currently participating in the study – or are proposed in response to the unanticipated problem.

Once a report has been filed, the IRB chair or his/her designee reviews the report along with materials from the protocol file (e.g., initial protocol, continuing reviews, modifications) and determines whether the event qualifies as an unanticipated problem or adverse event.

If it is determined the event does not qualify as an unanticipated problem or adverse event, this is communicated to the principal investigator. A copy of the report and notification is placed in the IRB file and the issue is considered closed.

If the determination is made that the event was, indeed, an unanticipated problem or adverse event, the report is reviewed at the next convened IRB meeting, or a special meeting is called if deemed necessary by the reviewer. The IRB administrator notifies the principal investigator of the IRB’s determination and actions to be taken and a copy of the report is placed in the IRB file. The IRB has a number of available actions it can take, depending on the severity of the event and the continuing risk to participants.

Possible actions the IRB may take include:

- Terminating the research
- Suspending the research
• Requiring modification to the research (such as to the informed consent process)
• Requiring additional monitoring of the research or consent process
• Requiring participants to be notified of the event
• Requiring current participants to be re-consented

In addition to possible actions relating to the research, the IRB administrator reports to the Institutional Official the event and action taken and/or planned. The Institutional Official then reports the event and action taken and/or planned to the Office for Human Research Protections, sponsors of the research (if applicable), and any other applicable entities.

The Institutional Official will include in his/her report to OHRP the following:

1) The name of the institution (Brandeis University)
2) Title of the research project
3) Name of the principal investigator on the protocol
4) Project number assigned by the IRB
5) Title and funding number of the funded grant proposal, if applicable
6) Name of principal investigator on the grant, if applicable
7) A detailed description of the problem
8) An explanation of the actions taken and/or planned by Brandeis University
9) If actions include suspension or termination of the research project, an explanation of the actions taken and/or planned by Brandeis University to address the suspension or termination

Serious or Continuing Noncompliance
It is the Principal Investigator’s responsibility to ensure that issues of noncompliance in human subject research do not occur. Allegations of noncompliance should be reported to the university’s IRB administrator and will be duly investigated. If the principal investigator becomes aware of any issues of noncompliance within his/her human subjects research study, s/he must report it immediately to the IRB administrator.

Review and Remediation of Allegations of Noncompliance
Once an allegation or report of suspected noncompliance is reported, the IRB chair or his/her designee conducts an investigative review to determine whether the issue meets the definition of noncompliance. If s/he determines the issue does not meet the definition of noncompliance, the issue will be considered closed.

If it is determined the issue meets the definition of noncompliance, the IRB chair or his/her designee makes a determination of the level of seriousness and whether the issue meets the definition of continuing noncompliance.

If it is determined the issue is non-serious and non-continuing noncompliance, a corrective action plan will be developed to prevent further noncompliance, to be instituted by the principal investigator. The IRB administrator notifies the principal investigator of the corrective action plan and a copy of the plan is placed in the IRB file. The report of noncompliance and its corrective action plan is reported at the next convened meeting of the IRB. Once the corrective action plan is implemented, the issue is considered closed.

If it is determined the issue is serious or continuing noncompliance and puts the subjects at immediate risk, the research may be suspended immediately. In such a case, a report of the suspension is sent to the principal investigator and a special meeting of the IRB is convened within 10 days to review the issue and determine a further course of action. The IRB administrator notifies the principal investigator and copies of the report are placed in the IRB file and forwarded to the Institutional Official.

If it is determined the issue is serious or continuing noncompliance but does not put the subjects at immediate risk, the issue is reported and reviewed at the next convened meeting of the IRB, and a course of action is determined. The IRB administrator notifies the principal investigator and copies of the report are placed in the IRB file and forwarded to the Institutional Official.
Possible actions of the Brandeis University IRB may include, but are not limited to:

- Requiring modification of the research protocol
- Requiring modification of the consent process
- Requiring re-education of the principal investigator and research team
- More frequent continuing review schedule
- Periodic audits
- Requiring re-consent of subjects
- Termination or suspension of the study

If noncompliance is determined and a corrective action plan developed, the IRB monitors the principal investigator’s implementation of the corrective action plan. If the corrective action plan is not fully implemented within the plan’s stated time frame, the IRB and the Institutional Official are informed within one week and a further course of action is determined.

Once the corrective action plan has been fully implemented, the IRB administrator drafts a final report to be reviewed at the next convened meeting of the IRB. Once finalized, the report is endorsed by the IRB chair and the principal investigator is notified. A copy of the report is placed in the IRB file and forwarded to the Institutional Official.

The Institutional Official informs and forwards all applicable reports regarding serious and/or continuing noncompliance to the Office for Human Research Protections, sponsors of the research (if applicable), and any other applicable entities.

The Institutional Official includes in his/her report to OHRP the following:

1) The name of the institution (Brandeis University)
2) Title of the research project
3) Name of the principal investigator on the protocol
4) Project number assigned by the IRB
5) Title and funding number of the funded grant proposal, if applicable
6) Name of principal investigator on the grant, if applicable
7) A detailed description of the problem
8) An explanation of the actions taken and/or planned by Brandeis University
9) If actions include suspension or termination of the research project, an explanation of the actions taken and/or planned by Brandeis University to address the suspension or termination

VI. Applicable Regulations and Guidance

The US government code of federal regulations for the protection of human subjects (45 CFR 46) contains the following requirements for ensuring prompt reporting to the IRB, appropriate institutional officials, any Department or Agency head, and OHRP of (a) any unanticipated problems involving risks to subjects or others, (b) any serious or continuing noncompliance with 45 CFR 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval:

An IRB shall have 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. Any suspension or termination of approval shall include a statement of the reasons for the IRB’s action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head. [§46.113]