1.0 Purpose:

1.1 Impaired decision-making capacity, or impaired consent capacity, occurs in a wide range of disorders and conditions that affect large numbers of Americans and cause suffering, morbidity, and mortality on a large scale. Traumatic brain injury, developmental disorders, intellectual disabilities, and serious mental illness are examples of common and devastating problems in which impaired consent capacity occurs. Current approaches to early detection, diagnosis, and treatment are inadequate, and there is a pressing need to advance therapeutics and understand basic mechanisms of disease and disease progression. Scientific progress requires the inclusion of individuals with impaired consent capacity in research. However, the protections 'provided by free and informed consent are not available to individuals with impaired decision-making capacity; these individuals are uniquely susceptible to exploitation and research related harm. The Common Rule (45 CFR 46) requires that when individuals vulnerable to coercion or undue influence take part in research, "additional safeguards are included."

1.2 The purpose of this policy, therefore, is to ensure the protection of potential and actual research participants with an impaired decision-making capacity, while not unduly preventing valuable research activities potentially involving this population from being conducted.

1.2.1 The policy defines the additional safeguards that all researchers must employ in order for a Hartford HealthCare Institutional Review Board (HHC IRB) to approve the participation of adult individuals with impaired decision-making capacity in research.

1.3 The HHC IRB, the Principal Investigator (PI) and research team will ensure that potential and actual research participants with an impaired decision-making capacity are treated equitably. The IRB is responsible for exercising heightened vigilance in the review of protocols involving individuals with questionable capacity in accordance with 45 CFR 46.111.

1.3.1 The PI and the research team are responsible for the protection of the research participants, exercising discretion as to whether or not additional measures are necessary to involve the participant in the research, and determining if the participant should not take part in the research.

2.0 Definitions:

2.1 **Advanced Directive** – A legal document prepared before any condition occurs which prevents the individual's participation in decision-making that states whether the person wishes to have life-sustaining procedures or treatment administered.

2.2 **Assent -** An individual's affirmative agreement to participate in research. This should be sought in addition to the consent of a legally authorized representative or surrogate when the individual is sufficiently cognitively capable of understanding the nature of his or her participation in a research study. Mere failure to object should not, absent affirmative agreement, be construed as assent.

2.3 **Decision Making Capacity** – refers to an individual's ability to make a meaningful, informed decision. It is generally thought to include the components of understanding, appreciation, reasoning, and expression.

2.4 **Durable Power of Attorney** – An adult person named in a legal document to make medical decision other than withdrawal of life support systems (CGS 19a-562(-5a)).

2.5 **Health Care Agent** – An adult person to whom authority to convey health care decisions involving withholding and/or withdrawing life support systems is delegated in a written document by another adult person, known as the principal (CGS 19a-570(5)).

2.6 **Impaired Consent Capacity** - A compromised capacity to understand information related to the research and to make a reasoned decision about initial or continuing participation in research that may preclude the individual from providing legally effective consent.

2.6.1 Such impairment or compromised capacity may be temporary, permanent, or may fluctuate. Examples of individuals who may have impaired consent capacity include women in active labor, individuals who have suffered a stroke or other acute and severe illness, individuals under the influence of drugs or alcohol, individuals experiencing considerable pain, individuals under extreme emotional distress (e.g., learning of a newly diagnosed life threatening or terminal illness for self or loved one, anticipating imminent major surgery), and individuals suffering from cognitive disorders or mental disorders. ***Impaired consent capacity as defined in this policy is distinct from legal incompetence.***

2.7 **Legally Authorized Representative (LAR) -** An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research.

2.8 **Legal Guardianship** – For a person with mental retardation, this involves a Probate Court's decision that an adult person with mental retardation requires a substitute decision maker for decisions about certain essential areas of the person's life.

2.9 **Legal Incompetence** - refers to a designation of status that has been adjudicated in a court proceeding, and it often refers to an inability to manage one or more significant areas of life such as business or monetary affairs. An individual who is designated as legally incompetent often will have impaired consent capacity in terms of consenting to research but, in some circumstances, will maintain capacity for informed consent. Equally important, an individual may be legally competent, but still have impaired consent capacity.

2.10 **Surrogate Permission** - Permission for an individual to participate in research given by an appropriate surrogate (e.g., next of kin – spouse, parent, child, sibling) when an individual is assessed as not capable of providing fully informed and legally effective consent.

2.11 **Therapeutic Misconception** - The belief that research studies are intended to benefit the participants who enroll in them and that an individual is asked to participate in a research trial as part of his or her clinical care.

3.0 Procedure:

3.1 **General Requirements -** Research involving persons with impaired decision-making capacity may only be approved when at least the following conditions are found to exist (the IRB may, in its discretion, impose additional conditions on the approval of a particular research study seeking to enroll persons with impaired decision-making capacity):

3.1.1 Persons with impaired decision-making capacity are necessary to and appropriate for the research study.

3.1.2 The research has as its goal either to study treatment designed to directly benefit the individual, or the development of important generalizable knowledge regarding the disease or condition of the targeted population.

3.1.2.1 The IRB will consider the nature and degree of anticipated impairment of the targeted study populations, the risk level of the proposed study, and the potential for direct benefit to the study participants.

3.1.3 Except as described in Section 3.2.2.2., a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

3.1.4 “Additional Protections” have been afforded in the protocol to ensure protection of their rights and welfare.

3.1.4.1 Examples of effective strategies include:

3.1.4.1.1 Involving Consent or Study Monitors - Someone independent of the study, e.g., an unaffiliated clinician, to serve as a monitor of the consent process or the entire study may be appropriate for some studies.

3.1.4.1.2 Employing techniques to assess capacity to consent

3.1.4.1.3 Use of Information/Educational Techniques - The way in which information about the study is conveyed to prospective subjects can enhance consent capacity.

3.1.4.1.4 Waiting Periods - Prospective subjects with consent capacity impairments may need to take more time to decide whether to participate in the study. It may be helpful to provide information incrementally and to build in a waiting period after the initial screening

interview, before seeking the subject's formal written consent. A two-step informed consent process would facilitate family conferencing and consultation, and allow more time to weigh the pros and cons of study participation.

3.1.4.1.5 Legally Authorized Representatives and Advance Directives - The HHS and FDA regulations provide for the use of LAR consent as an alternative to a subject's consent.

3.1.4.1.5.1 When LARs are involved, their role should be documented and, after the elements of consent have been reviewed, their consent should be recorded in the informed consent document in the same manner as if the subject were giving consent directly. In addition to receiving information about the study, it is important for LARs to be informed about the role of an LAR and provided information about the health status of the research subject.

3.1.4.1.5.2 Prospective subjects with impaired consent capacity may still have the capacity to use a DPA to designate an LAR. Under these circumstances, involving an independent expert to assess the LAR's knowledge and understanding and the appropriateness of the selection is an additional measure that could be taken.

3.2 **IRB Considerations**

3.2.1 **IRB Composition/Membership**

3.2.1.1 An IRB that regularly reviews research involving vulnerable subjects, such as those with impaired consent capacity, are required by DHHS and FDA regulations to consider whether one or more individuals who are knowledgeable about or experienced in working with such subjects should be included in the review of the protocol

3.2.1.1.1 There may be instances when the review of a research study might benefit from external input and consultation. For example, when there are significant questions about the risks and benefits, uncertainties about the study design, or concerns about the protocol, it may be helpful for the IRB to consult with outside experts in the review of research to provide a broader view of the ethical acceptability of the research.

3.2.1.1.2 To ensure that the HHC IRB is equipped to review studies involving this population of vulnerable subjects, the involvement of the following individuals, either through permanent membership or consultation, will be considered:

3.2.1.1.2.1 professionals with the appropriate background, knowledge and experience in working with individuals with impaired consent capacity;
3.2.1.1.2.2 representatives of patient advocacy groups;
3.2.1.1.2.3 experts in the assessment of consent capacity; and/or
3.2.1.1.2.4 experts on the scientific and ethical issues relevant to studies involving vulnerable populations.

3.2.2 **Responsibilities**

3.2.2.1 When the HHC IRB reviews protocols which study conditions that can result in impaired decision-making capacity it will consider whether additional safeguards are needed. Safeguards can increase on a sliding scale according to the IRB's best judgment. By considering proposed studies on a case by case basis, protections can be provided proportional to the expected severity of consent capacity impairment in prospective subjects, magnitude of experimental risk, anticipated benefits to the subject and/or society, complexity of the study design, and other relevant factors. As study risks and subject consent incapacity increase, additional IRB scrutiny may be needed. It is important to have provisions for additional safeguards in place prior to involving individuals with impaired consent capacity in research.

3.2.2.2 In line with ICH-GCP (E6) guidelines, the IRB will determine that Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

3.2.2.2.1 The objectives of the trial can not be met by means of a trial in subjects who can give informed consent personally.
3.2.2.2.2 The foreseeable risks to the subjects are low.
3.2.2.2.3 The negative impact on the subject's well-being is minimized and low.
3.2.2.2.4 The trial is not prohibited by law.
3.2.2.2.5 The approval/favourable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/ favourable opinion covers this aspect.
3.2.2.2.6 Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

3.3 **Investigator Responsibilities**

3.3.1 Research protocols proposing to involve subjects who have impaired decision-making capacity and cannot give informed consent should include the following information:

3.3.1.1 Thorough justification of the research study design, including why individuals with decisional impairments are necessary to and appropriate for the research, and what safeguards will be taken to minimize risk. Investigators should be sensitive to how a procedure that generally entails little to no physical or psychosocial risks may affect someone who has limited (or no) understanding of the situation.

3.3.1.2 A description of the level of understanding needed to consent to the specific research.

3.3.1.3 A description of who will perform individualized competency assessments and how. If fluctuations in any subjects' competency can be expected, the protocol should describe how the investigator will assess subjects' competency on an ongoing basis, what opportunity subjects will have to appoint legal representatives either early or later in the study, and what educational efforts are planned. In addition, investigators should consider whether a waiting period during the recruitment and consent processes would better permit an individual to reflect on his or her participation and to consult with family members.

3.3.1.4 Address the other safeguards to be used during the recruitment and consent processes to avoid coercion of subjects and surrogates to participate in the research. The safeguards provided should be appropriate for the extent of experimental risk and the severity of the subjects' decisional impairments.

3.3.1.5 An explanation of the type of surrogates proposed to rely upon.

3.3.1.6 Address how the assent of subjects who lack the capacity to consent will be sought and how dissent will be indicated and heeded.

3.3.1.7 If the population of subjects are expected to regain the capacity to consent, indicate consent to continue participating will be sought.

3.3.1.8 Address the investigator will ensure that subjects and their families understand the difference between research and treatment during the entire consent process. Clearly distinguish between treatment and research, and between clinician and investigator, in the consent form. Describe how informed consent document will be documented. Documentation of informed consent, while always important, is especially critical when a person has been determined to lack capacity to consent to research and someone else is giving informed consent. Relevant

support should be included in research records (including, for example, the basis of the determination of the subject's lack of consent capacity, and a copy of the appropriate LAR paperwork designating the individual as such).

3.3.1.8.1 Note that the IRB will not waive the requirement that a surrogate's consent be in writing, except in exceptional circumstances (consult with the HRPP office telephonic or other oral consent is proposed).

3.3.2 **Assessment of Capacity to Provide Consent**

3.3.2.1 It is important to take prospective subjects' abilities, impairments, and needs into account when considering whether to invite them to participate in research.

3.3.2.2 Research studies designed to involve some or all individuals with impaired consent capacity must include a means to assess a potential participant's capacity to provide consent and the criteria for identifying individuals who are impaired.

3.3.2.3 In general, an assessment of an individual's capacity to consent should be based on her/his:

- Ability to communicate a reasoned choice regarding participation;
- Ability to understand relevant information about the study, including consequences of participation for the participant's own situation (such as health condition) and consequences of the alternatives to participation;
- Ability to comprehend the nature of the situation and its likely consequences; and
- Ability to manipulate information rationally.

3.3.2.4 A range of methods may be used to assess decisional capacity. The assessment of decision-making will be protocol-specific and should be commensurate with the level of risk to the participant, the complexity of the research, and the anticipated duration of the participant's involvement.

3.3.2.4.1 In general a qualified professional should assess the individual's competency. This should include a formal psychiatric and/or medical assessment that considers what level of understanding is needed for the specific research.

3.3.2.4.2 General competency measures – such as the Clinical Dementia Rating (CDR), the Activities of Daily Living scale, or the Mini Mental Status Exam (MMSE) – may be helpful, but generally should not be the sole measure of competency.

3.3.2.4.3 More formal assessments may include a standardized assessment of decisional capacity, such as the MacArthur Competence Assessment Tool – Clinical Research (MacCAT-CR) or a post-

content quiz demonstrating the subjects' knowledge of critical elements in the informed consent document. Such questions could include the purpose of the study, voluntary nature of the study, ability to withdraw, confidentiality, risks of the study, or other key elements of consent. For subjects who score less than perfect on the initial presentation, educational procedures may be used to facilitate their understanding; including a more detailed discussion of the items they have difficulty recalling. The quiz can then be repeated.

3.3.2.5 In order to strengthen the integrity of the enrollment process, in any research involving more than a questionnaire or cognitive test – such as a study of a new medication – consideration should be given to using an independent professional (who is not part of the research team) to assess a potential subject's competency.

3.3.2.6 The assessment method must allow for a repeat assessment of the capacity to consent if the potential participant's condition changes or is expected to change. Subsequent assessment for capacity to provide continuing consent is especially important upon the introduction of a new or different intervention along the course of research.

3.4 **Consent/Assent Considerations**

3.4.1 Individuals who are temporarily impaired due to environmental or other factors (e.g., women in advanced and active labor, individuals under the influence of drugs or alcohol, individuals under extreme emotional distress) should not be asked to participate in research until they regain their sound decision-making ability and can provide consent.

3.4.1.1 However, in the event that the research is designed to study individuals in precisely those situations and/or states of mind, whenever practical, investigators should design the research project so that participants will be appropriately consented and enrolled prior to the temporary decisional impairments. If this is not feasible, the consent of the individual should be sought once the individual regains capacity. Investigators must respect the wishes of the individual, should the individual object to the use of his/her research information, and research data will be excluded from the study.

3.4.2 For research contemplating enrolling participants who are not able to provide informed consent at the outset of the study, **permission from a surrogate for their participation must be approved by the IRB**. Participants enrolled in research without their consent must be offered the opportunity to consent to or withdraw themselves (and their study information or samples) from the research once they regain capacity. Investigators must respect the decision of the participant.

3.4.2.1 To the extent that next of kin (surrogate) consent is not expressly permitted under the Connecticut State law, the HHC IRB will

apply a risk continuum similar to the rules relating to parental permission for participation by a child in a research study (45 CFR 46.404, 405, 404 and 21 CFR 50.2, 53). In general, if there is scientific evidence to show that the experimental treatment is better than the available treatment, poses minimal or not unreasonable risk, is likely to provide direct benefit to the patient, and additional protections are implemented, surrogate consent may be deemed appropriate by the IRB.

3.4.2.1.1 The order of authority to provide consent as an LAR/surrogate on behalf of another adult for participation in clinical research is as follows:
- Spouse
- Adult child
- Parent
- Adult sibling

3.4.3 The HHC IRB shall abide by Connecticut state statutes that explicitly prohibit court-appointed guardians of mentally retarded persons from giving permission for their wards to participate in research unless very specific terms and conditions are met (CGS Sec. 45a-677(e)).

3.4.4 For research involving participants who are able to provide informed consent at the outset of the study, but who are expected to have fluctuating, limited, or diminishing capacity to provide continuing consent during the course of the study, special procedures should be implemented to assure that participants' rights and safety are continually protected. Establishing an advanced directive for research purposes is one procedure that would be appropriate.

3.4.5 Assent must be sought when the individual is sufficiently cognitively capable of understanding the nature of his or her participation in a research study and capable of communicating. Where assent is required, mere failure to object may not, absent affirmative agreement, be construed as assent. The prospective participant's objection to participate in any way, at any time, must be taken as a refusal or withdrawal and be honored, even if the surrogate consenter or the study doctor disagrees with the decision. However, for some studies, withdrawal may still require research interventions such as tapering off of medication or other important procedures to protect participant safety and well-being. Withdrawal consequences should be made explicit in the consent and assent forms.

3.4.6 **Therapeutic Misconception and conflicting roles**

3.4.6.1 One of the key ethical challenges in informed consent is to ensure that subjects understand the difference between research and treatment, including the study investigator's focus on producing generalizable knowledge rather than providing clinical care. While this ethical challenge exists across the spectrum of clinical research, and is often referred to as the "therapeutic misconception," it can be heightened in research involving subjects with consent capacity impairments. It is, therefore, especially critical in this field for the informed consent process and documents to be very clear about these differences. The

description of the clinical study can be a particular source of confusion, so special attention to the wording of the study purpose and precision about experimental procedures is especially important. Another critical point that needs to be addressed clearly is whether study participation will have any effect on access to clinical care.

4.0 Documentation:

4.1 The IRB shall prepare and maintain adequate documentation of IRB activities related to research reviewed regarding the involvement of this vulnerable population. Minutes will document the risk category under which the protocol is approved, as well as determinations specific to surrogate permission.

4.2 The HHC HRPP office will maintain documentation related to IRB review of studies involving individuals with impaired decision-making capacity, 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 six (6) years after completion of the study.

5.0 References:

5.1 45 CFR 46.102(i)

5.2 45 CFR 46.111(b) and 45 CFR 46.116

5.3 21 CFR 50.3, 21 CFR 56.111(a), 21 CFR 56.111(b)

5.4 ICH-GCP: 4.8.13 and 4.8.14

5.5 NIH – "Research Involving Individuals with Questionable Capacity to Consent: Points to Consider" (November 2009) http://grants.nih.gov/grants/policy/questionablecapacity.htm

5.6 July 15, 2009 Secretary's Advisory Committee on Human Research Protections (SACHRP) letter to HHS Secretary (http://www.hhs.gov/ohrp/sachrp/20090715lettertohhssecretary.html)

5.7 Attachment to July 15, 2009 SACHRP Letter – Recommendations from the Subcommittee for the Inclusion of Individuals with Impaired Decision Making in Research (SIIIDR) (http://www.hhs.gov/ohrp/sachrp/20090715letterattach.html)

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

5.9 Appelbaum, PS, and Grisso, T: MacArthur Competence Assessment Tool for Clinical Research (MacCATCR), Professional Resource Press, Law and Psychiatry Program, University of Massachusetts Medical School, Worcester, MA, 2001

6.0 Revision History:

Rev #	Initials	Effective Date	Description of Change(s)
00	CLB	7/1/11	New Issue
02	CLB	7/22/15	Added requirements for consent by LARs for non-treatment trials as applicable to ICH-GCP (E6)
03	CLB	3/15/20	General review. Update definition of LAR per Revised Common Rule

Elements, II.4.A., II.4.B., and III.1.C.