1.0 Purpose:

1.1 To facilitate the proper review and billing procedures for research involving investigational and off-label uses of pharmaceuticals and medical devices at Hartford HealthCare (HHC).

1.2 All investigational or off-label uses of pharmaceuticals and medical devices will be conducted in accordance with the applicable procedures outlined below. This policy is not intended to discourage off-label use or innovation, rather it ensures protections of patients/subjects and regulatory compliance.

2.0 Definitions:

2.1 **Off-Label Use of Marketed Drugs, Biologics and Medical Devices** - use of a product for an indication not in the approved labeling.

2.1.1 When this is done, it is extremely important that the physician take on the "responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects."

2.1.2 According to the FDA, "Use of a marketed product in this manner when the intent is the "practice of medicine" does not require the submission of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE) or review by an Institutional Review Board (IRB)." However, HHC may require IRB review and/or other institutional oversight.

2.2 **Investigational Use of Marketed Drugs, Biologics and Medical Devices** - use of an approved product in the context of a clinical study protocol [see 21 CFR 312.3(b)].

2.2.1 It is important to note the distinction from "Off Label" use, as presented above. When the primary intent of the investigational use of a test article is to develop information about the product's safety or efficacy, submission of an IND or IDE may be required. However, according to 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug or biologic does not require submission of an IND if all six of the following conditions are met:

2.2.1.1 It is NOT intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;

2.2.1.2 It is NOT intended to support a significant change in the advertising for the product;

2.2.1.3 It does NOT involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

2.2.1.4 It is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];

2.2.1.5 It is conducted in compliance with the requirements concerning the promotion and sale of drugs [21CFR 312.7]; and

2.2.1.6 It does NOT intend to invoke 21 CFR 50.24 [Exception from informed consent requirements for emergency research].

3.0 Procedure:

3.1 Medical Device Review

3.1.1 Supply Chain Management must be notified of all medical devices not currently used at the hospital prior to product ordering. Supply Chain Management will determine if an application to the Materials Evaluation Committee or other review is required. Supply Chain Management will make the determination as to whether or not the cost of the device during the research trial is acceptable.

3.1.2 Individuals are encouraged to start this review early in the process because activities involving medical devices not currently used will not be approved, irrespective of other approvals, if the charge for the device is greater than the standard utilized for the planned procedure.

3.2 Off-Label Use in the Context of Research

3.2.1 According to Department of Health and Human Services (DHHS) regulations (45 CFR 46.102), research is defined as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.”

3.2.2 Proposed activities meeting this definition of research must follow HHC Research Institute and Human Research Protection Program (HRPP) policies and procedures to assure compliance with billing and regulatory issues.

3.2.3 *In cases were it is unclear whether or not the proposed activity is research or if the device use is subject to IRB review, (and the federal regulations governing obtaining informed consent), HRPP consultation should be sought.*

3.3 Off-Label Use that is Not Research

3.3.1 If the proposed off-label use does not constitute research, then consideration should be given by the physician as to whether or not a “Special Use Informed Consent Form” [or a note is entered into the Patient’s medical record indicating that the patient gave specific informed consent to the off-label use] should be signed by the patient. The determination of whether or not a proposed use is an off-label use will depend on whether it is consistent with the FDA-approved labeling of the particular device or pharmaceutical.

3.3.2 The physician must determine whether or not the Director of Health Information Management (HIM) needs to be notified to alert the department that the CPT code for the procedure or treatment may be changed to reflect that the special use alters the service as described by its CPT code description. For example, if a procedure becomes substantially more or less complex because of the off-label use of a medical device, there is likely to be a change in the CPT code designation.

3.3.3 Medicare reimbursement for the use of the device must be clarified. Medicare will not provide coverage for non-approved FDA devices ("Category B devices") used outside of a clinical trial. Accordingly, the Hospital's position is that such devices not FDA approved are not to be used outside of approved clinical trials.

Note of explanation: This position is predicated on the unlikely coverage of such services by Medicare. However, the law is unclear with respect to whether the medical services or procedures performed while using approved devices off label are covered. We assume that such services are covered if the use of the device is incident to the medical services and does not alter the service as described by its CPT code description. However, Medicare coverage of such services is unlikely, if a medical procedure or service is performed solely for the purpose of using the non-approved device and such use is outside of an approved clinical trial.

If the FDA has approved a medical device or drug, coverage for an off-label use of that drug or device is generally at the discretion of the individual Medicare contractor. Although the Medicare Program Manuals do not specifically address coverage decisions with respect to off-label uses of approved medical devices, such decisions seem to be analogous to coverage decisions regarding off-label uses of FDA-approved drugs. For example, coverage of an off-label use of an FDA-approved drug (as long as the FDA has not specified such use as non-approved) is determined by taking into consideration the generally accepted medical practice in the community (See Medicare Hospital Manual §210.3). According to the Medicare Carriers Manual, FDA-approved drugs used for off-label purposes may be covered if the carrier determines the use to be medically accepted by taking into consideration major drug compendia, authoritative medical literature and/or accepted standards of medical practice (See Medicare Carriers Manual §2049.4).

3.3.4 Coverage questions should be discussed with the Corporate Reimbursement Director in the Finance Department before submitting claims to Medicare. Information regarding the device, patient diagnosis, and treatment procedure must be provided in order for a coverage determination to be made.

3.4 Use of Investigational Devices (not FDA approved) in Research

3.4.1 The use of investigational devices, that is those devices which have not yet received approval by the FDA, must be covered under a research protocol, and approved by the Institutional Review Board (IRB). As a part of the research application process, an Investigational Device Exemption (IDE) application must be filed with the FDA. Many times the company

supplying the device will already have an IDE on file, and if the use of the device is as described by a company protocol, the company IDE will suffice. If this is not the case, the HRPP Office can provide guidance on how to submit an IDE application to the FDA.

3.4.2 Hospital reimbursement for the investigational device and patient hospitalization must be clarified prior to the scheduling of the patient's procedure, to ensure that there is adequate coverage of the costs associated with the use of this device. In order to accomplish this, the physician must consult the HHC Research Institute Grants Manager. If the patient is covered by Medicare, our local carrier must be notified of the planned use of such devices. For patients not covered by Medicare, approval for payment of the hospitalization and device by the patient's 3rd party payer must occur prior to scheduling the procedure. All of this activity must be coordinated by the HHC Research Institute Grants Manager.

3.4.3 Admitting must be notified that the patient is a research patient when the investigational procedure is scheduled. Therefore, scheduling for these procedures should be coordinated by the financial coordinator in Research Administration. This will help ensure that the proper billing occurs for such patients, and that charges that are not part of routine care and covered by research budgets are charged to the research project's cost center, and not to the patient or 3rd party payer.

3.4.4 The physician must either file a copy of the informed consent for research in the medical record or document in the patient's chart that he or she has been treated utilizing an investigational device, and specify the name of the research protocol for the particular procedure. This is extremely important, because it allows HIM coding staff to distinguish research procedures using investigational devices from conventional clinical care.

4.0 Documentation:

4.1 N/A

5.0 References:

5.1 FDA Guidance: "Off-Label" and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices - Information Sheet (http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm)

5.2 Centers for Medicare & Medicaid Services, Publication #10 – The Hospital Manual (210.3 – Drugs and Biological)

5.3 Centers for Medicare & Medicaid Services, Publication #14 – The Carriers Manual (2049 – Drugs and Biological)

6.0 Revision History:

Rev #	Initials	Effective Date	Description of Change(s)
00	LMB	2/12/02	New Issue – memo issued jointly from VP of Medical Affairs, VP of Professional Services, Director of Research, and Director of HIM; Implemented a process to address billing and risk management issues
01	LMB	6/3/04	Formalization of memo into policy document
02	CLB	7/1/11	Conversion to new policy template; general expansion of policy
03	CLB	3/15/20	General review

Element I.7.A.