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1.0 Purpose:

- 1.1 To define the requirements and procedures the Hartford HealthCare Human Research Protections Program/Institutional Review Board (HHC HRPP/IRB) follow for review of multi site collaborative non-exempt human-subjects research initiated by investigators who are employees or agents (e.g., professional staff) of HHC.
- 1.2 To define the requirements and procedures the HHC HRPP/IRB follow for review of operations centers or coordinating centers for multi site human-subjects research.

2.0 Definitions:

- 2.1 **Employees or Agents:** Members of the HHC workforce who: (1) act on behalf of the institution; (2) exercise institutional authority or responsibility; or (3) perform institutionally designated activities. Employees and agents include professional staff, students/interns, contractors, and volunteers, among others, regardless of whether the individual is being paid by the hospital.
- 2.2 **Collaborating Individual/Investigator:** An investigator who is: (a) not otherwise an employee or agent of the HHC; (b) conducting collaborative research activities whether on or off-site from the HHC; and (c) not acting as an employee of any institution with respect to his/her involvement in the research being conducted by HHC (independent investigator) OR acting as an employee or agent of an institution that does not hold an OHRP-approved FWA and does not routinely conduct human-subjects research (institutional investigator).

3.0 Policy:

- 3.1 When employees or agents of HHC conduct investigator-initiated non-exempt human-subjects research in collaboration with other institutions or with collaborating individual investigators as defined herein, each collaborating institution and/or collaborating individual investigator engaged in human-subjects research must obtain IRB approval for the research they are conducting. The OHRP guidance document "Guidance on Engagement of Institutions in Human Subjects Research" will be used as the basis for determining engagement in human-subjects research. Such determinations will be made in collaboration and consultation with authorized representatives of the collaborating institution and/or the collaborating individual investigators, as applicable.
- 3.2 Investigators must specify in the HHC Research Application the outside institutions and/or individuals involved in the research. When outside parties involved in the research are institutions, the HHC investigator must provide the HHC HRPP/IRB with: 1) contact information for the collaborating institution's IRB, if any, and if the institution has no IRB, with contact information for the institution's Institutional Official or other authorized representative for research; and 2) if applicable, the collaborating institution's Federalwide Assurance (FWA)#.
- 3.3 When employees or agents of HHC are responsible for the operations center or coordinating center for multi site human-subjects research, the HHC HRPP/IRB will review the standard operating procedures of the center to ensure that there are

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appropriate mechanisms in place to protect the rights, safety, and welfare of the subjects participating in the research at the collaborating sites.

4.0 Procedure:

4.1 Collaborating Institutions

4.1.1 Per relevant guidance from OHRP, when multiple institutions are engaged in the same non-exempt human-subjects research, the collaborating institutions may enter into joint review arrangements, rely upon the review of another qualified IRB, or make similar arrangements to avoid duplication of effort. When an institution is engaged in only part of the non-exempt human-subjects research, the institution must ensure that the part of the research project in which the institution is engaged is reviewed and approved by the institution's IRB or, on behalf of the institution, by another appropriately qualified IRB or Ethics Committee (EC) listed on the institution's FWA. Alternatively, each institution may decide to review the entire research project, even if the information about the entire project is not necessary to approve the part(s) of the research in which the institution is engaged.

4.1.1.1 Reliance of Collaborating Institutions on the HHC IRB (HHC IRB)

4.1.1.1.1 Non-HHC collaborating institutions engaged in non-exempt human-subjects research may request to rely on the HHC IRB for review of the research. In such cases, the HHC IRB will consider the request and, if it is granted, an IRB Authorization Agreement (IAA) must be executed by both institutions (if an effective Cooperative Agreement is not already in place between the two institutions). The relying institution must have an active/approved FWA and the HHC IRB must be listed on the relying institution's FWA. In the absence of such a reliance arrangement, each institution will independently review the research project.

4.1.1.2 Reliance of HHC on Collaborating Institution's IRB

4.1.1.2.1 The HHC may rely on the IRB of a collaborating institution when all or the majority of the non-exempt human-subjects research is being conducted at the collaborating institution or when the collaborating institution's IRB has more relevant or specialized expertise and/or knowledge of the site where the research will be conducted. In such cases, an IAA must be executed by both institutions. The institution relied upon for IRB review must have an active/approved FWA and its IRB must be listed on our institution's FWA. In the absence of such a reliance arrangement, each institution will independently review the research project.

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4.1.1.3 Joint Review Arrangements

4.1.1.3.1 When HHC and the collaborating institution are each engaged in only part of a non-exempt human-subjects research project, each may decide to review only the part(s) of the project in which they are engaged. In such cases, the HHC Principal Investigator is responsible for providing the HHC IRB with information about any changes to the research required by the collaborating institution's IRB that are material to the part(s) of the research in which HHC is engaged. If either institution wishes to rely on the other for review of the part(s) of the project in which it is engaged, the relying institution must list the reviewing IRB on its FWA and an appropriate IAA must be executed to document the reliance. For example, when the research is being conducted largely or entirely off-site, the HHC IRB may rely on the collaborating institution's IRB for review of the local research context or other aspects of the part of the project in which HHC is engaged for which the collaborating institution's IRB has more relevant or specialized expertise and/or knowledge. The HHC IRB will make decisions about appropriate joint review arrangements depending on the circumstances of the particular project.

4.1.2 In all cases where the collaborating institution is conducting its own review of non-exempt human-subjects research (not relying on the HHC IRB for review), documentation of the collaborating institution's IRB approval of the research and, if federally-funded, the institution's FWA# will be required and maintained by the HHC IRB as part of its review. When the research is not federally-funded, in its discretion, the HHC IRB may find it acceptable that the research has been reviewed and approved on the collaborating institution's behalf by an appropriately qualified IRB or other internationally recognized Ethics Committees; for example, those that adhere to the World Health Organization (WHO), Declaration of Helsinki, Council for International Organizations or Medical Sciences (CIOMS) or other similar guidelines, or to the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice guidelines (ICH-GCP).

4.2 Collaborating Individual Investigators

4.2.1 When a collaborating individual investigator, whether an independent investigator or an institutional investigator, is engaged in non-exempt human-subjects research, the HHC may choose to extend its FWA to cover the collaborating individual investigator. In such cases, an Individual Investigator Agreement outlining the terms and conditions of this arrangement must be executed by both parties. See Individual Investigator Agreement.

4.3 Investigators Serving as the Principal Investigator on a Multi-Site Research Project

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- 4.3.1 When a HHC investigator is responsible for the overall conduct of a multi-site study that is federally funded, both the investigator and HHC are engaged in research according to OHRP guidance (October 16, 2008), whether or not identifiable private information is used for research by the investigator or others within HHC. To satisfy those responsibilities, the investigator must:
- 4.3.1.1 Submit a blanket (administrative) protocol if the scope of human research will involve multiple separate research questions and therefore multiple separate IRB protocols;
 - 4.3.1.2 Submit a coordinating center protocol (see 4.4 below) if HHC will also be the site of the coordinating center for this multi-site research;
 - 4.3.1.3 Submit a statistical center protocol (see 4.5 below) if HHC will also be the site of the statistical center for this multi-site research;
 - 4.3.1.4 Submit separate IRB protocols to cover each aspect of the multi-site research involving human subjects that will not occur at HHC in order for the HHC IRB to:
 - 4.3.1.4.1 Evaluate whether the management of information that is relevant to the protection of participants is adequate, including:
 - 4.3.1.4.1.1 Reporting of unanticipated problems involving risks to participants or others;
 - 4.3.1.4.1.2 Interim results;
 - 4.3.1.4.1.3 Protocol modifications;
 - 4.3.1.5 Submit separate IRB protocols to cover each aspect of the research involving human subjects that will occur at HHC;
 - 4.3.1.6 Submit a repository protocol (see the HHC HRPP Policy on Research Databases and Specimen Repositories) if HHC is the site of such a repository for this multi-site research.
- 4.3.2 These IRB protocols will be reviewed initially and at the time of periodic continuing review according to the HHC IRB policies and procedures that apply to them.
- 4.3.3 Federally Funded Multi-Site Research
- 4.3.3.1 If the research is federally funded, the HHC Principal Investigator will either: (i) at the time of initial review, provide an appropriate monitoring plan to the HHC IRB describing how the HHC study team will ensure that external sites maintain current IRB approval and a current FWA for the duration of the study; or (ii) at each continuing review, provide copies of current IRB approval and current FWA number to the IRB. The IRB primary reviewer, either at the convened IRB meeting or as the reviewer

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using the expedited procedure, will review the IRB submission and the grant associated with that submission to assess for concordance. The IRB will follow its Policy on "Reporting To Institutional Officials and Regulatory Agencies" for instances of unanticipated problems involving risks to participants, serious or continuing non-compliance, or suspension or termination of IRB approval.

4.3.3.2 A HHC investigator who wishes to add sites to his/her federally funded, multi site study must follow the procedures described in sections (4.1 and 4.2) above.

4.4 Review of Operations Centers or Coordinating Centers for Multi-Site Research

- 4.4.1 Investigators must specify in the HHC Research Application what operations center or coordinating center activities they are engaged in and provide a copy of the center's standard operating procedures. Although the HHC IRB does not need to approve the protocol as part of the operations center or coordinating center protocol, the investigator is asked to submit the protocol and model consent form and, when applicable, provide information about drugs, biologics, dietary supplements or devices being investigated so that the HHC IRB can ensure that the operations center or coordinating center's standard operating procedures are appropriate for the study. Note that when subjects will be enrolled in the study at Hartford Hospital (HH), MidState Medical Center (MSMC), Windham Hospital (WH), or Genomas, the protocol must be submitted separately to the HHC IRB for approval.
- 4.4.2 The HHC IRB will review the center's standard operating procedures and determine whether the operations center or coordinating center has sufficient mechanisms in place to ensure that, where applicable:
- 4.4.2.1 Management, data analysis, and data safety and monitoring plan is adequate, given the nature of the research involved;
 - 4.4.2.2 Sample protocols and informed consent documents are developed and distributed to each collaborating institution;
 - 4.4.2.3 Each collaborating institution holds an applicable approved Federal Wide Assurance (FWA);
 - 4.4.2.4 Each protocol is reviewed and approved by the IRB at the collaborating institution prior to the enrollment of subjects;
 - 4.4.2.5 Any substantive modification by the collaborating institution of sample consent information related to risks or alternative procedures is appropriately justified; and
 - 4.4.2.6 Informed consent is obtained from each subject in compliance with DHHS regulations.
- 4.4.3 During the period of approval, investigators are required to report to the HHC IRB any changes in the center's standard operating procedures that are related to the six criteria above. Changes to the protocol and/or

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consent form do not need to be reported to the HHC IRB until continuing review.

4.4.4 At continuing review, investigators are required to report any unanticipated problems involving risks to subjects or others, protocol modifications, and interim findings.

4.5 Review of Statistical Centers for Multi-Site Research

4.5.1 When a statistical center for a multi-site research project is to be based at HHC, both the leadership and the staff of the center and HHC as an institution will be engaged in research with humans according to OHRP guidance (October 16, 2008). To satisfy the responsibilities of a statistical center, where institutional activities involve no interaction or intervention with subjects, and the principal risk associated with institutional activities is limited to the potential harm resulting from breach of confidentiality, the IRB need not review each collaborative protocol. However, the IRB will determine and document that the statistical center has sufficient mechanisms in place to ensure that (i) the privacy of subjects and the confidentiality of data are adequately maintained, given the sensitivity of the data involved; (ii) each collaborating institution holds an applicable OHRP-approved Assurance; (iii) each protocol is reviewed and approved by the IRB at the collaborating institution prior to the enrollment of subjects; and (iv) informed consent is obtained from each subject in compliance with DHHS regulations.

4.5.2 The IRB will initially receive from the statistical center lead investigator an IRB protocol submission containing documentation of how the center will ensure that the above four activities will be performed appropriately, and a listing of active sites and contact information for each site where research participation is to occur. At the time of initial review, the IRB will assess the procedures for prompt dissemination of protocol information to all participating sites. Assessment of protocol information includes reports of unanticipated problems involving risks to participants, protocol modifications and interim findings. At the time of each periodic continuing review, the investigator will provide the IRB with updated information about each of these items, including the four items noted above.

5.0 **Documentation:**

5.1 HHC will maintain documentation related to IRB review of pertinent study materials for multi-site research as describe for a minimum of 6 years after completion of the study.

6.0 **References:**

6.1 OHRP Guidance on Extension of an FWA to Cover Collaborating Individual Investigators and Introduction to the Individual Investigator Agreement – January 31, 2005 (<http://www.hhs.gov/ohrp/policy/guidanceonalternativetofwa.html>)

6.2 OHRP Guidance on Engagement of Institutions in Human Subjects Research – October 16, 2008 (<http://www.hhs.gov/ohrp/policy/engage08.html>)

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7.0 Revision History:

Rev #	Initials	Effective Date	Description of Change(s)
00	SAB	7/1/11	New Issue

Elements II.2.H. and III.2.D.