

## 3.0 CONTINUING IRB REVIEW OF RESEARCH PROTOCOLS

### 3.1 Modifications to the Research Protocol and Informed Consent Document(s)

It is recognized that modifications to research protocols and informed consent documents may be required as the research study proceeds. *However, any proposed modification to an IRB-approved research protocol or informed consent document must be approved by the IRB prior to implementation.* The only exception to this requirement is a change in procedure that may be necessary to eliminate an apparent immediate hazard to a given research subject. It is not acceptable to modify extemporaneously (i.e., without prior IRB approval) an IRB-approved research protocol or consent form to permit the enrollment of a given individual who does not meet current eligibility criteria or to address any other specific issues related to the needs or desires of, a given individual or patient who may want to participate in the study. Requests for protocol exceptions should be made in writing to the IRB Chair at the same time the request for exception is submitted to the sponsor.

#### 3.1.1 Categories of Modification Review - Submission Requirements

IRB approval of modifications to research protocols and informed consent documents can be requested at any time. **The approval of a modification request by the IRB will not, in general, alter the original IRB-approval date and expiration of IRB-approval dates assigned to the protocol. However, if the requested modification alters substantially the risk-to-benefit ratio of study participation, the IRB responsible for review and approval of the modification request may alter the expiration date assigned to the research protocol. However, the new expiration date will never exceed the original date.**

The category of review (i.e., expedited or full board) of proposed modifications to an IRB-approved research protocol or informed consent document is dependent upon whether the proposed changes are considered minor or major. The IRB chairperson or his/her designee shall have final responsibility for this designation.

- 1) Minor modifications: The IRB chairperson or his/her designee can expedite the review and approval of minor modifications to an IRB-approved research protocol or informed consent document. A minor modification is defined as a change that would not materially affect an assessment of the risks and benefits of the study or does not substantially change the specific aims or design of the study. Examples of minor modifications may include:
  - the addition of research activities listed under sections 2.1 Exempt Review or 2.2 Expedited Review
  - an increase or decrease in proposed human research subject enrollment supported by a statistical justification
  - narrowing the range of inclusion criteria
  - broadening the range of exclusion criteria
  - alterations in the dosage form (e.g., tablet to capsule or oral liquid) of an administered drug, provided the dose and route of administration remain constant
  - decreasing the number or volume of biological sample collections, provided that such a change does not affect the collection of information related to safety evaluations
  - an increase in the length of confinement or number of study visits for the purpose of increased safety monitoring
  - a decrease in the length of confinement or number of study visits, provided that such a decrease does not affect the collection of information related to safety evaluations

- alterations in human research subject payment or liberalization of the payment schedule with proper justification
- changes to improve the clarity of statements or to correct typographical errors, provided that such a change does not alter the content or intent of the statement
- the addition or deletion of study sites
- minor changes specifically requested by the IRB; Human Use Subcommittee, Radiation Safety Committee; Radioactive Drug Research Committee; or Clinical and Translational Research Center

PAPER SUBMISSIONS: For minor modifications to a research protocol or informed consent document submit two (2) copies of the following paperwork stapled in the order given:

- a completed IRB Cover Sheet (see IRB Forms) marked Modification
- a Modification form (see IRB Forms) listing the proposed modification(s) and giving a rationale for the modification(s) PLEASE NOTE: "REQUESTED BY SPONSOR" IS NOT CONSIDERED TO BE AN APPROPRIATE RATIONALE FOR A MODIFICATION.
- the current research protocol with any modifications highlighted
- the current informed consent document with any modifications highlighted
- if applicable, a copy of the sponsor's research protocol amendment addressing the respective modification(s)
- notification of modification approval from UPMC Fiscal (i.e., for modifications involving research related procedures)

OSIRIS SUBMISSIONS: The modification online submission process must be utilized in order to request changes to an approved study. The smart form questions will prompt a response to issues related to the modification.

*Note: Modifications to the informed consent document must take into account both prospective research subjects and, if applicable, research subjects already enrolled in the study. The latter may be addressed using an addendum to the initial informed consent document (see [Appendix H](#)) or, less preferably, by re-consenting the subject using the modified informed consent document.*

2) Major modifications: Major modifications to an IRB-approved research protocol or informed consent document must undergo full board review and approval. A major modification is defined as any change which materially affects an assessment of the risks and benefits of the study or substantially changes the specific aims or design of the study. Examples of major modifications may include:

- broadening the range of inclusion criteria
- narrowing the range of exclusion criteria
- alterations in the dosage or route of administration of an administered drug
- extending substantially the duration of exposure to the test material or intervention
- the deletion of laboratory tests, monitoring procedures, or study visits directed at the collection of information for safety evaluations
- the addition of serious unexpected adverse events or other significant risks
- changes which, in the opinion of the IRB chairperson or his/her designee, do not meet the criteria or intent of a minor modification

PAPER SUBMISSIONS: For major modifications to a research protocol or informed consent document submit twenty-six (26) copies of the following paperwork stapled in the order given:

- a completed IRB Cover Sheet (see Appendix A) marked Modification
- a Modification form (see Appendix A) listing the modification(s) and giving a rationale for the modification(s). PLEASE NOTE: "REQUESTED BY SPONSOR" IS NOT CONSIDERED TO BE AN APPROPRIATE RATIONALE FOR A MODIFICATION.
- the current research protocol with any modifications highlighted
- the current informed consent document(s) with any modifications highlighted
- notification of approval from the scientific review committee, department chair, school, or center/institute administrator (i.e., for substantial modifications to the specific aims and /or design of the research protocol)
- if applicable, a copy of the sponsor's research protocol amendment addressing the respective modification(s)
- notification of modification approval from the Radioactive Drug Research Committee (RDRC) and/or radiation safety committee (HUSC) (i.e., for modifications involving radioactive drug or radiation emitting procedures)
- notification of modification approval from the Institutional Biosafety (rDNA) Committee (i.e., for modifications involving the gene transfer intervention)
- notification of modification approval from UPMC Fiscal (i.e., for modifications involving research related procedures)

OSIRIS SUBMISSIONS: The modification online submission process must be utilized in order to request changes to an approved study. The smart form questions will prompt a response to issues related to the modification.

*Note: Modifications to the informed consent document must take into account both prospective research subjects and, if applicable, research subjects already enrolled in the study. The latter may be addressed using an addendum to the initial informed consent document (see Appendix H) or, less preferably, by re-consenting the subject using the modified informed consent document.*

### 3.1.2 Modification Turnaround Time

Minor modifications which qualify for expedited review will be reviewed by the IRB chairperson or his/her designee in the order in which they were received in the IRB office. Turnaround time varies depending upon the number of submissions received. Major modifications require full board review and investigators will receive correspondence from the IRB within approximately 5 working days following a scheduled meeting.

## 3.2 Research Protocol Renewals

### 3.2.1 Frequency of Renewals

Annual renewal of all research protocols (except protocols determined by the IRB to qualify for exempt status) is mandatory including research protocols in which human research subject accrual has been closed and the research interventions completed, but data continue to be collected or analyzed. (IRB approval of the research protocol must remain active until such time that 1) analysis of the data has concluded that no new information needs to be provided to enrolled subjects or 2)

*there is no need to re-contact enrolled subjects to obtain additional research information and/or 3) it has been determined that the data collected will not be used in support of a separate, new research study.)* The IRB strongly encourages investigators to keep a protocol active (e.g., 'data analysis only') so long as investigators are currently using or planning to utilize identifiable data from the IRB protocol.

The IRB may, however, require more frequent review of certain research protocols based on a risk assessment. Principal investigators will be informed by the IRB Office of the expiration date of approval granted by the IRB. Reminder letters will be sent by the IRB Office 60 and 30 days in advance of the research protocol expiration date. However, it is the principal investigator's responsibility to assure timely submission of the research protocol for IRB renewal approval prior to the expiration date. It is also the responsibility of the Principal Investigator to complete, in its entirety, the Research Renewal Report Form including the submission of required supporting information (e.g., a summary of unanticipated problems involving risks to subjects or others, reports from the data and safety monitoring plan).

Research protocol renewals should be submitted to the IRB Office at least five weeks prior to the expiration of current approval.

### 3.2.2 Lapses in IRB Approval

If the study is not reviewed and approved by the IRB prior to the expiration date of the previous IRB approval, the principal investigator is required to cease all research activities described in the IRB protocol (including data analysis) until notification of final IRB approval for continuation of the research has been issued. In this circumstance, the principal investigator shall be advised that, if it is felt that there is an overriding safety concern or ethical issue, s/he may petition the IRB Chair for permission to continue certain research activities that impact the rights and welfare of current research subjects. However, under no circumstances can new subjects be enrolled into a research study after expiration of IRB approval.

If the investigator wishes to continue the study, a new submission through the OSIRIS system is required. The OSIRIS system will prompt the investigator to indicate whether the new study has been previously approved by the University IRB and to provide the IRB number originally assigned to the submission. The investigator will also be required to submit a renewal report form so the IRB reviewer has information related to conduct of the study to date.

### 3.2.3 Categories of Renewal Review - Submission Requirements

The category of renewal review of a research protocol is dependent on the category of its original review and approval and the risk level of the research study.

- 1) Exempt research activities: Submissions that are determined to meet exempt criteria do not require a renewal to be submitted.
- 2) Expedited renewal review: The renewal review of a research protocol approved initially by expedited review or a research protocol approved initially by full-board review but which currently meets the criteria addressed under Section 2.2 (8) will be performed by the IRB chairperson or his/her designee using an expedited procedure. The IRB chairperson/designee may re-designate the research protocol for full board renewal

review dependent on any proposed modifications to the research protocol or the occurrence of events that challenge the minimal risk status of the research.

PAPER SUBMISSIONS: If the renewal is currently being submitted via paper, submit two (2) copies of the following paperwork stapled in the order given:

- a completed IRB Cover Sheet (see Appendix A) marked *Renewal*
- a completed Research Renewal Report Form **with supporting information, as specified**
- a completed Modification form (if applicable), and if applicable, a copy of the sponsor's research protocol amendment addressing the respective modification(s)
- the current research protocol with any modifications highlighted
- current informed consent document with any modifications highlighted.

OSIRIS SUBMISSIONS: If the study was initially approved through OSIRIS, the renewal must be submitted through OSIRIS. The investigator will be required to respond to a series of smart form questions related to the renewal of the project.

In addition, if the study is commercially sponsored, submit fee of \$250 in the form of a check, industry-sponsor fee form ([www.irb.pitt.edu](http://www.irb.pitt.edu)), or a memo requesting a fee waiver

- 3) Full Board renewal review: The renewal review of a research protocol approved initially by full board review will be performed by the full board unless it meets the criteria for expedited review addressed under Section 2.2 (8).

PAPER SUBMISSIONS: If the renewal is being submitted via paper, submit twenty-six (26) copies of the following paperwork stapled in the order given:

- a completed IRB Cover Sheet (see Appendix A) marked *Renewal*
- a completed Research Renewal Report Form **with supporting information, as specified.**
- a completed Modification form (if applicable) and, if applicable, a copy of the sponsor's research protocol amendment addressing the respective modification(s)
- the current research protocol with any modifications highlighted
- the current informed consent document(s) with any modifications highlighted
- current investigator brochure and FDA Correspondence (if applicable)
- notification of Institutional Biosafety (rDNA) Committee renewal approval of the gene transfer research (if applicable).

OSIRIS SUBMISSIONS: If the study was initially approved through OSIRIS, the renewal must be submitted through OSIRIS. The investigator will be required to respond to a series of smart form questions related to the renewal of the project.

In addition, if the study is commercially sponsored, submit fee of \$500 in the form of a check, industry-sponsor fee form ([www.irb.pitt.edu](http://www.irb.pitt.edu)), or a memo requesting a fee waiver

### 3.3 Reporting of Unanticipated Problems Involving Risks to Human Subjects or Others

Federal regulations at 45 CFR 46.103(b)(5) and 21 CFR 56.108(b) require IRBs to have written procedures for ensuring prompt reporting to the IRB of any unanticipated problems involving risks to subjects or others. Consistent with these regulations and IRB policies, investigators are required to report unanticipated problems involving risks to human subjects or others following the procedures outlined below. Reportable problems include, but are not limited to:

- a. adverse events which meet the reporting requirements of the University of Pittsburgh IRB under Section 3.3.2 (please utilize the Adverse Event form for this type of report);
- b. any deviation from the IRB-approved protocol that involves risks or has the potential to recur (e.g., over enrollment, incorrect dosing or labeling);
- c. any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a given research subject;
- d. any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected increase in the risk to benefit ratio of the research;
- e. any complaint of a subject that indicates an unanticipated risk or which cannot be resolved by the research staff; or
- f. any other untoward event that affects the welfare or the privacy, confidentiality or other rights of research subjects or members of their family; or that presents a risk to investigators and research staff involved in the conduct of the research;
- g. any enrollment which is greater than what was approved by the IRB.

#### 3.3.1 Definitions

Adverse Event: Any untoward medical occurrence, which may include abnormal signs (for example, abnormal physical exam or laboratory findings), symptoms, or disease, temporally associated with, but not necessarily considered related to, the subject's participation in the research study.

Continuing Non-Compliance: Repeated failure to understand and consistently comply with federal regulations and University IRB policies governing human subject protections and that, in the judgment of the University IRB, seriously compromises human research protection or the integrity of the University's human research protection program.

Serious Non-Compliance: Failure to comply with any of the federal or state regulations or institutional policies governing human subject research that, in the judgment of the University IRB, seriously compromises human research subject protection or the integrity of the University's human research protection program. Examples of serious non-compliance include, but are not limited to:

1. performing non-exempt human subject research without obtaining University IRB approval;
2. implementing substantial modifications to a research study without obtaining formal University IRB approval;
3. failing to systematically obtain research subject's informed consent as required by the IRB approved protocol;;

4. failing to comply with federal regulations governing human subject protections (this includes activities of the University IRB and/or University IRB Office staff).

External Adverse Event: An Adverse Event that occurs at a site external to the authority of the University IRB and is reported to a University or UPMC investigator.

Internal Adverse Event: An Adverse Event that occurs at a University, UPMC, or other site that falls directly under the authority of the University IRB.

Possibly Related to the Research Intervention: In the opinion of the principal investigator, there is a *reasonable possibility* that the incident, experience, or outcome may have been caused by the procedure involved in the research.

Research Intervention: An intervention or procedure performed specifically for the purpose of the research study.

Serious Adverse Event: An Adverse Event that:

- is fatal or life-threatening
- requires or prolongs hospitalization
- results in a persistent or significant disability/incapacity
- results in a congenital anomaly/birth defect
- 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

Unanticipated: Unforeseeable at the time of its occurrence.

Unanticipated Problems Involving Risk to Subjects or Others: Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency
- related or possibly related to a subject's participation in 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

Unexpected: Not identified by nature, severity or frequency in the current University IRB-approved research protocol or informed consent document.

### 3.3.2 Reporting (i.e., to the IRB) of Adverse Events Occurring During the Conduct of an IRB-Approved Research Study

Outlined below are the requirements for reporting Adverse Events to the IRB. Note that the reporting of Adverse Events to external sponsors of research studies or to the Food and Drug Administration (i.e., for investigator-sponsored clinical trials) will be subject to different requirements.

### 3.3.2.1 General Adverse Event Reporting Requirements

Unless subject to different IRB reporting requirements by a federal agency, investigators involved in the conduct of IRB-approved research studies shall promptly report to the IRB:

1. Internal Adverse Events that are (i) Unexpected; (ii) Serious; and (iii) Related or Possibly Related to the Research Intervention.
2. External Adverse Events that are (i) Unexpected; (ii) Serious AND suggests that the research places subjects or others at greater risk than was previously recognized; and (iii) Related to the Research Intervention.

Expected Adverse Events; Unexpected Adverse Events of minor or moderate severity; or Adverse Events which are determined by the investigator to be unrelated to the Research Intervention need not be reported to the IRB.

### 3.3.2.2 General IRB Reporting Timelines for Adverse Events

Investigators involved in the conduct of IRB-approved research studies shall report, to the IRB Office in accordance with the following timelines, Adverse Events that meet the University IRB's reporting requirements:

1. Internal Adverse Events which are Unexpected, fatal or life-threatening, and Related or Possibly Related to the Research Intervention must be reported to the IRB within 24 hours of the reaction. *(Note: It is recognized that the information available during this 24 hour period may not be sufficient to permit accurate completion of the required adverse event reporting forms. However, the IRB should, at a minimum, be notified of the fatal or life-threatening internal adverse event during this time frame, with subsequent followup submission of a more detailed written report.)*
2. Internal Adverse Events which are Unexpected, Serious (but not fatal or life-threatening), and Related or Possibly Related to the Research Intervention shall be reported to the IRB within 5 working days of the investigator becoming aware of the reaction.
3. External Adverse Events (i.e., external sponsor generated safety reports) which are Unexpected, Serious AND suggests that the research places subjects or others at greater risk than was previously recognized, and Related to the Research Intervention shall be reported to the IRB within 30 working days of their receipt by the University/UPMC investigator. *(Note: only sponsor-generated safety reports that meet the Adverse Event reporting of the IRB should be submitted to the IRB. Sponsors requesting different IRB reporting criteria should be referred to the IRB Office.)*

### 3.3.2.3 Special Reporting Requirements - Gene Transfer Interventions

1. All Unexpected, Serious Internal Adverse Events related to the gene transfer intervention must be reported to the external sponsor of the research study (if applicable) and to the IRB, Institutional Biosafety (rDNA) Committee, NIH Office of Biotechnology Activities (OBA), and Food and Drug Administration.
  - a. Unexpected, fatal or life-threatening internal Adverse Events related or possibly related to the gene transfer intervention shall be reported to the external sponsor (if applicable), IRB and Institutional Biosafety (rDNA) Committee within 24 hours of the reaction. If the sponsor of the human gene transfer research study is a University investigator, reporting of the adverse event to the OBA and FDA should occur as soon as possible but no later than 7 working days following the sponsor's initial receipt of the information. (If the human gene transfer research study is externally sponsored, it is the responsibility of the external sponsor to report the adverse event to the OBA and FDA.)
  - b. Unexpected, Serious (but not fatal or life-threatening) Internal Adverse Events Related or Possibly Related to the gene transfer intervention, shall be reported to the external sponsor (if applicable), IRB and Institutional Biosafety (rDNA) Committee as soon as possible but no later than 5 calendar days of the reaction. If the sponsor of the human gene transfer research study is a University investigator, reporting of the adverse event to the OBA and FDA should occur as soon as possible but no later than 15 working days following the sponsor's initial receipt of the information. (If the human gene transfer research study is externally sponsored, it is the responsibility of the external sponsor to report the adverse event to the OBA and FDA.)
  - c. Any follow up information related to an Unexpected, Serious Adverse Event Related or Possibly Related to a gene transfer intervention should be reported promptly to the external sponsor (if applicable), IRB, and Institutional Biosafety (rDNA) Committee. If the sponsor of the human gene transfer research study is a University investigator, reporting of the follow up information to the OBA and FDA should occur as soon as possible but no later than 15 working days following the sponsor's receipt of the information. (If the human gene transfer research study is externally sponsored, it is the responsibility of the external sponsor to report the follow up information to the OBA and FDA.)
  - d. If an Unexpected, Serious Adverse Event occurs after the end of the clinical trial and it is determined to be related or possibly related to the gene transfer intervention, the reaction should be reported promptly to the external sponsor (if applicable), IRB, and Institutional Biosafety (rDNA) Committee. If the sponsor of the human gene transfer research study is a University investigator, reporting of this Adverse Event information to the OBA and FDA should occur as soon as possible but no later than 15 working days following the sponsor's receipt of the information. (If the human gene transfer research study is externally

sponsored, it is the responsibility of the external sponsor to report this adverse event information to the OBA and FDA.)

- e. If, after further evaluation, an Unexpected, Serious Internal Adverse Event initially considered not to be related to the gene transfer intervention is determined to be Related, then the Unexpected, Serious Internal Adverse Event should be reported promptly to the external sponsor (if applicable), IRB, and Institutional Biosafety (rDNA) Committee. If the sponsor of the human gene transfer research study is a University investigator, reporting of the adverse event to the OBA and FDA should occur as soon as possible but no later than 15 working days of this determination. (If the human gene transfer research study is externally sponsored, it is the responsibility of the external sponsor to report this determination to the OBA and FDA.)
2. The above reporting requirements apply to all research studies involving gene transfer interventions regardless of the source of the research funding.

### 3.3.2.4 Submission Format for the Reporting of Adverse Events

#### PAPER SUBMISSIONS:

1. Internal Adverse Events reported to the IRB in accordance with the requirements addressed above will be individually reviewed by the full-board IRB. Submit 26 copies of the following:
  - IRB Cover Sheet marked "Adverse Event Report" and "Modification" (if applicable)
  - Completed IRB Adverse Event Database Form and a narrative summary of the event
  - Completed sponsor adverse event reporting form or FDA MedWatch report form (For gene transfer interventions, the completed NIH Office of Biotechnology Activities (OBA) Serious Adverse Event Report Form)
  - Modification request form (if applicable)
  - Respective IRB Research Protocol, with modifications highlighted if applicable
  - Respective informed consent document, with modifications highlighted if applicable
  - Consent Form Addendum to provide new information to currently enrolled subjects (if applicable)
2. External Adverse Events reported to the IRB in accordance the requirements addressed above will be summarized for review by the full-board IRB. Submit 2 copies of the following for each adverse event reported by the sponsor:
  - Completed IRB Adverse Event Database Form
  - Sponsor safety report
  - Respective informed consent document (currently approved version)

OSIRIS SUBMISSIONS: For studies approved through the electronic submission system, the Unanticipated Problem online submission process must be utilized in order to submit a

report. The smart form questions will prompt a response to issues related to the adverse event.

### **3.3.3 Reporting of Other Unanticipated Problems Involving Risks to Human Subjects or Others to the IRB**

Outlined below are the requirements for reporting Unanticipated Problems Involving Risks to Human Subjects or Others (other than Adverse Events) to the IRB.

#### **3.3.3.1 General Reporting Requirements**

Investigators involved in the conduct of IRB-approved research studies shall submit all Unanticipated Problems Involving Risks to Human Subjects or Others that are Possibly or Definitely Related to the research in a timely manner, taking into account the nature and severity of the Unanticipated Problem and its potential risk to human subjects or others.

#### **3.3.3.2 Submission Format for Reporting Other Unanticipated Problems Involving Risks to Human Subjects or Others**

**PAPER SUBMISSIONS:** Investigators shall submit all Unanticipated Problems Involving Risks to Human Subjects or Others (other than Adverse Events) that occur during the conduct of an IRB-approved research study utilizing the form entitled "Report of Unanticipated Problems Involving Risks to Subjects or Others," which is available on the IRB website.

**OSIRIS SUBMISSIONS:** For studies approved through the electronic submission system, the Unanticipated Problem online submission process must be utilized in order to submit a report. The smart form questions will prompt a response to issues related to the Unanticipated Problem.

Reports that might represent an Unanticipated Problem Involving Risks to Human Subjects or Others or might represent Serious Noncompliance or Continuing Non-Compliance, will be referred by the IRB Chair or Vice Chair to a convened University IRB committee.

## **3.4 Revised Sponsor Protocols or Investigational Drug Brochures**

Revised sponsor protocols or investigator brochures must be submitted to the IRB in a timely manner.

**PAPER SUBMISSIONS:** If the revised protocol or brochure requires that changes be made to the IRB approved protocol and/or consent document, a modification should be submitted as outlined in Section 3.1 above. If changes are not deemed necessary by the principal investigator, a memo indicating his/her review of the document as well as a statement that changes are not required should be attached to the packet of information. The IRB Adverse Event Coordinator will review all updated sponsor protocols and/or investigator brochures to ensure that the IRB concurs with the investigator's assessment.

**OSIRIS SUBMISSIONS:** In order to submit a revised sponsor protocol or investigator brochure for electronic submissions, investigators are required to submit a modification through the system. However,

if changes are not deemed to be necessary by the principal investigator, a memo indicating his/he review of the document as well as a statement that changes are not required should be uploaded into the system for consideration by the IRB. The IRB Adverse Event Coordinator will review all updated sponsor protocols and/or investigator brochures to ensure that the IRB concurs with the investigator's assessment.

## 3.5 Research Protocol Termination or Suspension

### 3.5.1 Definitions

IRB-Initiated suspension of approval: IRB-initiated suspension of approval refers to a determination made by the University IRB to temporarily withdraw University IRB approval for some or all activities of a currently approved research study.

IRB-Initiated termination of approval: IRB-initiated termination of approval refers to a determination made by the University IRB to permanently withdraw University IRB approval for some or all activities of a currently approved research study.

Investigator-Initiated suspension of approval: Investigator-initiated suspension of approval refers to a determination made by the principal investigator or sponsor of the research study to temporarily suspend some all activities of a currently approved research study.

Investigator-Initiated termination of approval: Investigator-initiated termination of approval refers to a determination made by the principal investigator or sponsor of the research study to permanently terminate some or all activities of a currently approved research study.

### 3.5.2 IRB-Initiated Termination or Suspension of a Research Protocol

The IRB has the authority to terminate or suspend its approval of a research protocol that is not being conducted in accordance with regulatory or IRB requirements or that is associated with serious harm to human research subjects. Such suspension or termination of approval shall be reported promptly to the investigator and shall include a written statement of the reasons for the IRB's action. Termination or suspension of IRB approval initiated by the IRB shall be reported to the Authorized Institutional Official and, if applicable, to the Office for Human Research Protections (for federally funded research), the FDA (for research subject to FDA oversight, the sponsor (e.g., industry sponsor or federal granting agency), and/or other relevant regulatory agencies.

If exceptional human subject safety issues are identified, the IRB Chair has the authority to suspend some or all of research activities. This authority is only exercised if an action is required prior to a convened meeting and it is not feasible to assemble an emergency meeting. When this authority is exercised, it shall be reported at the next convened University IRB meeting.

### 3.5.3 Investigator/Sponsor-Initiated Termination or Suspension of a Research Protocol - IRB Notification

- 1) Termination or suspension of an IRB-approved research protocol by the principal investigator and/or sponsor of the research study shall be reported promptly (i.e., within 1

working day of the receipt of the sponsor termination/ suspension notice) to the IRB Office if the termination/suspension is based on a change in the risk-to-benefit ratio of study participation (e.g., serious adverse events, non-effectiveness of the research intervention). Termination/ suspension of a research study for other (e.g., administrative) reasons shall be reported to the IRB Office within 10 working days of receipt of the termination/ suspension notice. IRB notification shall include reference to the current IRB approval number and a letter that addresses:

- the reason for study termination or suspension (e.g., subject accrual complete and data analyzed; demonstrated absence of benefit based on interim data analysis; serious adverse event).
  - the number of subjects currently enrolled in the study at the University or UPMC sites and the status (e.g., currently undergoing research intervention and monitoring; completed intervention-follow-up monitoring only; completed study) of each of these enrolled subjects.
  - a description of the procedures that will be used to notify subjects currently participating in the study of the study termination/ suspension; and the procedures that will be undertaken to ensure their orderly and safe withdrawal from the study and their follow-up care, if applicable.
  - a description of the procedures that will be used to notify subjects who previously participated in the study of the study termination/suspension, if felt to be important to their rights or welfare.
- 2) For terminated research protocols, a final progress report shall be submitted promptly to the IRB office. This progress report shall address, at a minimum:
- the final number of subjects enrolled in the study at the University or UPMC sites and at external multi-center sites, if applicable.
  - a summary of outcomes and conclusions; to include a statement of the extent to which the specific aims of the protocol were addressed and the impact of the study on the relevant scientific/medical issues under investigation (e.g., a description of new knowledge, findings, or information bearing on the risks or benefits to human research subjects).
- 3) For research protocols suspended due to serious adverse events, IRB approval is required to reinitiate the research study. The written request for study re-initiation shall address:
- the outcome of investigations on the causality of the serious adverse event(s).
  - the frequency of occurrence of the serious adverse event at the University or UPMC sites or external sites, if applicable.
  - modifications of the protocol and consent form to address the serious adverse event.

#### **3.5.4 Research Protocol Termination or Suspension - Human Research Subject Notification and Withdrawal**

Human subjects currently participating in a research study must be notified of its termination or suspension due to safety issues. It is strongly recommended that such notification be in the form of a consent form addendum (see Appendix H for an example) to document subject receipt and understanding of this information. Procedures for withdrawal of enrolled human research subjects should consider their rights and welfare. If follow-up of the subjects for safety or effectiveness reasons is permitted or required by the IRB (e.g., under a research protocol that is suspended or closed to enrollment), the subjects should be so informed (i.e., through the use of a consent form addendum) and any adverse events or other outcomes

identified during follow-up should be reported to the IRB, the research study sponsor, Authorized Institutional Official, OHRP, and the FDA, if applicable.

### **3.6 AlertLine**

AlertLine is a toll-free telephone line, 1-866-858-4456, that University of Pittsburgh employees can use to report certain irregular or troublesome workplace issues so that these issues can be investigated and resolved.

AlertLine is available to all full-time and part-time faculty, staff, and research associates at the Pittsburgh and regional campuses and other off-campus work locations. Callers can remain anonymous. The line answers 24 hours a day, seven days a week, and can be accessed from any telephone in North America, including pay telephones.

Issues that can be reported on the AlertLine include:

- Financial improprieties, including fraud, theft, falsification of records, and improper use of University assets.
- Human resource matters, including perceived harassment, discrimination, misconduct, and other workplace issues.
- Research compliance concerns, including conflict of interest, improper charging of grants, violation of human subject research regulations, and violation of other research compliance rules.
- Other legal/regulatory matters, such as those pertaining to environmental health and safety.