1.0 Purpose:

1.1 Federal regulations for the protection of human subjects (45 CFR 46) require that organizations have written procedures to ensure prompt reporting to the Institutional Review Board (IRB), appropriate institutional officials, and appropriate federal officials concerning the occurrence of unanticipated problems/adverse events involving risks to subjects or others. Consistent with these regulations and IRB policies, this policy outlines the problems that investigators are required to report promptly to the IRB when unanticipated problems occur.

1.2 Some of the adverse events experienced by subjects enrolled in research studies will meet the criteria for unanticipated problems involving risks to subjects or others and so must be reported promptly. However, the vast majority of adverse events, both serious and non-serious, occurring in the context of research are **expected** in light of the known toxicities and side effects of the research procedures or are expected due to the natural history of subjects' underlying diseases and conditions. Thus, most individual adverse events do not represent unanticipated problems subject to the reporting requirements outlined in the federal regulations at 45 CFR 46.108(a)(4)(i) and 21 CFR 56.108(b)(1).

1.3 This policy will also differentiate between what needs to be reported promptly, at the time of continuing review, and what does not need to be reported at all, as well as define the timeline for reporting.

2.0 Definitions:

2.1 **Adverse Event**: 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, associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

2.2 **Serious adverse event**: Any event associated with the subject's participation in research that meets any of the following criteria:

2.2.1 Results in death;

2.2.2 Is life-threatening (places the subject at immediate risk of death from the event as it occurred);

2.2.3 Requires inpatient hospitalization or prolongation of existing hospitalization;

2.2.4 Results in a persistent or significant disability/incapacity;

2.2.5 Results in a congenital anomaly/birth defect;

2.2.6 An important medical event, 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; or

2.2.7 Results in a severely debilitating situation for the subject, such as psychological distress, financial hardship or damaging impact on social standing or employability.

2.3 **Non-serious Adverse Event:** Any undesirable symptom or occurrence a subject experiences during participation in a clinical trial which does not meet the "Serious" criteria above.

2.4 **Unexpected Adverse Event**: Any adverse event, occurring in one or more subjects in a research protocol, the nature, severity or frequency of which is not consistent with either:

2.4.1 The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol and the current IRB-approved informed consent form (ICF) and (b) other relevant sources of information, such as any applicable investigator brochure, product labeling and package inserts; or

2.4.2 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.*

2.5 **Anticipated problem/adverse event**: any foreseen or expected incident/experience that is described in the protocol-related documents, such as the IRB-approved research protocol and ICF.

2.6 **Possibly related to the research:** There is a reasonable possibility that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research.

2.7 **External Adverse Event:** Adverse events experienced by subjects enrolled by investigator(s) at other institutions engaged in the research study. Examples: Medwatch or safety reports.

2.8 **Internal Adverse Event:** Adverse events experienced by subjects enrolled by the investigator(s) at that institution. In the context of a single-center clinical trial, all adverse events would be considered internal events.

2.9 **Unanticipated Problem:** any unforeseen or unexpected incident or experience (including an unexpected adverse event) that is not described in the protocol-related documents, such as the approved research protocol and ICF.

2.10 **Unanticipated Problems <u>involving Risks to subjects or others</u>**: any incident, experience, or outcome that meets **ALL** of the following criteria:

2.10.1 **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 ICF; and (b) the characteristics of the subject population being studied;

2.10.2 **Related or possibly related** to the procedures involved in the research; and

2.10.3 **Suggests that the research places subjects or others at a greater risk of harm** (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

2.11 **Prompt Reporting:** Within 7 calendar days

3.0 Procedure:

3.1 **What** Needs to be Reported to the IRB**:**

3.1.1 An event that is:

3.1.1.1 Unexpected; **AND**

3.1.1.2 Related or possibly related to the research as determined by the investigator; **AND**

3.1.1.3 Involves increased or greater risk of harm to subjects or others than was previously known or approved by the IRB.

3.1.2 Internal adverse events that are unexpected, involve new or increased risks, and are related to the research.

3.1.3 External adverse events that are unanticipated problems involving risks to subjects or others.

3.1.4 Information that indicates a change to the risks or potential benefits of the research. For example:

3.1.4.1 An interim analysis or safety monitoring report, such as a Data Safety Monitoring Board (DSMB) report that indicates that the frequency or magnitude of harms or benefits may be different than initially presented to the IRB.

3.1.4.2 A paper is published from another study that shows that the risks or potential benefits of the research may be different than initially presented to the IRB.

3.1.5 Breach of confidentiality.

3.1.6 An event (other than noted in 3.1.1 above) that requires prompt reporting according to the protocol or the sponsor.

3.1.7 Suspensions for any reasons other than planned suspensions for interim analyses, including sponsor-imposed suspension for risk.

3.1.8 Accidental or unintentional deviations to the IRB-approved protocol that involved risks or have the potential to recur;

3.1.9 Emergency protocol deviations, or other changes made to the research, taken without prior IRB review to eliminate apparent immediate hazard to research subjects;

3.1.10 New information that might affect adversely the safety of the subjects or the conduct of the clinical trial.

3.1.11 Any changes significantly affecting the conduct of the clinical trial or increasing the risk to subjects.

3.1.12 Other unanticipated information that is related to the research and when subjects or others might be at increased risk of harm; and

3.1.13 Complaints of subjects that indicate unanticipated risk or which cannot be resolved by the investigator and their staff.

3.2 **When** should any type of event be reported to the IRB (Please see table at the end of this section for a complete timetable for reporting events):

Note: See Appendix D of the OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events for examples of Adverse Events that Represent Unanticipated Problems that Need to be Reported under the HHS regulations at 45 CFR 46.

3.2.1 Prompt Reporting for Internal Events:

3.2.1.1 All internal problems or adverse events that are **serious** or **life threatening**, AND **unexpected** AND **related** to the study procedures must be reported to the IRB within 7 calendar days of the investigator's receipt of the information by completing the on-line *Unanticipated Problem/Event Reporting Form*

3.2.1.2 If a problem or adverse event does not fall under the prompt reporting requirements, but in the PI's judgment, prompt reporting of the event(s) is in the best interest of the subject(s) because it may affect the safety and/or welfare of subjects and/or change the risk level of the study, the PI may submit the *Unanticipated Problem/Event Reporting Form*.

Please Note: If the events fit the criteria in 3.2.1.1 and changes to the protocol-related documents are required, then the report must be submitted to the IRB as noted above with the investigator's evaluation summary and the request for modification(s) to the original protocol documents.

3.2.2 Prompt Reporting for External Events:

3.2.2.1 Any event that requires prompt reporting according to the protocol or the sponsor

3.2.3 Continuing Review Reporting for Internal Events:

3.2.3.1 All internal adverse events that have occurred within the last approval period should be assessed, tracked, and submitted as a summary at the time of continuing review, EXCEPT those that are **not serious** (Unexpected, Related, but not serious adverse events should be submitted at the time of continuation, however).

3.2.3.2 Internal adverse events that are **unexpected, unrelated**, and non-serious do not need to be reported to the IRB. The *Event*

Accumulative Tracking Log (available on-line) or similar document may be used to track these events.

3.2.3.2.1 Be aware that some events may also be reportable to Patient Safety/Risk Management through the "Quantros Event Reporter", available on all hospital desktops or the intranet. Refer to Hartford Hospital's policy for "Reportable Events." (For example, a study participant falls on hospital property while taking part in a research study.)

Please Note: If the events do not fit the criteria in 3.2.1.1 and modifications to protocol related documents are not necessary, these reports may be submitted at the time of continuing review with a summary prepared by the PI

3.2.4 Continuing Review Reporting for External Events

3.2.4.1 External problems (adverse events) reported by a sponsor involving multi-center trials (i.e., Medwatch Reports) should be evaluated by the PI to determine the significance of the adverse events reported. Events that are **external, serious**, AND **expected** do not need to be reported until the time of continuing review. Events that are **external, serious**, **unexpected,** AND **related** do not need to be reported until the time of continuing review.

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3.2.5 Reporting Requirements for Deaths:

3.2.5.1 Any internal event that involves **unexpected** or **expected death** that occurs with a subject on a study that is **related** to the study procedures must be reported **within 7 calendar** days of the investigators receipt of the information using the *Unanticipated Problem/Event Reporting Form*.

3.2.5.2 Deaths that are **expected** and **unrelated** to the research (i.e., due to underlying disease progression) must be included in the summary of problems/adverse events submitted to the IRB at the time of continuing review.

Please Note: All problems noted above must be reported to the IRB regardless of whether they occur during the study or after subject withdrawal or completion.

3.2.6 Problems and Events that **DO NOT** require reporting:

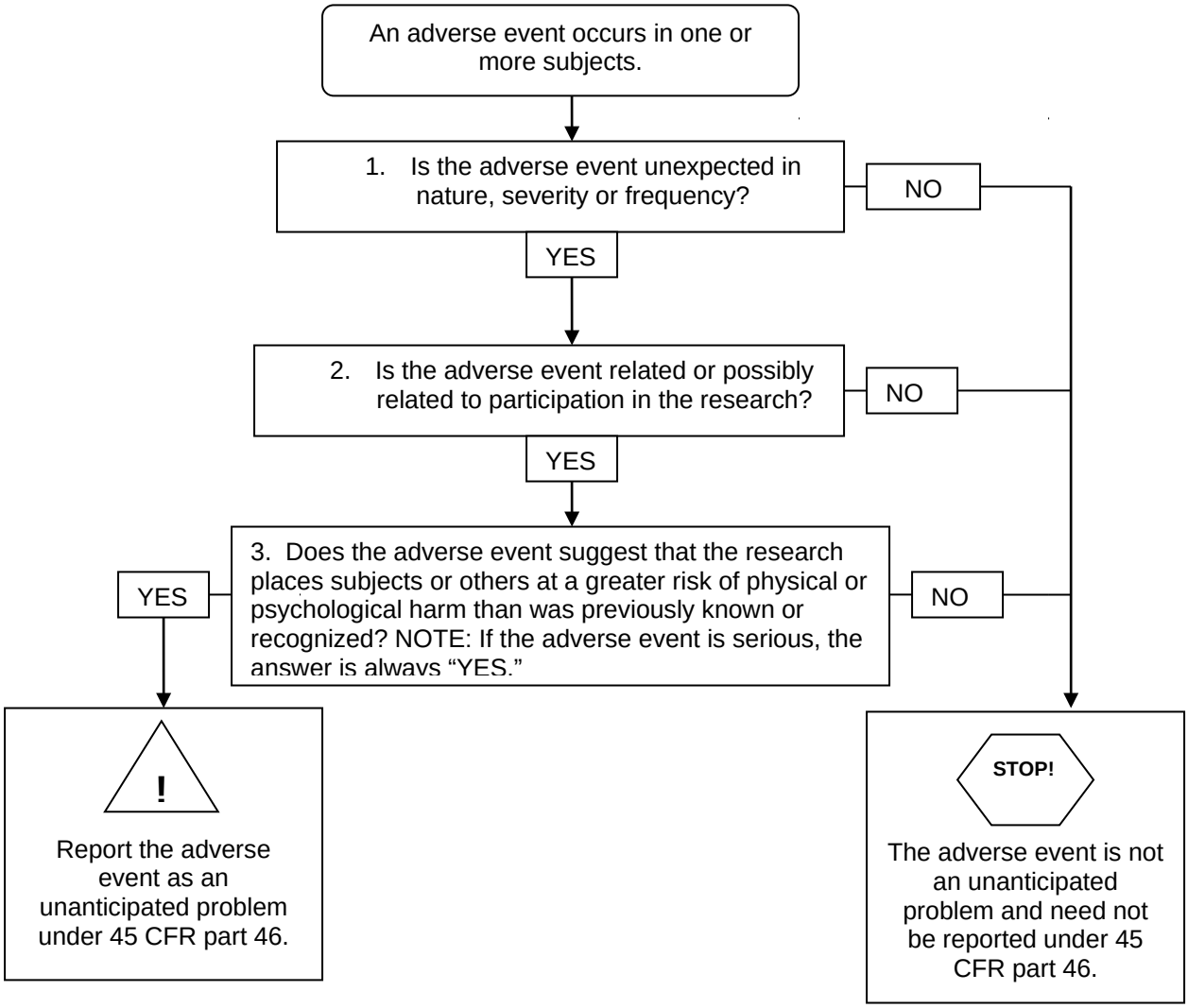
3.2.6.1 External adverse events that are **unexpected** and **unrelated** OR those that are **expected** do not need to be reported to the IRB. These reports are reviewed and dated by the PI and filed with the research regulatory documents. This record is to be made available to the IRB upon request *Event Accumulative Tracking Log* (located in the on-line submissions system), listing the event codes for external adverse events that do not meet the IRB's reporting requirements, may be submitted to the IRB if required by the sponsor.

Reporting Time Frames for all Adverse Events:

Internal	Expected	Related	Serious	Continuing Review
			Not serious	None
		Unrelated	Serious	Continuing Review
			Not serious	None
	Unexpected	Related	Serious	Prompt
			Not serious	Continuing Review
		Unrelated	Serious	Continuing Review
			Not serious	None
External	Expected	Related	Serious	Continuing Review
			Not serious	None
		Unrelated	Serious	Continuing Review
			Not serious	None
	Unexpected	Related	Serious	Continuing Review
			Not serious	None
		Unrelated	Serious	None
			Not serious	None

Note: For examples of adverse events that do not represent unanticipated problems and do not need to be reported under the HHS regulations at 45 CFR 46, refer to Appendix C of the OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events.

Algorithm for Determining Whether an Adverse Event is an Unanticipated Problem



3.3 **What** must be included in the reporting of Unanticipated Problems and Adverse Events:

3.3.1 The title of the research, name of the principal investigator, IRB project/account number, name of the sponsor and a description of the event;

3.3.2 Any associated materials.

3.3.2.1 For internal adverse events, the associated materials should include the following applicable materials: (1) reports sent to a sponsor about the event; (2) admission/discharge summaries; (3) relevant laboratory data; concomitant medications; and/or (4) medical record notations.

3.3.2.2 For external adverse events, the associated materials should include the sponsor's safety report form.

3.4 **IRB Process for Review and Handling Reported Problems**

3.4.1 All reports are submitted to the IRB.

3.4.2 Reports are evaluated by an IRB staff member for completeness.

3.4.2.1 If the report is incomplete, it is returned to the investigator with a request for the additional information.

3.4.2.2 The investigator's assessment of external events must be provided or the report is considered to be incomplete and is returned to the investigator.

3.4.3 Complete reports are reviewed by the Human Research Protection Program (HRPP) Director, IRB Chair, or designated IRB member with appropriate expertise for initial review (IRB reviewer). The IRB reviewer is provided with the protocol file containing the IRB-approved protocol and consent form.

3.4.4 The IRB reviewer is responsible for determining whether the reported problem represents an unanticipated problem involving risks to subjects or others as defined above. The investigator's assessment of the event is reviewed and considered in this determination.

3.4.5 If in the judgment of the IRB reviewer the problem is not an unanticipated problem involving risks to subjects or others, the report is documented as such, signed by the reviewer and filed in the IRB study file.

3.4.6 If the IRB reviewer is unable to determine if the event represents an unanticipated problem involving risks to subjects or others, the report is referred for review by the IRB at a convened meeting as described below for serious unanticipated problems.

3.4.7 If the IRB reviewer determines that the event is an unanticipated problem involving risks to subjects or others, the IRB reviewer is responsible for determining and documenting on the review form whether the event involves more than minimal risk or not.

3.4.7.1 Expedited Process for Reviewing Unanticipated Problems and Adverse Events

3.4.7.1.1 Unanticipated problem reports that are not serious are reviewed by the IRB reviewer. The IRB reviewer may take one or more of the following actions:

- Accept the report and approve the proposed changes, if any, with no further action required;
- 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; or
- Any other actions deemed appropriate by the IRB reviewer.

3.4.7.1.2 For a report of an accidental or unintentional deviation to the IRB-approved protocol that involved risks or has the potential to recur, the IRB reviewer also considers if the event represents serious or continuing non-compliance according to the procedure on “Handling of Non-Compliance”.

3.4.7.1.3 For a report of an emergency protocol deviation taken without prior IRB review, the IRB reviewer considers if the changes were consistent with the rights and welfare of subjects.

3.4.7.1.4 The IRB reviewer is responsible for documenting findings and actions.

3.4.7.1.5 The HRPP director is responsible for communicating findings and actions to the Principal Investigator.

3.4.7.2 Unanticipated problems that involve more than minimal risk are referred for review by the IRB at a convened meeting.

3.4.7.2.1 If, in the judgment of the IRB reviewer, subjects may be at immediate risk of harm and there is insufficient time to wait for review by the convened IRB, the IRB Chair or HRPP Director is consulted. If the Chair or Director determines that subjects are at immediate risk of harm, the principal investigator will be required to suspend the study according to IRB policy for suspension or termination of research.

3.4.7.2.2 For reports that are sent to the convened IRB for review, the report is added to an IRB meeting agenda and is assigned to a primary reviewer by the IRB staff on the basis of the scientific expertise of the review.

3.4.7.2.3 The primary reviewer and all other board members receive the following information:

- The problem report form;
- All supplemental materials attached to the report;
- All tracking logs, if applicable;

- The sponsor adverse event report form, if applicable
- The DSMB or safety report, if applicable;
- A summary of the study;
- Current, IRB-approved informed consent document(s) and revised informed consent document(s); and
- Any other relevant materials.

3.4.7.2.4 The primary reviewer is responsible for an in-depth review of the report of the event and materials provided and completion of the reviewer form for problem reports. All other members are responsible for review of the report of the event and the consent form(s) in sufficient depth to vote at the meeting.

3.4.7.2.5 By majority vote of a quorum of the membership present at the convened meeting, the IRB determines if the reported problem represents an unanticipated problem involving risks to subjects or others as defined above and may take one or more of the following actions:

- Accept the report and approve the proposed changes, if any, with no further action required;
- Require additional information;
- Require modification to the protocol and/or informed consent document(s) for future subjects;
- Require notification of current or past subjects by phone, letter or addendum to the informed consent document;
- Modify the continuing review schedule;
- Require monitoring of the research or consent process;
- Request a directed post-approval on-site review by a Compliance officer/post approval monitor.
- Suspend or terminate the research according to IRB policy on “Suspension or Termination of IRB Approved Research”;
- Referral to legal counsel, risk management or the institutional official; and/or
- Other appropriate action as determined by the IRB.

3.4.7.2.6 For a report of an accidental or unintentional deviation to the IRB-approved protocol that involved risks or has the potential to recur, the IRB also considers if the event represents serious or continuing non-compliance according to the procedure on “Handling of Non Compliance”.

3.4.7.2.7 For a report of an emergency protocol deviation taken without prior IRB review, the IRB considers if the changes were consistent with the rights and welfare of subjects and determine if any additional follow-up action is warranted.

3.4.7.2.8 The HRPP staff are responsible for recording the findings and actions of the IRB and, when relevant, the discussion of controverted issues and their resolution in the minutes of the meeting.

3.4.7.2.9 The HRPP Director is responsible for notifying the principal investigator in writing of the findings and actions of the IRB.

3.4.8 The IRB submits a report of the events determined to be unanticipated problems involving risk to subjects or others to appropriate institutional officials and entities accordingly.

3.4.9 Investigators may appeal the IRB determinations regarding the report of an unanticipated problem involving risks to subjects or others. In order to appeal an IRB decision, the investigator must submit his/her rationale or that of the sponsor and any supporting information. An appeal must be reviewed by the IRB Panel that made the original decision.

3.5 **IRB Process for Handling Reports that Do Not Require Prompt Reporting**

3.5.1 Internal events submitted on the *Event Accumulative Tracking Log* at the time of continuing review are reviewed according to the IRB SOP’s for Continuing Review.

3.5.2 Accidental or unintentional deviations to the IRB-approved protocol that do not involve risks are reviewed by a designated IRB reviewer. The investigator’s plan to prevent future occurrences is considered during the review.

3.5.2.1 If the report is incomplete, it is returned to the investigator with a request for the additional information.

3.5.2.2 If the IRB reviewer determines that the deviation involved risks or has the potential to recur, the deviation report is reviewed according to Section 3.2.of this policy.

3.5.2.3 Otherwise, the IRB reviewer stamps the form acknowledging receipt by the IRB office, signs, dates the form and returns a copy of the form to the investigator.

3.5.3 External events submitted to the IRB reviewed by designated IRB reviewer.

3.5.3.1 If the report is incomplete, it is returned to the investigator with a request for the additional Information.

3.5.3.2 If the investigator indicates that any event meets the definition of a reportable problem, the IRB reviewer contacts the investigator to request that the investigator complete the *Unanticipated Problem Report Form* as required in Section 4.1.of this policy.

3.5.3.3 Otherwise, the IRB reviewer stamps the form acknowledging receipt by the IRB office, signs, dates the form and returns a copy of the form to the investigator

4.0 Documentation:

4.1 Research Administration will maintain all records related to the implementation of this policy, electronic communications, and notifications to investigators, funding or regulatory agencies, etc.

4.2 Records will be archived for a period of at least three years following the termination or completion of the research activities.

5.0 References:

5.1 45 CFR 46.103(b)(5) – *Assuring compliance with this policy-research conducted or supported by any Federal Department or Agency*

5.2 45 CFR 46.116(b)(5) – *General requirements for informed consent*

5.3 21 CFR 50.25(b)(5) – *Elements of Informed Consent*

5.4 21 CFR 56.108(b)(1) – *IRB functions and operations*

5.5 21 CFR 312.32(a) – *Investigational New Drug (IND) Safety Reports - Definitions*

5.6 21 CFR 812.150(a)(1) – *Investigational Device Exemptions – Reports*

5.7 Reporting Incidents to OHRP: Guidance on When and How to File Incident Reports (June 20,2011)

5.8 OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (January 15, 2007)

5.9 FDA Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs – Improving Human Subject Protection (January 2009)

5.10 Hartford Hospital Policy Manual – *Policy for Reportable Events*

6.0 Revision History:

Rev #	Initials	Effective Date	Description of Change(s)
01	SAB/CLG	7/1/11	Conversion to new policy template; significant expansion of policy
02	CLB	7/22/15	Addition of several items in Section 3.1 regarding “what” needs to be reported to the IRB
03	CLB	3/15/20	General review and clarifications.

Element II.2.G. and III.2.D