1.0 Purpose:

1.1 Hartford HealthCare Human Research Protection Program (HHC HRPP) policies and procedures describe the review of research at convened meetings of the Institutional Review Board (IRB) and by the expedited review procedure, including initial review, continuing review, and review of modifications to previously approved research.

1.1.1. Policies and procedures describe the information provided to primary reviewers and all other IRB members (when applicable) for expedited or full review.

1.2 These policies should allow the IRB to carry out its functions effectively and consistently according to applicable laws, regulations, codes, and guidance and institutional policies and procedures.

1.3 These policies will be the guidelines followed for all IRB business, regardless of study funding source.

2.0 Definitions:

2.1 **Experienced member**: A scientific member who has been on the board for at least one year, and has attended a minimum of 9 meetings. This member must have no known or suspected conflicts with the research activity to be reviewed.

2.2 **Key personnel**: All study personnel serving in any capacity other than an advisory role.

2.3 **Minor modification**: A change initiated by the investigator that involves no more than minimal risk to subjects, falls within the criteria for expedited review, or does not substantially change the specific aims or design of the study; or a change requested by the IRB to secure approval, that requires only concurrence and formal revision by the investigator.

2.4 **Major modification**: Any change that does not meet the definition of a minor modification; for example, a change initiated by the investigator, that may present more than minimal risk to subjects or substantially changes the specific aims or design of the study; or a change requested by the IRB to secure approval, that would require composition by the investigator.

2.5 **Minimal risk**: Risk in which the probability and magnitude of harm or discomfort anticipated are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

3.0 References:

3.1 45 CFR 46.108(a)(3)

3.2 45 CFR 46.109

3.3 45 CFR 46.110

3.4 45 CFR 46.116(c)(5)

3.5 21 CFR 50.25(b)(5)

3.6 21 CFR 56.108(a)

3.7 21 CFR 56.109

3.8 21 CFR 56.110

3.9 ICH-GCP 3.2.2, 3.2.3, 3.3.3, 3.3.4, 3.3.5

4.0 Procedures:

4.1 Submission

4.1.1. Initial Review

4.1.1.1. Applications for new research proposals are submitted electronically. They should include the Research Application form, protocol, budget, consent(s)/waiver(s), HIPAA authorization, and, as applicable, any ads and patient materials, Investigator Brochure/package insert, external grant application, and contract.

4.1.2. Continuing Review/Termination

4.1.2.1. Reports submitted for projects requesting continuation should include a copy of the report form, including a summary of activity within the report period, as well as a summary of adverse events, copies of the signature pages of consents of participants enrolled during the period, and any abstracts or publications that have resulted from the study. Reports generated from multicenter trials (e.g. from a DSMB) also should be evaluated.

4.1.2.2. Reports for projects to be terminated should include a final report and copies of any abstracts or publications (if available) that have not been submitted previously. Projects should not be terminated until all activities involving human subjects, including use of identifiable specimens or data, are completed, with no possibility of needing further access to these materials. Terminations are reported to the IRB via the agenda.

4.1.3. Proposed modifications to previously approved research

4.1.3.1. Modifications initiated by the investigator or sponsor and any new items not previously submitted should be submitted using the “Request for Modification/Amendment” form. Revised items should be provided in a format that clearly indicates what has been revised, with a copy of the item marked with the changes and/or a summary of specific changes. A revised protocol and any other items requiring revision as a result of the modifications should be included,

as well as any correspondence explaining the reasons for the changes.

4.2 **Pre-review Process**

4.2.1 All submissions are reviewed by HRPP staff, who make the initial determination of type of review required, and completeness and appropriateness of the submitted items. If anything is missing or is found to require revision in order to be ready for IRB review, HRPP staff will contact the research staff to request the needed materials.

4.2.2. Simultaneously for initial submissions, one of the Research Institute Senior Scientists will review the protocol when necessary for scientific merit, and may contact the investigator for revisions/clarifications. When feasible, these reviews will be coordinated. Revisions and clarifications will be incorporated into the submission for review by the IRB.

4.2.3. Grants & Contracts staff review the budget and contract when applicable. If internal funding is requested, the study will be scheduled for review by the Scientific Review Committee (SRC). Those projects that are not funded by the SRC generally will not be reviewed by the IRB until funding is secured. Once a decision to fund is made, this will be communicated to the investigator and HRPP staff, and IRB review will proceed.

4.2.4. If the project is being funded by external funds, IRB review may be simultaneous with the Grants review, but final approval will not be granted until all requirements of both are met.

4.2.5. If the initial application indicates that radiation is involved, whether it is standard-of-care or being used solely for the research, the application automatically will be routed to the Radiation Safety Office for determination of the need for Radiation Safety Committee review. This review may occur at any time during the IRB review process; however, approval by the IRB prior to a decision by this committee would be contingent upon their approval. If no further review is necessary, or when approval has been given, HRPP staff will be notified, and final IRB approval can be given. If a full IRB review was tabled pending a Radiation Safety decision, the study will return to the full committee for further review.

4.2.6. HRPP staff ensure that Financial Disclosures for investigators and CITI training for all key personnel are done as required. If an investigator declares that a potential conflict of interest exists, the SRC will review the study in this regard, and determine if a statement about the potential conflict must be added to the informed consent, or if any other action is warranted. The IRB will be notified of the decision, and the consent will be modified as necessary. Final approval for a study to proceed will not be given until these requirements are met.

4.2.7. The Research Institute database is updated by Senior Scientists, Grants, and HRPP staff as new information is available. A database query is run every week and is discussed at the HRPP meeting to determine which pending projects are ready for IRB review or final approval.

4.3. Review Process

4.3.1. Criteria for approval

4.3.1.1. In order to approve research, the IRB shall determine that all of the following requirements are satisfied:

4.3.1.1.1. Risks to subjects are minimized:

4.3.1.1.1.1. By using procedures that are consistent with sound research design, and that do not unnecessarily expose subjects to risk, and

4.3.1.1.1.2. Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

4.3.1.1.2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits from therapies that subjects would receive even if not participating in the research). The IRB will not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

4.3.1.1.3. Selection of subjects is equitable. In making this assessment the IRB will take into account the purposes of the research and the setting in which the research will be conducted. The IRB will be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, , handicapped, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, or persons recruited or enrolled in an emergent care setting.

4.3.1.1.4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, as previously described.

4.3.1.1.5. Informed consent will be appropriately documented, or appropriately waived as previously described.

4.3.1.1.6. Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

4.3.1.1.7. Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of their data (such as coding of data, removing or not including identifying information, limiting access, use, and disclosure to the minimum necessary).

4.3.1.1.8. For purposes of conducting the limited IRB review required by §46.104(d)(7), the IRB need not make the determinations at paragraphs (a)(1) through (7) §46.111(a), and shall make the following determinations:

(i) Broad consent for storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens is obtained in accordance with the requirements of §46.116(a)(1)-(4), (a)(6), and (d);

(ii) Broad consent is appropriately documented or waiver of documentation is appropriate, in accordance with §46.117; and

(iii) If there is a change made for research purposes in the way the identifiable private information or identifiable biospecimens are stored or maintained, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

4.3.1.1.9. Investigators' potential financial conflicts will not significantly impact the safety or outcomes of the study.

4.3.1.2. When some or all of the subjects, such as children, prisoners, handicapped, or individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence, the IRB will ensure that additional safeguards are included in the study to protect the rights and welfare of these subjects, and that they are adequate.

4.3.1.3. Remuneration, monetary or otherwise, offered to research participants and/or legally authorized representatives (LAR) is an acceptable practice in so far as it fairly offsets the incidental costs and inconveniences inherent in study participation, such as travel, meals, parking, and time commitment. The IRB must review and approve the remuneration plan, including type and amount of remuneration, prior to its implementation. The IRB must determine that the remuneration is reasonable given the nature of the study and that it does not unduly influence or coerce enrollment into or continued participation in the study.

4.3.1.4. The IRB will exercise heightened vigilance when reviewing proposed remuneration for studies involving vulnerable populations to ensure that the decisions of the potential participants or their LAR are not influenced by the remuneration associated with the study (e.g., offering children toys, which may unduly influence their decision to assent, or offering the parents or guardians monetary compensation may influence them to coerce their children into participation).

4.3.1.5 The IRB or Chair/Vice Chair or other designated reviewer may request verification of submitted information, independent of the researchers.

4.3.1.5.1 Such verification may include, but is not limited to:

- DSMB reports
- FDA, NIH, or sponsor correspondence
- An internal or sponsor audit
- Reviews by outside IRB's
- Back translations of patient materials

4.3.1.5.2. When such verification is required, the investigator will be so notified, and approval of the research activity will be contingent upon the receipt of a satisfactory response, as determined by the IRB or designated reviewer.

4.3.2. Approval Period and Frequency of Review

4.3.2.1. The approval period and frequency of review will be decided for each new protocol and continuing review, based on the level of risk, taking into consideration the subject population, enrollment criteria, and any other relevant factors of the proposed research. This period is generally one year from the review date, unless the IRB determines that the degree of risk is such that a shorter interval or other criterion shall define the approval period (such as a set number of patients enrolled). In no case shall the approval exceed one year.

4.3.3. Checklists

4.3.3.1. Checklists are utilized to document that criteria for approval are met. Primary reviewers are expected to complete a checklist for each initial and continuing review, and to present to the board for discussion any areas not meeting the criteria, that have not been resolved. Completed checklists are returned to HRPP staff after the review.

4.3.3.2. Checklists are utilized to document that the required findings have been made with regard to the inclusion of pregnant women/fetuses/neonates, prisoners, and children.

4.3.4. Full review

4.3.4.1. All items deemed to be research involving human subjects, which have not been deferred to another IRB for review, and that do not meet the criteria for exemption or expedited review, will be scheduled for review at a convened meeting by the full IRB. Other items may be given full review if felt to be warranted by the Chair/Vice Chair, or, if upon notification of those items given expedited review, any IRB member calls for a full review, or, if an item otherwise eligible for expedited review would have been disapproved by the reviewer.

4.3.4.1.1. Revisions to previously approved research involving more than minimal risk to research participants or substantive changes must be reviewed by the full IRB. These include major changes in the direction of the study that may substantially change the purpose of the study or the risk/benefit ratio, or may impact a participant's decision to remain in the research. Examples include:

- Changes that might increase the physical and/or psychological risks of harm or discomfort to the subject
- Major change in study design that increases risk (e.g., revisions to broaden eligibility criteria, additions or deletions of research groups);
- Major change in the purpose of the study;
- Alterations in the treatment or drug dosage, frequency, or route of administration;
- Changes to the consent form to include newly identified side effects or adverse events;
- Adding questions that ask for sensitive information (e.g., depression or sexual behavior questions where data are linked to subjects' identities);
- Adding a new procedure that substantively changes risks of harm (e.g., addition of a procedure involving radiation hazard, a questionnaire on sensitive information not previously included, addition of a drug or device.

4.3.4.2. HRPP staff distribute materials to the IRB members one week or more prior to the meeting to allow sufficient time for review.

4.3.4.3. HRPP staff assigns a primary reviewer to each item being presented for full review. This reviewer has the responsibility for conducting an in-depth review of the information submitted. The assignment is based primarily on area of expertise of the member as appropriate to the research under review, and also with consideration of potential conflicts of the member with the research being reviewed. The reviewer assigned receives a full copy of the pertinent materials submitted, and is expected to review them. A full copy of the materials is available to all members via the electronic research management system.

4.3.4.4. For initial review, material provided to the assigned primary reviewer may include the Research Application, protocol (DHHS-approved if one exists), , budget, consents, waivers, HIPAA authorization, advertisements or other patient materials, and the Investigator Brochure, as well as a reviewer checklist. The reviewer is also provided and reviews the investigator's current curriculum vitae or other documentation evidencing qualifications, as applicable to ICH-GCP (E6). All other members receive the full packet of items to be reviwed. All members are expected to have reviewed at least the protocol and consent documents. Reviewers are encouraged to contact researchers before the IRB meeting if clarifications are needed.

4.3.4.5. For continuing review, material provided to all members includes the progress report (with a summary of adverse events), current protocol and consents and/or waivers. At least one member of the IRB is assigned as the primary reviewer and is responsible for reviewing the current complete protocol and any protocol modifications previously approved by the IRB. All members are expected to have reviewed the materials.

4.3.4.6. Amendments and modifications to be given full review may include a summary of what has been changed, a revised protocol and any other items requiring revision such as the informed consent, and any pertinent correspondence. All members receive these materials.

4.3.4.7. The IRB has the authority to approve, require modifications to secure approval, or disapprove all research activities involving human subjects, including proposed changes in previously approved research. The assigned reviewer presents the item to the committee and proposes items for revision or clarification. Any member may comment on the item after the formal presentation and may suggest revisions.

4.3.4.8. Consultants may be engaged to assist with the review if it is determined that the field of study is not represented on the IRB, or if additional expertise may be needed for reasons such as inclusion of vulnerable populations, or potential conflict of interest.

4.3.4.9. Determinations of significant/non-significant risk will be made as required for FDA-governed device studies.

4.3.4.10. If clarifications are needed before a decision can be made by the IRB, or if major modifications are deemed to be necessary to secure approval, discussion of an item will be tabled by the IRB pending such modifications/clarifications, the reasons for this action will be communicated to the investigator, and the item will be re-reviewed at a future convened meeting.

4.3.5. Expedited review

4.3.5.1. Items determined by HRPP staff to be research involving human subjects, which have not been deferred to another IRB for review, that do not meet the criteria for exemption, and that fall under one or more of the categories specified below, may be presented for expedited review. Minor modifications to previously approved research and other items that are determined by the Chair/Vice Chair or full committee to present no more than minimal risk may also be given expedited review.

Categories of such research include:

1) Clinical studies of drugs and medical devices only when condition a) or b) is met.
   a) Research on drugs for which an investigational new drug application is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
   b) Research on medical devices for which (i) an investigational device exemption application is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
   a) from healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
   b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

3) Prospective collection of biological specimens for research purposes by noninvasive means.
4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. This includes moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.
5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis).
6) Collection of data from voice, video, digital, or image recordings made for research purposes.
7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.
8) Continuing review of research previously approved by the convened IRB as follows:
   a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
   b) where no subjects have been enrolled and no additional risks have been identified; or
   c) where the remaining research activities are limited to data analysis.
9) Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories 2) through 8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

4.3.5.1.1. The following are examples of the types of minor changes/revisions to previously approved research that may be reviewed by the expedited procedure:

- Any added procedure that is minimal risk and fits the criteria for expedited review categories 1-7;
- Informational revisions with no potential impact on the risks for participants such as minor changes involving editorial, grammar, semantic or format changes to the consent

form or protocol that do not affect context or substance;

- Resolution of discrepancies within the IRB review materials (application form, protocol, consent materials) such as numbers of subjects, number and identity of research sites, identification of research staff and co-investigators, timing, nature, and duration of research procedures provided that the corrections are being made to reflect what the IRB has reviewed and approved at the convened meeting;
- Changes in the recruitment plan or recruitment materials to improve clarity, enhance comprehension, or respond to minor discrepancies;
- Changes in consent materials to improve clarity, enhance comprehension, change telephone numbers and contact information, to update materials to incorporate IRB approved boiler plate language, or to include IRB-required changes;
- Changes in research procedures that have a minor impact on risks of harm, such as changes in the size and frequency of blood draws while still within the guidelines for expedited activities; addition of a clinic visit that involves no new procedures, or addition of a questionnaire that does not introduce new subject matter;
- 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;
- Extending the time period of the study to include only follow-up with the research participants;
- Minor changes in the participant compensation (that would not constitute undue influence);
- Changes in data collection instruments to add or delete non-sensitive questions that do not increase risks of harm to subjects; adding a standardized test or a quality-of-life questionnaire;
- Addition or deletion of qualified investigators
- The addition of study sites (which may require a Federalwide Assurance (FWA) and appropriate IRB approval) or the deletion of study sites.

4.3.5.2. Items sent for expedited review for initial approval, continuing review, and minor amendments and modifications to previously approved research will include the same

materials that would be sent to a reviewer for full review. The Chair, Vice Chair, or other Designated Reviewer (another experienced IRB member) will conduct the necessary reviews.

4.3.5.3. The designated expedited reviewer will have the authority to approve the item or require modifications in order to secure approval. Minor modifications will be handled in the same manner as for full review. If the reviewer would have disapproved the item, or believes that it is not appropriate for expedited review, it must be sent to the IRB for full review at a convened meeting.

4.3.5.4. IRB members will be notified via the agenda of all items that have been given expedited approval. These items are made available to any member for review via the IRB electronic research management system. If any member requests that an item which has been approved by the expedited procedure be given review by the full committee, a vote of the members shall be taken concerning the request, and the majority shall decide the issue.

4.4. Post-review Process

4.4.1. Approval and revision letters will be sent by HRPP staff to the investigator electronically, (and generally by the day following an expedited review and within 3 days of a full review). Revision letters will indicate the status of the study (pending revisions or tabled), and will delineate all revisions and clarifications required in order to secure approval and reasons for the requirement.

4.4.2. Requested modifications to study documents should be submitted for IRB consideration in a manner that clearly indicates what has been revised, with a copy of the item marked with the changes and/or a summary of specific changes made. Any item not revised as requested must have written justification.

4.4.3. Minor modifications will go back to the Chair/Vice Chair or other member designated to do the review. This person will decide if the revisions are adequate. The reviewer may request additional revisions/clarifications before granting approval, or the item may be sent for full committee consideration.

4.4.4. Once all required revisions are made, or a satisfactory explanation is given for not making a requested change, a final IRB approval letter will be sent. This will specify at least that the item is approved, the date of review, type of review, approval date, which will be the date the conditions were met, and period through which the approval is valid, and, if expedited (for initial and continuing reviews), the categories pre-determined by the HRPP staff, the form of consent approved, and will include notifications regarding the next progress report due date, any future modifications, and adverse event reporting. A copy of any approved consents and patient materials and the HIPAA authorization will be stamped with the approval date and valid period (if applicable)

and will be included with the approval letter. Items approved will be noted on the next agenda.

4.4.5. The IRB approval period begins as of the day specified in the letter as the agenda date (for initial reviews), and the approval for continuation date (for continuing reviews). The IRB approval period ends at the end of the "valid through" or "extension through" date specified in the approval letter. This is typically one day prior to the one-year anniversary of the previous review. Approval will be considered expired on the following day. If the IRB stipulates an approval period of less than a year, the approval may be considered to end on the last day of the specified period.

4.4.6. If an item is not approved by the full IRB, the letter will indicate the reasons and what options are available to the investigator, such as whether the IRB would reconsider the proposal after major revision.

4.4.7. The IRB approval letter for initial reviews indicates in order to proceed with the study approval must be granted by both the IRB and the Grants and Contracts Office.

4.4.8. If a radiation component is added to a study after the initial approval, a copy of the modification, protocol, and consent(s) will be forwarded by HRPP staff to the Radiation Safety Office for evaluation as described in 4.2.5.

5.0 Documentation:

5.1 The HHC HRPP office will maintain documentation related to IRB review of study materials for expedited and full reviews, including initial submissions, continuing reviews, and modifications, as well as reports of unanticipated problems, complaints, deviations, non-compliance, and correspondence related to review of such items, as well as checklists pertinent to the reviews, for a minimum of 6 years after completion of the study. Adverse event reports and Investigator Brochures will be maintained for a minimum of 3 years.

5.2 Requirements for retaining documentation differ for investigators. These are delineated in HRPP Policy# 200 – "Investigator Responsibilities".

5.3 The HHC HRPP office will maintain documentation of IRB membership, attendance at convened meetings, and records relating to financial disclosures and training requirements completed by IRB members and staff for a minimum of 3 years.

6.0 Revision History:

Rev #	Initials	Effective Date	Description of Change(s)
01	SMH	7/1/11	Conversion to new policy template; general expansion of policy
02	CLB	5/24/13	Expansion of major/minor modification definitions; addition of specific examples of changes to previously approved research that may be expedited or reviewed by the fully convened committee (Sections 4.3.4.1.1. and 4.3.5.1.1)

03	CLB	7/22/15	Added clarifying details regarding the types of documents that the primary reviewer will receive based on DHHS or ICG-GCP (E6); clarified that the approval date will the date conditions were met if research was approved with conditions.
04	CLB	3/15/20	General review. Updated sections as relevant to the Revised Common Rule. Updated AAHRPP element for which the policy applies.

Elements II.2.E and II.2.F.