1.0 Purpose:

1.1 This policy defines how the Hartford HealthCare Human Research Protection Program (HHC HRPP) and the Institutional Review Board (IRB) verify the potential risk (significant or non-significant) to subjects participating in studies that utilize medical devices. The HRPP and IRB evaluate applicability of the United States Code of Federal Regulations, 21 CFR Part 812 - Investigational Device Exemptions (IDE) to determine whether an IDE is needed for a device investigation.

1.2 In addition to the 21 CFR Part 50 and 56 requirements for review of protocols, all non-exempt human subjects research and clinical investigations reviewed and approved by the IRB must determine whether the device to be used poses a significant or non-significant risk to subjects, and ensure that the investigations comply with FDA regulations for devices intended for human use.

2.0 Definitions:

2.1 **Subject -** a human who participates in an investigation, either as an individual on whom or on whose specimen and investigational device is used or as a control. A subject may be in normal health or have a medical condition or disease. [21 CFR 812.3(p)]

2.2 **Investigation -** research involving one or more subjects to determine the safety and efficacy of a device. [21 CFR 812.3(h)]

2.3 **Sponsor -** a person who initiates, but does not actually conduct, the investigation. The investigational device is administered, dispensed, or used under the direction of another individual. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators. [21 CFR 812.3(n)]

2.4 **Sponsor-investigator -** an individual who both initiates and conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed or used. The term does not include any person other than an individual. The obligations of a sponsor-investigator include those applicable to an investigator and a sponsor. [21 CFR 812.3(o)].

2.5 **Medical Device -** an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component part or accessory, which is:

- recognized in the official National Formulary or the United States Pharmacopoeia, or any supplement to them;
- intended for use in the diagnosis of disease, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes [21 U.S.C. 321(h)].

2.6 **Custom Device -** a device that:

- Necessarily deviates from devices generally available or from an applicable performance standard or premarket approval requirement in order to comply with the order or an individual physician or dentist;
- Is not generally available to, or generally used by, other physicians or dentists;
- Is not generally available in finished form for purchase or for dispensing upon prescription;
- Is not offered for commercial distribution through labeling or advertising; and
- Is intended for use by an individual patient named in the order of a physician or dentist, and is to be made in a specific form for that patient, or is intended to meet the special needs of the physician or dentist in the course of professional practice.

2.7 **Investigational Device -** a device, including a transitional device that is the object of an investigation.

3.0 Procedure:

3.1 Classification of Medical Devices:

3.1.1 In accordance with the Federal Food, Drug and Cosmetic Act, all medical devices are placed into one of three regulatory classes based on the level of control necessary to ensure safety and effectiveness of the device.

3.1.2 Devices in all three classes are subject to general controls which require, in part, that companies:

3.1.2.1 Register their establishments and list the medical devices they market with the FDA;

3.1.2.2 Manufacture their devices in accordance with Good Manufacturing Practices; and

3.1.2.3 Label their devices in accordance with labeling requirements.

3.1.3 Class I devices are subject only to general controls. They represent the lowest potential for harm and are simpler in design than Class II or Class III devices. Examples include elastic bandages, examination gloves and hand-held surgical instruments.

3.1.4 Class II devices are those for which general controls alone are insufficient to provide a reasonable assurance of safety and effectiveness. In addition to complying with general controls, these devices are also subject to special controls identified by the FDA, which may include special labeling requirements, performance standards and postmarket surveillance. Examples include powered wheelchairs, infusion pumps and surgical drapes.

3.1.5 Class III devices are those for which insufficient information exists to determine that general or special controls are sufficient to provide a reasonable assurance of safety and effectiveness. Examples include replacement heart valves, silicone gel-filled breast implants, and implanted cerebellar stimulators.

3.1.6 Medical devices also include diagnostic products. Examples include in vitro diagnostic reagents and test kits such as pregnancy test kits.

3.2 A premarket notification, or 510(k), is submitted to FDA before a manufacturer proposes to market a medical device. If FDA agrees that the new device is substantially equivalent to a legally marketed device for which premarket approval is not required, the manufacturer may market it immediately. However, if clinical data are necessary to demonstrate substantial equivalence, the clinical study must comply with the IDE, IRB, and human subject protection (informed consent and additional safeguards for children in research) regulations (21 CFR Parts 812, 56 and 50).

3.3 A premarket approval (PMA) application is the most stringent type of device marketing application for medical devices. FDA approves a PMA if it determines that the application contains sufficient valid scientific evidence to provide reasonable assurance that the device is safe and effective for its intended use(s).

3.3.1 Until a PMA is issued, the device may only be distributed for investigational use. Therefore, any clinical study must comply with the IDE, IRB, and human subject protection (informed consent and additional safeguards for children in research) regulations (21 CFR Parts 812, 56 and 50).

3.4 Three types of studies are described in the regulations at 21 CFR Part 812:

3.4.1 Significant risk (SR)device studies,

3.4.2 Nonsignificant risk (NSR) device studies, and

3.4.3 Exempt studies

3.5 A **significant risk device** is an investigational device that:

3.5.1 Is intended as an implant and presents a potential for serious risk to the health, safety or welfare of a subject;

3.5.2 Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or

3.5.3 Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or

3.5.4 Otherwise presents potential for serous risk to the health, safety, or welfare of a subject.

3.6 Sponsors of investigational SR device studies are required to get an approved IDE from FDA before starting their study. (FDA assigns each IDE a number – for

example #GXX0000, where XX denotes the year of the submission). Sponsors and clinical investigators of these studies must comply with the regulations at 21 CFR Part 812, *Investigational Device Exemptions*.

3.7 If FDA disapproves an IDE, FDA's letter will describe the reasons for the disapproval. If the sponsor submits an IDE amendment satisfactorily addressing the issues in FDA's letter, the agency sends an IDE approval letter to the sponsor. **The study may not start until both the FDA and the IRB have given approval.**

Note: A conditional approval letter from the FDA allows the study to begin if the study is approved by the IRB, but requires the sponsor to provide additional clarifying information in order to obtain full approval for the study.

3.8 The IRB does not have to make the SR or NSR determination if the FDA has already made the risk determination. Most often, clinical investigators submit SR device investigations for IRB review after the study has already received IDE approval from FDA.

3.9 To ensure the SR device investigations have an FDA-approved IDE, the clinical investigator must submit a copy of the FDA's IDE approval letter to the IRB before final approval is given.

3.10 The IRB may be requested to review a SR device study before the sponsor receives FDA approval of an IDE submission. Because there is a possibility that the FDA may not approve the IDE or may request significant changes to the research protocol, the IRB will need to re-evaluate the protocol prior to final approval. This eliminates the risk that subjects are mistakenly enrolled before the FDA approves the IDE.

3.11 A **nonsignificant risk device** is an investigational device that does not meet the definition of a SR device.

3.11.1 If the IRB determines the investigational medical device study poses a NSR, the sponsor does not need to submit an IDE to the FDA before starting the study, and the IRB may continue to review the study under 21 CFR 56.109 and 21 CFR 56.111.

3.11.2 FDA considers an NSR device study to have an approved IDE after IRB approval and when sponsors meet the abbreviated requirements at 21 CFR 812.2(b). In most cases, the FDA is not aware of NSR studies.

3.12 The IRB considers the following information in determining whether a device study poses a SR or NSR:

3.12.1 The sponsor's description of why the study is not SR. (*Is the sponsor basing the risk determination on the proposed use of the device in the investigation, and not just on the device alone?*)

3.12.2 Whether the proposed NSR research study meets the definition of "significant risk" as defined in Section 3.5 above. (*What is the nature of harm that may result from use of the device? Does the study present a potential for serious risk to the health, safety, or welfare of a subject?*)

3.12.3 The proposed use of the device as well as any protocol related procedures and tests, not just the device alone. (*What is the potential for harm that the procedure could cause as well as the harm that could be caused by the device?*)

3.12.4 Additional information from the sponsor, such as a description of the device, reports of prior investigations with the device, a description of the patient selection criteria and monitoring procedures, the FDA's assessment of the risk if such an assessment has been made, etc. (*Will the subject need to undergo an additional procedure as part of the investigational study, for example, a surgical procedure?*)

3.13 If the IRB reviews a protocol that is submitted as a NSR device and the IRB disagrees with the determination made by the sponsor, the investigator and where appropriate, the sponsor, are notified that the study involves a significant risk device.

3.13.1 The sponsor is responsible for submitting an IDE to the FDA, or, if electing not to proceed with the study, notifies the FDA of the SR determination.

3.13.2 The study may not be approved until the FDA has reviewed and either granted the IDE or determines that the device is, in fact, NSR.

3.13.3 Once the IDE is granted, the IRB may continue to review the study under 21 CFR 56.109 and 21 CFR 56.111.

3.14 An **Exempt Study** is one in which the sponsor and investigator are exempt from the requirements of 21 CFR Part 812, with the exception of Part 812.119 (disqualification of a clinical investigator). Examples of exempt studies are consumer preference testing, testing of a device modification, or testing of two or more devices in commercial distribution if the testing does not collect safety or effectiveness data or put subjects at risk [21 CFR 812.2(c)(4)]

3.14.1 Studies of an already cleared medical device or a PMA approved device in which the device is used or investigated in accordance with the indications in the cleared labeling [21 CFR 812.2(c)(1)(2)] are exempt.

3.14.2 Diagnostic device studies (e.g., in vitro diagnostic studies) under certain circumstances are exempt as long as the sponsor complies with the requirements for labeling, and if the testing is (i) noninvasive; (ii) does not require an invasive sampling procedure that presents significant risk; (iii) does not by design or intention introduce energy into a subject; and (iv) is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure. [21 CFR 812.2(c)(3)]

3.14.3 Studies of a cleared device for a **new use** must comply with the human subject protection (informed consent and additional safeguards for children in research), IRB and IDE regulations.

3.15 IDE exempt studies that are being conducted to collect data to support either a clinical investigation or a marketing application must comply with the requirements for IRB review and the requirements for informed consent.

3.16 When a physician uses a legally marketed device outside its labeling (off-label) to treat a patient and no research is being done, IRB review is not required. The IRB may choose on its own initiative to review such use.

3.17 When off-label use of a legally marketed device is part of a research study collecting safety and effectiveness data involving human subjects, IRB review and approval is required.

3.18 Custom devices made in a specific form for a given patient on the order of a physician or dentist as part of their professional practice are not subject to the requirements for device investigations **unless** the devices are being evaluated for safety and effectiveness. In such cases, custom devices are subject to the requirements of device investigations as described above.

3.19 Non-FDA approved devices used in research to study human physiology are not subject to the 812 IDE regulations, but must meet the criteria for NSR devices to be used in human subjects. When the device is electrically powered, the device must also be evaluated for electrical safety by the Biomedical Engineering department.

3.20 Non-Hospital Inventory FDA-Approved Medical Devices Used for monitoring or Data Collection:

3.20.1 Commercially available FDA-approved medical devices used in research according to the FDA-approved labeling are not subject to the 812 IDE regulations, but must meet the same hospital safety standards as medical devices being used for patient care and as such are subject to the requirements of the Hartford Hospital Standards Committee.

3.21 Once the risk status of a device that is to be used in a research study involving human subjects is determined, the IRB may continue to review the study under 21 CFR 56.109 and 21 CFR 56.11.

3.22 The IRB minutes will document the rationale for the SR/NSR determination and subsequent approval or disapproval for the clinical investigation.

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 six (6) years following the termination or completion of the research activities.

5.0 References:

5.1 21 CFR 50 – *Protection of Human Subjects*

5.2 21 CFR 56 – *Institutional Review Boards*

5.3 21 CFR Part 812 – *Investigational Device Exemptions*

5.4 FDA Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors - Frequently Asked Questions About Medical Devices (January 2006) http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127067.pdf

5.5 FDA Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors - Significant Risk and Nonsignificant Risk Medical Device Studies (January 2006) http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf

5.6 Institutional Review Board Management and Function, Bankert, E. A., Amdur, R. J., 2nd Edition, 2006

6.0 Attachments:

6.1 Examples of NSR/SR Devices

7.0 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.

Element I.7.A.

Examples of NSR/SR Devices

The following examples are provided to assist sponsors and IRBs in making SR/NSR determinations. The list includes many commonly used medical devices. Inclusion of a device in the NSR category should not be viewed as a conclusive determination, because the proposed use of a device in a study is the ultimate determinant of the potential risk to subjects. It is unlikely that a device included in the SR category could be deemed NSR due to the inherent risks associated with most such devices.

NONSIGNIFICANT RISK DEVICES

- Low Power Lasers for treatment of pain (Note: an IDE is required when safety and effectiveness data are collected which will be submitted in support of a marketing application.)
- Caries Removal Solution
- Daily Wear Contact Lenses and Associated Lens Care Products not intended for use directly in the eye (e.g., cleaners; disinfecting, rinsing and storage solutions)
- Contact Lens Solutions intended for use directly in the eye (e.g., lubricating/rewetting solutions) using active ingredients or preservation systems with a history of prior ophthalmic/contact lens use or generally recognized as safe for ophthalmic use
- Conventional Gastroenterology and Urology Endoscopes and/or Accessories
- Conventional Laparoscopes, Culdoscopes, and Hysteroscopes
- Dental Filling Materials, Cushions or Pads made from traditional materials and designs
- Denture Repair Kits and Realigners
- Digital Mammography (Note: an IDE is required when safety and effectiveness data are collected which will be submitted in support of a marketing application.)
- Electroencephalography (e.g., new recording and analysis methods, enhanced diagnostic capabilities)
- Externally Worn Monitors for Insulin Reactions
- Functional Electrical Neuromuscular Stimulators
- General Biliary Catheters
- General Urological Catheters (e.g., Foley and diagnostic catheters)
- Jaundice Monitors for Infants
- Magnetic Resonance Imaging (MRI) Devices within FDA specified parameters
- Menstrual Pads (Cotton or Rayon only)
- Menstrual Tampons (Cotton or Rayon only)
- Nonimplantable Electrical Incontinence Devices
- Nonimplantable Male Reproductive Aids with no components that enter the vagina
- Ob/Gyn Diagnostic Ultrasound within FDA approved parameters
- Transcutaneous Electric Nerve Stimulation (TENS) Devices for treatment of pain
- Wound Dressings, excluding absorbable hemostatic devices and dressings (also excluding Interactive Wound and Burn Dressings)

SIGNIFICANT RISK DEVICES

GENERAL MEDICAL USE

- Catheters
    - Urology urologic with antiinfective coatings
    - General Hospital longterm percutaneous, implanted, subcutaneous and intravascular

  - Neurological cerebrovascular, occlusion balloon
  - Cardiology transluminal coronary angioplasty, intraaortic balloon with control system
- Collagen Implant Material for use in ear, nose and throat, orthopedics, plastic surgery, urological and dental applications
- Surgical Lasers for use in various medical specialties
- Tissue Adhesives for use in neurosurgery, gastroenterology, ophthalmology, general and plastic surgery, and cardiology

ANESTHESIOLOGY

- Breathing Gas Mixers
- Bronchial Tubes
- Electroanesthesia Apparatus
- Epidural and Spinal Catheters
- Epidural and Spinal Needles
- Esophageal Obturators
- Gas Machines for anesthesia or analgesia
- High Frequency Jet Ventilators greater than 150 BPM
- Rebreathing Devices
- Respiratory Ventilators
- Tracheal Tubes

CARDIOVASCULAR

- Aortic and Mitral Valvuplasty Catheters
- Arterial Embolization Devices
- Cardiac Assist Devices: artificial heart (permanent implant and short term use), cardiomyoplasty devices, intraaortic balloon pumps, ventricular assist devices
- Cardiac Bypass Devices: oxygenators, cardiopulmonary nonroller blood pumps, closed chest devices
- Cardiac Pacemaker/Pulse Generators: antitachycardia, esophageal, external transcutaneous, implantable
- Cardiopulmonary Resuscitation (CPR) Devices
- Cardiovascular/Intravascular Filters
- Coronary Artery Retroperfusion Systems
- Coronary Occluders for ductus arteriosus, atrial and septal defects
- Coronary and Peripheral Arthrectomy Devices
- Extracorporeal Membrane Oxygenators (ECMO)
- Implantable Cardioverters/Defibrillators
- Laser Coronary and Peripheral Angioplasty Devices
- Myoplasty Laser Catheters
- Organ Storage/Transport Units
- Pacing Leads
- Percutaneous Conduction Tissue Ablation Electrodes
- Peripheral, Coronary, Pulmonary, Renal, Vena Caval and Peripheral Stents
- Replacement Heart Valves

- RF Catheter Ablation and Mapping Systems
- Ultrasonic Angioplasty Catheters
- Vascular and Arterial Graft Prostheses
- Vascular Hemostasis Devices

DENTAL

- Absorbable Materials to aid in the healing of periodontal defects and other maxillofacial applications
- Bone Morphogenic Proteins with and without bone, e.g., Hydroxyapatite (HA)
- Dental Lasers for hard tissue applications
- Endosseous Implants and associated bone filling and augmentation materials used in conjunction with the implants
- Subperiosteal Implants
- Temporomandibular Joint (TMJ) Prostheses

EAR, NOSE AND THROAT

- Auditory Brainstem Implants
- Cochlear Implants
- Laryngeal Implants
- Total Ossicular Prosthesis Replacements

GASTROENTEROLOGY AND UROLOGY

- Anastomosis Devices
- Balloon Dilation Catheters for benign prostatic hyperplasia (BPH)
- Biliary Stents
- Components of Water Treatment Systems for Hemodialysis
- Dialysis Delivery Systems
- Electrical Stimulation Devices for sperm collection
- Embolization Devices for general urological use
- Extracorporeal Circulation Systems
- Extracorporeal Hyperthermia Systems
- Extracorporeal Photopheresis Systems
- Femoral, Jugular and Subclavian Catheters
- Hemodialyzers
- Hemofilters
- Implantable Electrical Urinary Incontinence Systems
- Implantable Penile Prostheses
- Injectable Bulking Agents for incontinence
- Lithotripters (e.g., electrohydraulic extracorporeal shockwave, laser, powered mechanical, ultrasonic)
- Mechanical/Hydraulic Urinary Incontinence Devices
- Penetrating External Penile Rigidity Devices with components that enter the vagina
- Peritoneal Dialysis Devices
- Peritoneal Shunt
- Plasmapheresis Systems

- Prostatic Hyperthermia Devices
- Urethral Occlusion Devices
- Urethral Sphincter Prostheses
- Urological Stents (e.g., ureteral, prostate)

GENERAL AND PLASTIC SURGERY

- Absorbable Adhesion Barrier Devices
- Absorbable Hemostatic Agents
- Artificial Skin and Interactive Wound and Burn Dressings
- Injectable Collagen
- Implantable Craniofacial Prostheses
- Repeat Access Devices for surgical procedures
- Sutures

GENERAL HOSPITAL

- Implantable Vascular Access Devices
- Infusion Pumps (implantable and closedloop depending on the infused drug)

NEUROLOGICAL

- Electroconvulsive Therapy (ECT) Devices
- Hydrocephalus Shunts
- Implanted Intracerebral/Subcortical Stimulators
- Implanted Intracranial Pressure Monitors
- Implanted Spinal Cord and Nerve Stimulators and Electrodes

OBSTETRICS AND GYNECOLOGY

- Antepartum Home Monitors for NonStress Tests
- Antepartum Home Uterine Activity Monitors
- Catheters for Chorionic Villus Sampling (CVS)
- Catheters Introduced into the Fallopian Tubes
- Cervical Dilation Devices
- Contraceptive Devices:
    - Cervical Caps
    - Condoms (for men) made from new materials (e.g., polyurethane)
    - Contraceptive In Vitro Diagnostics (IVDs)
    - Diaphragms
    - Female Condoms
    - Intrauterine Devices (IUDs)
    - New Electrosurgical Instruments for Tubal Coagulation
    - New Devices for Occlusion of the Vas Deferens
    - Sponges
    - Tubal Occlusion Devices (Bands or Clips)
- Devices to Prevent Postop Pelvic Adhesions

- Embryoscopes and Devices intended for fetal surgery
- Falloposcopes and Falloposcopic Delivery Systems
- Intrapartum Fetal Monitors using new physiological markers
- New Devices to Facilitate Assisted Vaginal Delivery
- Thermal Systems for Endometrial Ablation

OPHTHALMICS

- Class III Ophthalmic Lasers
- Contact Lens Solutions intended for direct instillation (e.g., lubrication/rewetting solutions) in the eye using new active agents or preservatives with no history of prior ophthalmic/contact lens use or not generally recognized as safe for ophthalmic use
- Corneal Implants
- Corneal Storage Media
- Epikeratophakia Lenticulas
- Extended Wear Contact Lens
- Eye Valve Implants (glaucoma implant)
- Intraocular Lenses (IOLs) [21 CFR part 813]
- Keratoprostheses
- Retinal Reattachment Systems: fluids, gases, perfluorocarbons, perfluorpropane, silicone oil, sulfur hexafluoride, tacks
- Viscosurgical Fluids

ORTHOPEDICS AND RESTORATIVE

- Bone Growth Stimulators
- Calcium TriPhosphate Hydroxyapatite Ceramics
- Collagen and Bone Morphogenic Protein Meniscus Replacements
- Implantable Prostheses (ligament, tendon, hip, knee, finger)

RADIOLOGY

- Boron Neutron Capture Therapy
- Hyperthermia Systems and Applicators
- Image Guided Surgery