1.0 Purpose:

1.1 The Hartford HealthCare Human Research Protection Program (HHC HRPP) recognizes that deviations to approved protocols may occur.

1.2 Investigators are responsible for conducting human subjects research in accordance with all applicable federal and state regulations, HHC HRPP policies and procedures, and the specific requirements of the Institutional Review Board (IRB) that reviewed the research study. During the conduct of the study, changes to the protocol may be proposed or unintentional changes may be discovered. Changes to the IRB-approved protocol, planned or otherwise, are governed by federal regulations and HRPP policies and procedures.

1.3 The federal regulations specifically require the IRB to review proposed changes in a **research activity**, and to ensure that such changes in approved research are not initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject [45CFR46.108(a)(3)(iii) and 21CFR56.108(a)(4)]. **Research activity** includes all aspects of the conduct of the research study, e.g., recruitment methods, consent process, procedures used to protect privacy and confidentiality, etc. In other words, all of the information outlined in the protocol submission and reviewed and approved by the IRB.

1.4 Non-compliance with these regulations, HRPP policies and procedures, or IRB requirements during the conduct of a research study results in a protocol deviation/violation, and as such must be reported to the IRB.

1.5 Planned changes to the IRB-approved protocol must be submitted as formal protocol **amendments** or **protocol exceptions** to the IRB and be approved prior to initiation or implementation of the change.

1.6 The purpose of this policy, therefore, is to describe how these departures from the approved research are to be reported by the investigator and processed by the HHC HRPP.

2.0 Definitions:

2.1 **OHRP** – Office for Human Research Protections

2.2 **Non-compliance -** Any action or activity associated with the conduct or oversight of research involving human subjects that fails to comply with either the research plan as approved by the IRB, federal regulations, or institutional policies governing such research.

2.3 **Serious non-compliance** - Any behavior, action or omission in the conduct or oversight of human research that has been determined to:

2.3.1 Affect the rights and welfare of participants and others;

2.3.2 Increase risks to participants and others, decreases potential benefits or otherwise unfavorably alters the risk/benefit ratio;

2.3.3 Compromise the integrity or validity of the research; or

2.3.4 Result from the willful or knowing misconduct on the part of the investigator(s) or study staff.

2.4 **Protocol Deviation -** Any inadvertent change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IRB.

The deviation has no substantive effect on the risks or benefits to the individual research subject, the value of the data collected and did not result from willful or knowing misconduct on the part of the investigator(s) or study staff.

2.5 **Protocol Exception:** A one time, intentional action or process that departs from the IRB-approved study protocol, intended for one occurrence or applied to a single individual. This action is approved by the sponsor or funding agency, IRB, and the FDA, if applicable, prior to its implementation. An example of an exception may include: the potential enrollment, following approval of the sponsor, of a participant who fails to meet all of the protocol eligibility criteria.

2.6 **Protocol Violation:** Any intentional protocol deviation that may affect the subject's rights, safety, or well being and/or the completeness, accuracy and reliability of the study data.

The following are examples of protocol violations:

- Failure to obtain informed consent, i.e., there is no documentation of informed consent(s) or informed consent obtained after initiation of study.
- Informed consent for IND/IDE studies obtained by someone other than individuals authorized by IRB to obtain consent, e.g. someone other than a licensed physician investigator.
- PI prescribing or administering the wrong drug on the study
- Performing study procedure not approved by the IRB.
- PI failure to report a serious adverse event to the IRB and/or sponsor.

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

2.8 **Unanticipated problems involving risks to subjects or others**: any incident, experience, or outcome that meets <u>all</u> of the following criteria:

2.8.1 **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 informed consent document; and (b the characteristics of the subject population being studied;

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

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

3.0 Procedure:

3.1 The HHC HRPP considers **protocol deviations** to be instances of non-compliance with the approved protocol and processes them as such.

3.1.1 A minor deviation (typically considered non-compliance that is neither serious nor continuing) does not expose research subjects to increased risks or fewer benefits or affect the study integrity

3.1.2 Minor protocol deviations must be tracked and reported in summary at the time of continuing review by the Principal Investigator (PI).

3.1.2.1 In reviewing the summary of deviations with the progress report, the IRB will look for patterns and frequency of incidence to identify whether continuing non-compliance is taking place and implement corrective action plans as necessary.

3.1.3 If the research sponsor requires reporting of protocol deviations to the IRB, these must be must be reported to the IRB within 30 calendar days of discovery using the *Protocol Deviation Report* form available on the HHC Research website.

3.1.3.1 The investigator must include corrective actions that have been put into place to prevent any future occurrences of the deviation.

3.1.3.2 The HRPP Director reviews the Protocol Deviation Report and have the authority to acknowledge the submission. If he or she feels the deviation has the potential to impact subject safety or welfare, it may be referred to the IRB Chair or convened IRB.

3.2 **Protocol violations**, because they potentially expose subjects to increased risk, fewer benefits, or compromise the study integrity, are likely to be considered serious non-compliance and thus must be reported to the IRB within seven (7) calendar days of discovery, and reported to the sponsor as outlined in the sponsor's protocol.

3.2.1 Protocol violations should be reported to the IRB by submission of the "*IRB Unanticipated Problem/Event Report Form*".

3.2.2 Within three (3) days of receipt, the HRPP Director or designee will complete an initial of the report review utilizing the following criteria:

3.2.2.1 If the reported deviation/violation has no substantive effect on the risks or benefits to the individual research subject, the value of the data collected and did not result from willful or knowing misconduct on the part of the investigator(s) or study staff, the investigator may be instructed to report the deviation in the annual "Request for Continuation (Progress Report)".

3.2.2.2 If the reported deviation/violation involves a drug, device or biologic or other interventional activity, the HRPP Director may assign it to the IRB Chair or designee with the appropriate clinical experience, as appropriate. For the purposes of this document, "interventional activity" means any activity described in the protocol that directly involves the administration of a

drug/device/biologic or that comprises a clinical or research procedure administered to the research subject.

3.2.2.3 If the reported deviation/violation involves the consent process or other non-interventional activity, the HRPP Director or designee can either complete the review and define the corrective actions necessary, or assign it to the IRB Chair or designee.

3.2.2.4 Deviations/violations that meet the qualifications for expedited review as defined by 45 CFR 46.110(b)(2) can be reviewed and finalized by the HRPP Director or designee.

3.2.2.5 All other deviations/violations will be assigned to the IRB Chair or designee for review and presentation at a convened IRB meeting.

3.2.2.6 If the reported deviation/violation rises to the level of an Unanticipated Problem, it will be reviewed in accordance with *HRPP Policy #910 – "Unanticipated Problems/Adverse Events Reporting"*.

3.2.2.7 If the reported deviation/violation involves a failure to follow federal regulations, institutional policies governing human subject research, or requirements or determinations of the IRB, then *HRPP Policy #925 - "Handling of Non-Compliance"* will be followed.

3.3 The assigned reviewer will complete the review and define corrective actions, if any, within five business days of receipt. If a reply is required, the assigned reviewer will attach his/her comments for the PI.

3.4 The PI may be instructed to provide additional information or documents via email or respond to the corrective actions defined by the reviewer.

3.5 If no reply is required from the PI, the assigned reviewer will sign off on the review process.

3.6 If the principal investigator fails to agree to any part of the corrective action plan, this will be considered serious non-compliance and be referred to a convened IRB for review and action as denoted in *HRPP Policy #925 - "Handling of Non-Compliance".*

4.0 Documentation:

4.1 The HHC HRPP office 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 six (6) years following the termination or completion of the research activities.

5.0 References:

5.1 45 CFR 46.108(a)(4)(i), 45 CFR 46.116(c)(5)

5.2 21 CFR 50.25(b)(5), 21 CFR 56.108(b)(2), 21 CFR 56.113

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

5.4 21 CFR 812.150 (a)(1)– *Investigational Device Exemptions - Reports*

6.0 Revision History:

Rev #	Initials	Effective Date	Description of Change(s)
01	EHP	7/1/11	Conversion to new policy template; significant expansion of policy
02	CLB	3/15/20	General review; update regulatory citations

Element I.5.D. and III.2.D.