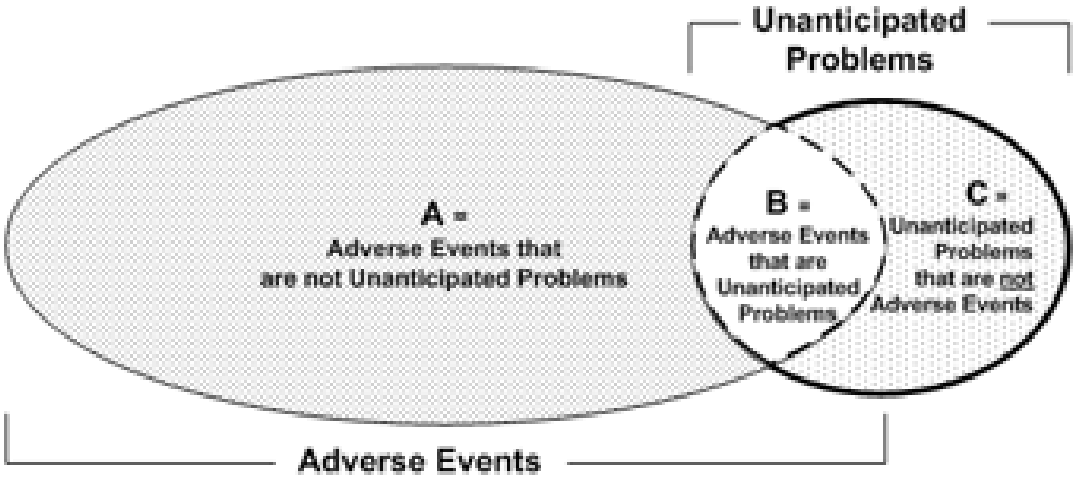
Title: Reporting to the Institutional Review Board (IRB) of Adverse Events and Unanticipated Problems Involving Risks to Study Participants or Others Policy Number: A-COM-0007 **Replaces (supersedes): none** CHA Cambridge Health Alliance	**Policy Chronicle:** Effective Date: 09/08/25 Date the Original Version of Policy was Effective: April 1, 2003 Most Recent Review (month/year): July/2025 **Owner: (Name/Title)** J. Glover Taylor Director, Sponsored Research Previous Review: January 2017 Previous Review: June 2023
Area of Operations: Research Institutional Review Board (IRB)	**Regulatory /Accreditation Standard(s)** JCAHO Dept. of Health & Human Services/IRB 45 CFR 46 21 CFR 56, 312, 812
Keyword(s): Adverse Reaction, Adverse Event, Event Reporting, IRB, Interventional, Unanticipated Problem	

Purpose: To define Cambridge Health Alliance guidelines, policies, and procedures, in accordance with Federal and Massachusetts law, regarding unanticipated problems involving risks to study participants or others and adverse events and their reporting to the IRB.

Personnel: All Cambridge Health Alliance Research Staff.

Definitions:



Under 45 CFR part 46: Do not report A, Do report (B+C)

Source: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html#Q2

1) Unanticipated Problem:

An Unanticipated Problem involving risks to study participants or others is any incident, experience, or outcome that meets ***all*** of the following criteria:

a. Unexpected (in terms of nature, severity, or frequency) given
   i. the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent form; and
   ii. the characteristics of the subject population being studied;

b. Related or possibly related* to participation in the research
   (*in this policy *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

c. 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.

Note: An unanticipated problem can be an adverse event, but is not necessarily an adverse event.

2) Adverse Event (AE):

An Adverse Event is any untoward or unfavorable physical or psychological occurrence in a study participant, including any abnormal sign (for example, abnormal physical

exam or laboratory finding), symptom, or disease, temporally associated with the volunteer's participation in the research, whether or not considered related to the volunteer's participation in the research.

a. Serious Adverse Events (SAEs) (21 CFR 312.32):
A Serious Adverse Event is any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:
   i. Results in death;
   ii. Is life threatening;
   iii. Results in inpatient hospitalization or prolongation of existing hospitalization;
   iv. Results in a persistent or significant disability/incapacity or permanent incapacity or substantial disruption of the ability to conduct normal life functions;
   v. Results in a congenital anomaly/birth defect; or
   vi. Based upon appropriate medical judgment may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

b. Unexpected Adverse Events:
An Unexpected Adverse Event is any adverse event (serious or otherwise) occurring in one or more participants in a study protocol, the nature, severity, or frequency of which is **not** consistent with either:

   i. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in

      1. the protocol-related documents, such as the **IRB-approved research** protocol, any applicable investigator brochure, and the current IRB-approved informed consent form, and
      2. other relevant sources of information, such as product labeling and package inserts;

      OR

   ii. The expected natural progression of any underlying disease, disorder, or condition of the participant(s) experiencing the adverse event and the participant's predisposing risk factor profile for the adverse event.

Note: Per FDA regulation (21 CFR 312.32), an unexpected adverse event also refers to adverse events or suspected adverse reactions that are

mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

c. External Adverse Events:

In the context of multicenter research, external adverse events are defined as those events experienced by participants enrolled by an investigator at an institution other than CHA that is engaged in the research

d. Internal Adverse Events:

In the context of multicenter clinical trials, internal adverse events are defined as those events experienced by participants enrolled by an investigator at CHA. If a study is only conducted at CHA all adverse events would be considered internal adverse events.

3) Unexpected Adverse Device Effect (21 CFR 812.3(s)):

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of the participants.

Policy:

It is the responsibility of the CHA Site Principal Investigator (PI) to track and document all adverse events and unanticipated problems. Certain types of adverse events and all unanticipated problems need to be reported to the Institutional Review Board (IRB) and, in some circumstances, Federal agencies, as determined by Federal regulation, including the Common Rule [45 CFR 46.108(a)(4)] and US Food and Drug Administration regulations [21 CFR 56.108(b)(1); 21 CFR 312.66].

Note:

- *This policy applies to all human subjects research taking place at CHA.*
- *This policy applies when the CHA IRB is the Reviewing IRB, or when another IRB serves as Reviewing IRB on behalf of CHA.*
- *CHA Site PIs are responsible for ensuring compliance with this policy regardless of whether CHA is serving as the Reviewing IRB, or CHA has agreed to rely upon another IRB (not operated by CHA). CHA Site PIs are also responsible for ensuring any Relying Site PIs comply with this policy.*
- *This policy also applies to Collaborating Independent or Institutional Investigators brought under CHA FWA by means of an Individual Investigator Agreement.*

Procedures:

All internal and external adverse events and unanticipated problems should be documented by the CHA Site PI.

The following types of events and problems need to be reported to the CHA IRB, following the procedures detailed below:

- Internal or external Unanticipated Problems
- Internal SAEs, whether expected or related or not
- Other types of events that do not meet criteria for Unanticipated Problems or SAEs, but require reporting, as detailed in the procedures below.

A. Reporting to the CHA IRB

To be reported to the IRB within 1 week of the investigator becoming aware of the event. (The CHA Site PI is responsible for completing an Incident Submission within Cayuse within this timeframe.):

1) Internal or External Unanticipated Problems that are also SAEs
   Any internal or external event that meets the definition of an SAE ***AND*** meets the definition of an Unanticipated Problem is to be reported to the CHA IRB within 1 week of discovery.

2) Internal SAEs that are not Unanticipated Problems
   Any internal event that meets the definition of a SAE is to be reported to the CHA IRB within 1 week of discovery.

3) Other types of events that do not meet criteria for Unanticipated Problems or SAEs, including:
   a. Breach of confidentiality.
   b. Suspension or early termination of the research study by the Sponsor or other agency.
   c. Incarceration of a research participant enrolled into the study.
   d. Medication error, regardless of whether participants experienced harm.
   e. New information (*e.g.,* interim analysis, safety monitoring report, publication, or other finding) that suggests that there are new or increased risks to participants or others
   f. A complaint by a research participant or others that suggests that rights, welfare, or safety of a participant has been adversely affected.

g. Any event or problem that is unanticipated (in terms of nature, severity, or frequency), related or possibly related, and suggests that there is an increased risk to subjects or others than was previously known.
h. Any other problem that suggests that the research places participants or others at an increased risk of harm or adversely affects the rights, welfare, or safety of participants or other.

Any of the above events are to be reported to the CHA IRB within 1 week of discovery.

To be reported to the IRB within 2 weeks of the investigator becoming aware of the event. (The CHA Site PI is responsible for completing an Incident Submission within Cayuse within this timeframe.):

4) Internal or external Unanticipated Problems that are *not* SAEs

Any internal or external event that meets the definition of an Unanticipated Problem but does not meet the definition of an SAE is to be reported to the CHA IRB within 2 weeks of discovery.

B. Submission to Sponsor or other applicable agency of an AE

The Principal Investigator is to submit reports of AEs in accordance with the requirements of the sponsor or funder.

C. Submission of reports to CHA Risk management

Submission of reports to the IRB does not fulfill the requirement of submission of incident reports to CHA Risk Management. Those reports are required and are to be reported per CHA incident reporting policy.

IRB Review Procedures:

1. The CHA IRB Administrator receives and screens Unanticipated Problem/Adverse Event form via Cayuse for completeness. If information is missing, the IRB Administrator will request the missing information from the Principal Investigator.

2. The IRB Administrator will forward the completed report form to the IRB Manager or Analyst, who will review and forward to the IRB Chair, Vice-Chair, or designee for review.

3. The IRB Chair/Vice-Chair/designee will determine whether the event meets the definition of an unanticipated problem involving risks to subjects or others.

4. If the event:

a. Does not meet the definition of an unanticipated problem involving risks to subjects or others, then the IRB Chair/Vice-Chair/designee may review the submission via expedited review procedures.

b. Does meet the definition of an unanticipated problem involving risks to subjects or others, it will be referred to the convened IRB for review and determination.

Note: If the IRB Chair/Vice-Chair/designee is unable to determine if the event is an unanticipated problem involving risks to subjects, it will be referred to the convened for review and determination.

5. The IRB Reviewer or convened IRB, as the case may be, will review the report and determine whether the event meets the definition of an unanticipated problem involving risks to others and further action needs to be taken.

Potential action may include:

- Modification to the protocol.
- Modification to the consent form or consent process.
- Past or current participant notification.
- More frequent continuing review.
- Monitoring of the research and/or the consent process.
- Placing the study on temporary hold to new enrollment and/or study procedures are discontinued.
- Suspension or involuntary termination of the study (see IRB Operations Manual for policies).

If the event is determined to be an unanticipated problem the IRB will facilitate reporting to the applicable agency within the required timeframe.

6. The Principal Investigator will be notified in writing of the review and whether any modifications or actions are required.

References:

- Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events: OHRP Guidance (2007) https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html#Q2
- Adverse Event Reporting to IRBs — Improving Human Subject Protection Guidance for Clinical Investigators, Sponsors, and IRBs (January 2009) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adverse-event-reporting-irbs-improving-human-subject-protection

Reviewed by:

Committee Name / Content Expert	Chair Person / Name	Date
Compliance	J Glover Taylor	

This policy has been reviewed and approved electronically by:

Approver	Title	Initials	Date
J. Glover Taylor	Sr. Director, Sponsored Research	JGT	9/2/2025
Sarah E Nelson	Chair, Institutional Review Board	SEN	9/8/2025
Assaad Sayah, MD	Chief Executive Officer	AJS	9/2/2025