

**Policies and Procedures**  
Human Studies Committee  
Reporting Adverse Events and Unanticipated Problems

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**Purpose:**

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The purpose of this policy is to define the requirements for reporting adverse events (AE) and unanticipated problems (UAP) involving risks to subjects or others to the Human Studies Committee (HSC).

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**Scope:**

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All Principal Investigators (PIs) conducting clinical research that has been approved by the MEEI HSC are subject to the reporting requirements specified in this policy.

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**Definitions (AE):**

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**Adverse Event (AE):** Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), 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.

**AE Related to Research:** There is a reasonable possibility that the adverse event, incident, experience or outcome may have been caused by the research procedures, e.g. blood draw, interview, survey, etc.

**AE Unrelated to Research:** Adverse events related to circumstances independent of the research, e.g. relating to the underlying disease, disorder, or condition of the subject.

**Expected Adverse Event:** Any adverse event that does not meet the definition of unexpected adverse event.

**External Adverse Events (Safety Reports):** In the context of multi-center studies, adverse events experienced by research participants enrolled at study sites that are not under MEEI HSC's jurisdiction.

**Internal Adverse Events:** Adverse events experienced by research participants enrolled at study sites that are under MEEI HSC's jurisdiction. In the context of a single-center study, all adverse events would be considered internal adverse events.

**Non-Serious Adverse Event:** Any adverse event that does not meet the definition of a serious adverse event.

**Serious Adverse Event (SAE):** Any event temporally associated with the subject's participation in research that meets any of the following criteria:

- ✧ Results in death
- ✧ Is life threatening
- ✧ Requires hospitalization/prolongation of hospitalization
- ✧ Results in congenital anomaly
- ✧ Results in persistent or significant disability/incapacity
- ✧ Required intervention to prevent permanent impairment/damage

**Unexpected Adverse Event:** Any adverse 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 that are described in the protocol-related documents; or (2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

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## **Definitions (UAP):**

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**Data Loss:** The unauthorized acquisition, access, use, or disclosure of protected health information (PHI) or personally identifiable information (PII). The theft or loss of electronic devices or media, or paper that contain PHI or PII is considered data loss for purposes of this policy.

**Protected Health Information (PHI):** Past, present, or future information about the physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual **together with** any of the following identifiers:

- ✧ Names;
- ✧ All geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of the Census:
  - ✧ The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and
  - ✧ The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.

- ✧ All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older;
- ✧ Telephone numbers;
- ✧ Fax numbers;
- ✧ Electronic mail addresses;
- ✧ Social security numbers;
- ✧ Medical record numbers;
- ✧ Health plan beneficiary numbers;
- ✧ Account numbers;
- ✧ Certificate/license numbers;
- ✧ Vehicle identifiers and serial numbers, including license plate numbers;
- ✧ Device identifiers and serial numbers;
- ✧ Web Universal Resource Locators (URLs);
- ✧ Internet Protocol (IP) address numbers;
- ✧ Biometric identifiers, including finger and voice prints;
- ✧ Full face photographic images and any comparable images; and
- ✧ Any other unique identifying number, characteristic, or code.

**Personally Identifiable Information (PII):** A person's first name and last name or first initial and last name in combination with any one or more of the following data elements:

- ✧ Social Security number;
- ✧ Driver's license number or state-issued identification card number; or
- ✧ Financial account number, or credit or debit card number, with or without any required security code, access code, personal identification number or password, that would permit access to the person's financial account.

**Unanticipated Problems (UAP):** Any incident, experience, or outcome (including data loss, see above) that meets all of the following criteria:

- ✧ It is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as protocol and informed consent documents; and (b) the characteristics of the subject population being studied;
- ✧ It is related or possibly related to participation in the research (possibly 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
- ✧ It 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.

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# Investigator's Responsibilities:

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## 1. Reporting of Unexpected and Related/Possibly Related Events

### a. Serious Adverse Event (SAE)

Principal Investigators (PIs) must report to the HSC any serious adverse events that both (i) are unexpected and related/possibly related to research; and (ii) occur while the subject is enrolled in the study or that occur within 30 days of the conclusion of the subject's participation in the study, of which the PI becomes aware.

In order to determine whether a specific adverse event is unexpected, the PI must consider whether the event is consistent with the risks described in the protocol-related documents (e.g. protocol, consent form, Investigator's Brochure).

In order to determine whether a specific adverse event is related or possibly related to subject's participation in the research, the PI must consider the temporal relationship between the event and the investigational product being studied or study procedure. If an adverse event is at least partially caused by the procedures and /or investigational products, it is considered related/possibly related to research.

- ✧ *Any adverse events that are serious, unexpected and related or possibly related to the study must be reported to the HSC within 7 calendar days from the time the PI becomes aware of the event.*
- ✧ *Any unexpected and study-related death must be reported to HSC within 24 hours of the PI's knowledge of the event by e-mail or telephone.*

A completed AE report form must be submitted to HSC within 7 calendar days of initial HSC notification. If the PI becomes aware more than 30 days after the conclusion of a subject's participation of a serious adverse event that is both related to the research and unexpected, the PI must report the event to HSC at the time he/she becomes aware of it.

### b. Non-Serious Adverse Event

PIs must report to the HSC all non-serious adverse events that are unexpected and related or possibly related to the research *within 30 calendar days from the time the PI becomes aware of the event.*

## 2. Reporting of Expected and Related/Possibly Related Events

PIs must submit a summary report to the HSC for all serious and non-serious events that are expected and related/possibly related to the study *at the time of continuing review.*

### 3. Reporting of Unrelated Events

Do not report definitely unrelated events. The HSC will not review any serious or non-serious events that are, in the opinion of the PI following the procedures in this policy, definitely not study related.

### 4. Reporting of External Adverse Events

When investigators participate in a multi-center study, adverse events will occur at other sites. The investigator typically becomes aware of these external adverse events upon the receipt of a report from the Sponsor, Data and Safety Monitoring Board, Data Coordinating Center, or Project Director at another site. The PI must review such events and determine whether a change to the protocol is necessary. If deemed necessary, the PI must submit a revision request to the HSC outlining appropriate changes to the study. If, in the opinion of the PI, a change to the protocol is not necessary, external adverse event reports do not need to be submitted to the HSC.

### 5. Reporting of Unanticipated Problems

PIs must promptly report to the HSC Unanticipated Problems (UAPs) involving risks to subjects or others.

In order to determine whether a specific problem constitutes a UAP, the PI is advised to consider the following:

- ✧ the vast majority of adverse events occurring in human subjects do not represent UAP because most AEs are expected in the context of known toxicities or side effects of the research procedures and/or are due to the natural history of subjects' underlying diseases and conditions;
- ✧ a small proportion of AEs do represent UAPs; and
- ✧ UAPs may include events that are not adverse events.

All UAPs involving risks to subjects or others must be reported in writing to the HSC *within 7 calendar days* from the time the PI becomes aware of the event. If a UAP or an unexpected SAE results in a subject's death or was potentially life-threatening, the PI must notify HSC through e-mail or phone *within 24 hours* from the time the event is identified. A follow-up report must be submitted at a later date when more information is available. The PI must notify HSC through e-mail or phone *within 24 hours* from the time the event is identified for UAPs that take the form of a data loss.

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## Reporting Chart:

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Reporting Schedule	Not Serious (AE)		Serious (SAE)		Unanticipated Problems (UAP)
	Expected	Unexpected	Expected	Unexpected	7 Days (24 hours for death or data loss)
Possibly, Probably, or Definitely related	Continuing Review	30 Days	Continuing Review	7 Days	

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## HSC's Responsibilities:

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Upon receipt of a UAP report involving a data loss, the HSC Chairperson and/or designee will notify the Compliance and Privacy Officer, and if the data loss involves an electronic device or media, will also notify Support Center Operations within Information Services.

For all UAPs, the HSC Chairperson and/or designee will review the PI's report and determine whether the problem or event meets the definition of an unanticipated problem involving risks to subjects or others. The HSC Chairperson and/or designee alternate(s) will use the following criteria to make the determination:

- ✧ the problem or event was unforeseeable at the time of its occurrence, i.e., the likelihood and severity of the event is not consistent with the information provided to the HSC at the time of review and approval and/or the specificity and severity of the event is not consistent with the current approved consent document;
- ✧ the problem or event placed a subject or another person at increased risk of harm; and
- ✧ the problem or event is more likely than not to be related to the research.

When the HSC Chairperson determines that the problem or event does not meet all three of the above criteria, the PI is notified in writing and the report is filed with the protocol folder.

When the HSC Chairperson determines that the problem or event meets all of the criteria, the problem or event is considered a UAP involving risks to subjects or others, and is referred for review by the HSC at a convened meeting.

Primary and secondary reviewers are assigned and receive a copy of the report, a copy of the protocol and consent form, and when relevant, a copy of the Investigational Brochure, and any other information relevant to the problem or event. All other HSC members receive a copy of the report and a copy of the consent form.

By majority vote, the HSC will take one or more of the following actions:

- ✧ Accept the report and approve the proposed changes, if any, without any further action;
- ✧ Require additional information;
- ✧ Require modifications to the protocol and/or consent form;
- ✧ Require that subjects currently on protocol be notified of the event;
- ✧ Require that subjects whose participation has ended be notified of the event;
- ✧ Require that subjects currently on protocol be re-consented;
- ✧ Modify the continuing review schedule;
- ✧ Request a directed internal audit;
- ✧ Vote to suspend or terminate the research; or
- ✧ Other actions deemed appropriate by the HSC.

For federally supported research, when the HSC concurs with the determination that the problem or event meets the definition of an unanticipated problem involving risks to subjects or others, the HSC Chairperson and/or the Research Compliance Officer will prepare a report to the Office for Human Research Protections (OHRP). Copies of the report are sent to the following, as applicable:

- ✧ Principal Investigator
- ✧ PI's Department Chief
- ✧ Vice President, Research and Academic Affairs
- ✧ Director, Regulatory Compliance
- ✧ Office of General Counsel
- ✧ Compliance and Privacy Officer (for data losses)

In the event the HSC determines that the problem or event does not meet the criteria for a UAP involving risks to subjects or others, the above reporting is not required.

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## References:

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45 CFR 46.103(b)(5)  
45 CFR 46.113  
21 CFR 56.108(b)  
21 CFR 56.113  
45 CFR Parts 160 and 164  
201 CMR 17.00

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## Supporting Documents:

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- ✧ Adverse Event Report Form
- ✧ Unanticipated Problem Report Form