1.0 Purpose:

1.1 The purpose of this policy is to define the applicability of the definitions of research and human subject found in 45 CFR 46 and clinical investigation, human subject and subject found in 21 CFR 50, 56 and 812 to activities overseen and conducted by employees or agents of Hartford HealthCare (HHC) and the procedures investigators, administrators, and the HHC HRPP follow when making such determinations.

1.2 "Human-subjects research" conducted by employees or agents of HHC must be reviewed and approved by the HHC Institutional Review Board (IRB). Activities that meet the definition of *research* and involve a *human subject* as defined by DHHS or meet the definition of *clinical investigation* and involve a human subject or subject as defined by FDA are subject to HHC IRB review and approval.

2.0 Definitions:

2.1 Institutional Review Board – IRB

2.2 Human Research Protection Program – HRPP

2.3 Office of Human Research Protection - OHRP

2.4 Department of Health and Human Services – DHHS

2.4.1 **Research** [45 CFR 46.102(l)] - a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

2.4.1.1 For the purposes of this policy, a *systematic investigation* is considered an activity that involves a prospective research plan which incorporates data collection, either quantitative or qualitative, and data analysis to answer a research question.

2.4.1.2 Systematic investigations that are designed to develop or contribute to *generalizable knowledge* are those that allow the knowledge gained from the research to be applied to populations other than the study population, inform policy, or generalize findings.

2.4.1.3 For the purposes of this policy, the following activities are deemed not to be research:

2.4.1.3.1 Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.

2.4.1.3.2 Public health surveillance activities conducted by a public health authority, limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance

2.4.1.3.2.1 Including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. I

2.4.1.3.2.2 Including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products.

2.4.1.3.2.3 Including those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

2.4.1.3.3 Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.

2.4.1.3.4 Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

2.4.2 **Human Subject** [45 CFR 46.102(e)] - a living individual about whom an investigator (whether professional or student) conducting research (1) Obtains information or biospecimens through *intervention* or *interaction* with the individual, and uses, studies, or analyzes the information or biospecimens or (2) Obtains, uses, studies, analyzes, or generates *Identifiable private information or identifiable biospecimens.*.

2.4.2.1 ***Intervention*** includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes

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2.4.2.2 ***Interaction*** includes communication or interpersonal contact between investigator and subject.

2.4.2.3 ***Private information*** includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual

can reasonably expect will not be made public (e.g., a medical record).

2.4.2.4 ***Identifiable private information*** is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

2.4.2.5 An ***identifiable biospecimen*** is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associate with the biospecimen.

2.4.3 **Clinical Trial** [45 CFR 46.102(b)] - A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.

2.4.4 **Public Health Authority** [45 CFR 46.102(k)] - means an agency or authority of the United States, a state, a territory, a political subdivision of a state or territory, an Indian tribe, or a foreign government, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate.

2.4.5 **Written, or in writing** [45 CFR 46.102(m)] – refers to writing on a tangible medium (e.g., paper) or in an electronic format.

2.5 **DHHS Office for Civil Rights (OCR)** - enforces federal civil rights laws, conscience and religious freedom laws, the Health Insurance Portability and Accountability Act (HIPAA) Privacy, Security, and Breach Notification Rules, and the Patient Safety Act and Rule.

2.5.1 ***Covered Entity*** [45 CFR 160.103] – means:

2.5.1.1 A health plan

2.5.1.2 A health care clearinghouse

2.5.1.3 A health care provider who transmits any health information in electronic form in connection with transactions for which HHS has adopted standards

2.5.2 ***Research*** [45 CFR 164.501] - a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.

2.5.3 ***Protected Health Information (PHI)*** [45 CFR 160.103] - individually identifiable health information, held or maintained by a covered entity or its business associates acting for the covered entity, that is transmitted or maintained in any form or medium. This includes identifiable demographic and other information relating to the past, present, or future physical or mental health or condition of an individual, or the provision or payment of health care to an individual that is created or received by a

health care provider, health plan, employer, or health care clearinghouse.

2.5.4 ***De-Identified*** [45 CFR 164.502(d)(2)] - Health information that meets the standard and implementation specifications for de-identification under § 164.514(a) and (b) is considered not to be individually identifiable health information, *i.e.,* de-identified.

2.5.4.1 ***45 CFR 164.514(b)(2)(i) –*** A covered entity may determine that health information is not individually identifiable health information only if the following identifiers ("The 18 HIPAA Identifiers") of the individual or of relatives, employers, or household members of the individual, are removed:

2.5.4.1.1 Names
2.5.4.1.2 All geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of the Census:
2.5.4.1.2.1 The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and
2.5.4.1.2.2 The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
2.5.4.1.3 All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older;
2.5.4.1.4 Telephone numbers;
2.5.4.1.5 Fax numbers;
2.5.4.1.6 Electronic mail addresses;
2.5.4.1.7 Social security numbers;
2.5.4.1.8 Medical record numbers
2.5.4.1.9 Health plan beneficiary numbers;
2.5.4.1.10 Account numbers;
2.5.4.1.11 Certificate/license numbers;
2.5.4.1.12 Vehicle identifiers and serial numbers, including license plate numbers;
2.5.4.1.13 Device identifiers and serial numbers;
2.5.4.1.14 Web Universal Resource Locators (URLs);
2.5.4.1.15 Internet Protocol (IP) address numbers;
2.5.4.1.16 Biometric identifiers, including finger and voice prints;
2.5.4.1.17 Full face photographic images and any comparable images; and
2.5.4.1.18 Any other unique identifying number, characteristic, or code

2.6 United States Food and Drug Administration – FDA

2.6.1 **Clinical Investigation** [21 CFR 50.3(c), 21 CFR 56.102(c)] - any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical studies. The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part.

2.6.1.1 "Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) of the Federal Food, Drug, and Cosmetic Act" means any use of a drug other than the use of an approved drug in the course of medical practice. [21 CFR 312.3(b)]

2.6.1.2 "Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 520(g) of the Federal Food, Drug, and Cosmetic Act" means any activity that evaluates the safety or effectiveness of a device. [21 CFR 812.2(a)]

2.6.1.3 Any activity in which results are being submitted to or held for inspection by FDA as part of an application for a research or marketing permit is considered to be FDA-regulated research. [21 CFR 50.3(c), 21 CFR 56.102(c)]

2.6.2 **Human Subject** [21 CFR 56.102(e); 21 CFR 812.3(p)] - an individual who is or becomes a participant in research, either as a recipient of the *test article* or as a control. A subject may be either a healthy individual or a patient. For research that evaluates the safety or effectiveness of a device, the definition includes a human on whom or on whose specimen an investigational device is used. A subject may be in normal health or may have a medical condition or disease. In the latter case, medical device studies involving in vitro diagnostics and unidentified tissues specimens, the FDA defines the unidentified tissue specimens as human subjects.

2.6.2.1 ***Test article*** - means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

3.0 Procedure:

3.1 Before employees or agents of HHC undertake activities that might be considered human-subjects research, they should consider whether the activity is research involving human subjects as defined in DHHS regulations 45 CFR 46 or a clinical investigation involving human subjects as defined in FDA regulations 21 CFR 50, 56 and 812 and consult the HHC HRPP office as necessary to ensure that human-subjects research activities, including clinical investigations, are reviewed prospectively by the HHC IRB.

3.2 Some activities, such as developing a case report or a limited case series (<3 cases) for publication, or quality improvement activities that do not meet the definition of research, or research involving deceased individuals may be considered research not involving human subjects according to DHHS and FDA. These activities should be submitted to the HRPP office for formal evaluation and determination. Procedures and guidance are provided elsewhere in more detail (*see HRPP Policy #605 – "Single Case Reports and Case Series"*).

3.3 Generally, individuals seeking a determination from the HHC HRPP should complete and submit a "Request for Determination that a Proposed Activity is Not Research or is Not Human Subjects Research" Form describing the activity in sufficient detail for the required determinations to be made. The HRPP Director or designee may request additional written information to make the determination.

3.4 In such cases, the HRPP Director or designee will follow the procedures outlined below.

3.4.1 The HRPP Director or designee uses or refers to the "Reviewer Checklist for Non-Research/Human Subjects Research Determination" when reviewing and documenting human-subject research determinations.

3.4.2 DHHS-Regulated Research

3.4.2.1 Determine whether the activity meets the DHHS definition of research;

3.4.2.2 When the activity is determined to meet the DHHS definition of research, determine whether the activity involves human subjects as defined by DHHS.

3.4.2.3 When the activity does not meet the DHHS definitions of research involving human subjects, make FDA-Regulated Research determinations.

3.4.3 FDA-Regulated Research

3.4.3.1 Determine whether the activity meets the FDA definition of clinical investigation.

3.4.3.2 When the activity is determined to meet the FDA definition of clinical investigation, determine whether the activity involves human subjects or subject as defined by FDA.

3.4.3.3 When the activity does not meet the FDA definitions of clinical investigation involving human subject or subject, no further action is required.

3.4.4 When the FDA definitions are met, the activity is Research Involving Human Subjects that is FDA regulated. If the DHHS definitions are met, the activity is Research Involving Human Subjects that is DHHS regulated. If both sets of definitions are met, the activity is Research Involving Human Subjects and is both DHHS- and FDA-regulated.

3.5 When the HRPP Director or designee determines that the activity does not meet the definition of Research Involving Human Subjects, the Investigator is notified in writing that the activity does not meet the definition of Research Involving Human Subjects, and that the activity does not require further IRB consideration. Investigators are provided with the basis for the determination and are informed that they may not make changes to the activity without first reviewing the changes with the HRPP Director or designee to determine whether the changes are consistent with the determination. If the changes would require that the activity is now subject to IRB review, the investigator must resubmit the research for initial review as described elsewhere.

3.5.1 Determinations are typically made and communicated in writing to investigators within five (5) business days, given that sufficient information is provided to make the determination.

3.6 When the activity is determined to be Research Involving Human Subjects, the investigator must submit a Research Application for initial review. The research will then be evaluated as to whether it may qualify for an exemption from IRB oversight under the federal regulations. This process is described in detail elsewhere (*see HRPP Policy #614 – "Exemptions: Review and Determinations"*).

3.7 When the HRPP Director or designee determines that the activity is Research Involving Human Subjects that is not exempt from IRB oversight, s/he further determines whether the institution is engaged in research. The HRPP Director or designee uses the OHRP guidance on "Engagement of Institutions in Research" to determine whether the institution and its investigators would be engaged in research and the research subject to HHC IRB review. At any point in this process, the HRPP Director or designee may request additional information from the PI to make the determination. If still unclear, HRPP Director or designee may contact OHRP or FDA officials for guidance.

3.8 The IRB will review and approve research conducted outside the United States by HHC employees or students, even if the foreign research activity has no U.S. federal funding. The IRB may approve such non-U.S. funded research, provided it determines that: (a) the research conforms to proper codes of ethics (such as the Declaration of Helsinki and/or the Belmont Report), and (b) the research is approved by the foreign research site's ethical review authority. Requirements for the informed consent process will follow the laws and customs of the country in which the research is being conducted. If a U.S. Department or Agency funds the research, then the IRB would expect the foreign research site to have an approved Federal-wide Assurance and meet all applicable DHHS and FDA regulations and guidance.

4.0 Documentation:

4.1 Documentation related to a formal determination by the HRPP will be maintained for a minimum of three (3) years.

5.0 References:

5.1 45 CFR 46.101(a), 45 CFR 46.102(l), 45 CFR 46.102(e, 45 CFR 46.102(b)(45 CFR 46.102(k)

5.2 21 CFR 50.1, 21 CFR 50.3(a), 21 CFR 50.3(c), 21 CFR 50.3(g), 21 CFR 50.3(j), 21 CFR 56.101, 21 CFR 56.102(c), 21 CFR 56.102(l)

5.3 45 CFR Parts 160, 162, 164

5.4 Guidance for Industry and FDA Staff: In Vitro Diagnostic (IVD) Device Studies – Frequently Asked Questions (Issued June 25, 2010)

6.0 Revision History:

Rev #	Initials	Effective Date	Description of Change(s)
01	CLB	7/1/11	Conversion to new policy template; expansion of policy; reference to new submission form to request a determination and corresponding reviewer checklist
02	CLB	10/13/11	Added explanation that FDA defines the unidentified tissues used in medical device studies involving in vitro diagnostics as human subjects; added a reference for this to this statement.
03	CLB	3/15/20	Updated definitions to comply with the Revised Common Rule. Added HIPAA Privacy Rule definitions. Reviewed procedure.

Elements I.1.A. and III.1.A.