YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE
Instructions for the Application to Involve Human Subjects in Biomedical Research
100 FR 1a (2012-3)

Answer all questions on the form with font size 12. If a section is not applicable, please indicate "Not Applicable" under the section heading. DO NOT STAPLE DOCUMENTS SUBMITTED. Submit one (1) original and two (2) copies to the HIC.

INTRODUCTION: WHEN THE HIC APPLICATION SHOULD BE USED

Researchers at the Yale University School of Medicine, School of Nursing and School of Public Health are required to submit to the Human Investigation Committee (HIC) for review any biomedical research protocol that requires review or approval by an Institutional Review Board (IRB) as defined pursuant to federal regulations or University policy. See Policy 1360 Human Research Protection at http://www.yale.edu/hrpp/resources/docs/1360_revised06-10-10.pdf

Investigators must utilize the Application to Involve Human Subjects in Research http://www.yale.edu/hrpp/forms-templates/biomedical.html to complete their submission to the HIC unless noted below. (For further information or guidance call the HIC at 203.785.4688, or email at YSMHIC@yale.edu.)

- The research is conducted either fully, or for the most part, at another institution and an IRB other than the HIC has been designated by that institution to review the protocol on the institution's behalf (Example: A protocol largely conducted at the West Haven VA or at Hartford Hospital that will be reviewed by their respective IRBs.) In this scenario, the Yale researcher should submit the protocol in the format of the institution where the research will be fully/largely conducted and use the HIC application to include information that is not accounted for in the application or protocol for the other IRB. Note the enrollment of persons at a Yale or YNHH facility will require that the consent document be written utilizing the Yale consent template format. http://www.yale.edu/hrpp/forms-templates/biomedical.html
- The research is conducted in accordance with the University's Assurance in which another IRB is designated as Yale's IRB of record through an established IRB Authorization Agreement ("IAA") between the parties. Example: Western IRB or National Cancer Institute
- Central IRB. Informed consent documents must be written utilizing the Yale consent template format.
- The researcher aims to collect data or biological specimens for the purpose of developing a repository to be used for future research projects. Investigators should use the Repository Application http://www.yale.edu/hrpp/forms-templates/biomedical.html.
- The researcher believes that the research may qualify for exemption from IRB review. The researcher should submit the protocol utilizing the Exemption Request form to obtain an exemption determination from the HIC. http://www.yale.edu/hrpp/forms-templates/biomedical.html
- The researcher aims to conduct a retrospective analysis of identifiable data stored either in a University system or the patient's medical record(s). The research should submit the protocol utilizing the Medical Record Review Form http://www.yale.edu/hrpp/forms-templates/biomedical.html

- The researcher aims to conduct an analysis of currently available data or biologic specimens, which are received by the researcher in a coded manner (no direct identifiers) and believes that the HIC may determine that the project does not involve human subjects. Use the Not Human Subjects Research Form http://www.yale.edu/hrpp/forms-templates/biomedical.html

SECTION I: ADMINISTRATIVE INFORMATION

Insert the title of the project, the principal investigator (PI) name, Yale academic appointment, degrees (MD, DO, PhD, JD, MS, MPH etc.) and contact information (campus address, phone and fax numbers, e-mail address). Include the name and contact information of the correspondent responsible for this protocol if different from the PI.

The following members of the research team are required to disclose protocol-related interests:

Principal Investigators, any research personnel who are responsible for the design, conduct or reporting of this project. The Principal Investigator (Project Director), upon consideration of the individual's role and degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

List any of the above-referenced study personnel who have a conflict of interest for this study.

Department Chairs or their designees are required to continue to disclose any personal financial or non-financial relationships related to the protocol to the Principal Investigator and the IRB.

- When an interest is identified has having or having the potential to adversely affect the protection of research participants or the integrity of the research, then the PI and/or IRB must determine whether or not the interest needs to be managed, minimized or eliminated.

All investigators and study personnel as described above are required to read the Yale HRPP Policy 500, Disclosures and Management of Personal Interests in Human Research (http://www.yale.edu/hrpp/policies/index.html#COI) and the Yale University Policy http://www.yale.edu/provost/html/coi.html .) The HRPP policy addresses protocol-specific conflict of interest, and is distinct from the annual disclosure required by the Yale University Policy on Conflict of Interest and Conflict of Commitment.

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends to Yale University personnel and to Yale New Haven Hospital co-investigators listed on a protocol with a Yale University Principal Investigator. All other researchers listed on the protocol are only required to disclose to the PI any interests that are specific to this protocol.

SECTION II: GENERAL INFORMATION

1.a. Performing Organizations or Location[s] of the Study: Identify all hospital(s), in-patient or outpatient facilities, schools or other location(s) where the Yale PI, study personnel or other researchers are performing or participating in research activities associated with the protocol. This includes all international locations. Protocols conducted in community agencies or organizations must include a letter from the organization giving permission for the conduct of research at their site, using their facilities, and/or accessing their client population. If agency staff are included in the conduct of the research, contact the HRPP for information and instructions.

1.b. External Performing Organizations and Locations: Additional Institutional Review Board (IRB) approvals may be required from the other participating location(s) when representatives or agents from the location are engaged in the research and overseen by a duly appointed IRB or Ethics Committee (e.g. when research scientists representing another domestic or foreign academic research institution, school or healthcare facility are participating in the research). Some institutions require IRB approval for research that is conducted at their institution or aims to study the institution's patients, staff or other personnel, even when the institution's representatives are not listed as members of the research team (e.g., a Yale researcher wanting to conduct research at a state university on its student population may be required to obtain the approval from that university's IRB prior to enrolling the students in the research). Finally, note that a special license may be required for international research planned with an individual or entity from a country on the embargoed list (currently Iran, Cuba, North Korea, Sudan, Syria, and Burma/Myanmar), Contact Don Deyo in GCA for additional instruction.

Protocols Requiring External IRB Approval:

Research activities that are conducted by Yale investigators at a location other than Yale, or that are conducted at Yale in collaboration with investigators representing an institution or organization other than Yale University may require approval from that location's local IRB. Generally, IRB review must be provided by the location's local IRB when employees or agents from that location, for the purposes of the research project, obtain (1) data about the research subjects through intervention or interaction with them or (2) identifiable private information about the subjects. Yale investigators collaborating with researchers from external institutions or organizations must submit a copy of the local IRB's review to the HIC (e.g., Yale researcher serving as the Principal Investigator of a research project which includes collaborating with colleagues from the UCONN Health Center. Approval is required from the UCONN IRB when the activities performed by the colleagues include those cited above). To determine whether a collaborating site is represented by a local IRB, see http://ohrp.cit.nih.gov/efile/

When a Yale researcher wishes to collaborate with investigators from an organization that is not represented by a local IRB or an investigator who is not represented by any organization, other agreements may be necessary. Some of the organizations listed in the Location section of the HIC application Section II have filed Federalwide Assurances with federal authorities and are permitted by formal agreement with Yale to designate the Yale IRBs as their "IRB of record". This means that the

Yale IRB review, conducted on behalf of the Yale investigators, will also satisfy the IRB review requirement for researchers from these external organizations. Note, however, that the agreement with Yale may limit the IRB designation to a single research project, and the agreement would require modification to cover new research projects. Contact the HRPP office should additional information be needed regarding Research Affiliates. When Yale investigators collaborate with individuals from an external institution without a local IRB or an agreement with Yale, it may be necessary for that institution/organization to record its own Assurance with OHRP and designate an IRB to review its research. An institution/organization that is routinely involved in the conduct of federally-funded human research is required to file an Assurance and designate an IRB. If the collaborating institution/organization wishes to designate Yale as its IRB, and become a Research Affiliate, they should review the Research Affiliate web site, http://www.yale.edu/hrpp/affiliates/index.html , and contact the HRPP office. Research affiliate agreements are generally limited to studies in which a Yale full time faculty member serves as Principal Investigator. The review of the research by an IRB representing the external institution/organization must take place prior to such representatives participating in the research.

In some cases, as an alternate to the research affiliate process, Yale may extend the application of its own Assurance to include investigators from institutions/organizations without an IRB or those investigators acting independent of an organization, by exercising a Collaborating Investigator Agreement. For more information regarding the conditions when an external investigator may collaborate with a Yale principal investigator in the conduct of research via a Collaborative Investigator Agreement see HRPP Policy 910, Collaborating Investigators, at: http://www.yale.edu/hrpp/policies/index.html#MembershipsAgreements

Finally, the local IRB review and approval of the involvement of a consultant or other investigator may not be required if he/she does not obtain (1) identifiable data about the subjects through intervention or interaction or (2) identifiable private information about the subjects of the research. For more information about when the research activities of these persons may require IRB approval, call the HRPP office.

1.c. Additional Required Documents: Some studies may need committee review and/or approval from other research oversight committees, or their designee, **before** the protocol may be submitted to the HIC. The HIC may not **finalize** its **approval** of the study until documentation of approval by some of the committees listed on the application **is received** by the HIC from the investigator or the committee.

Review by the oversight committees noted below, or their designated reviewers, must be conducted before submitting the protocol to the HIC. A letter documenting that the review and approval has taken place must be attached to the protocol when submitting it to the HIC. At times an oversight committee may not issue final approval until explicit revisions are made, but the committee still permits the investigator to submit the protocol to the HIC for review. In this circumstance, the protocol submitted to the HIC must have incorporated or otherwise addressed the revisions required by the oversight committee(s).

Oversight committees that must review the protocol prior to its being submitted to the HIC include; the **Yale Center for Clinical Investigation** (YCCI), the **Pediatric Protocol Review Committee** (PPRC),

the **Radioactive Drug Research Committee** (RDRC) and the **Yale Cancer Center- Protocol Review Committee** (PRC).

For studies conducted exclusively at the **Department of Veterans Affairs,** or conducted both at the VA and Yale facilities, a letter of approval from the Human Subjects Sub-Committee (VA- HSS) **must** accompany the protocol submission. Additional information regarding which protocols must be reviewed by these committees is noted below.

Protocols Utilizing, the Yale Center for Clinical Investigation (YCCI) Resources and/or Services:
Protocols requiring utilization of YCCI service(s) and/or its resource(s) require submission to the YCCI Office for Research Services (ORS) for review and approval prior to submitting the protocol to the HIC. The ORS will determine whether approval can be granted or whether the protocol requires further review by the YCCI-Science and Safety Committee (YCCI-SSC). For instruction on how to proceed please contact Theresa Katz at theresa.katz@yale.edu

Pediatric protocols requiring utilization of YCCI service(s) and/or its resource(s) require submission to the YCCI-ORS for review and approval. The ORS will determine whether the protocol can be approved or requires further review by the PPRC prior to submission to the HIC. For instruction on how to proceed contact Theresa Katz at theresa.katz@yale.edu

Protocols Requiring Review by the Pediatric Protocol Review Committee (PPRC):
Protocols that include children as research subjects and (a) are conducted by a Principal Investigator whose primary faculty appointment is from the Yale School of Medicine, Epidemiology and Public Health, or (b) use the resources of YNHH (whether conducted by Yale School of Medicine, Yale School of Nursing, Yale the YNHH Pediatric Dental Clinic, or Yale research affiliates) must be submitted to the Pediatric Protocol Review Committee (PPRC). Review by the PPRC is necessary prior to submitting the protocol to the HIC. (Note the exception: pediatric oncology protocols must utilize the PRC below.) For instruction on how to proceed with PPRC review contact Theresa Katz at theresa.katz@yale.edu

Protocols Requiring Yale Cancer Center Protocol Review Committee (PRC) Review:
Under the guidelines of the National Cancer Institute (NCI), and in conjunction with the Cancer Center Core Grant, PRC review and approval is required for all protocols related to cancer. This review must be obtained prior to submission of the research proposal to the HIC. The HIC will not accept any submission that does not have PRC review or approval documentation, including meeting minutes for initial protocol submissions. PRC approvals with recommendations must be submitted to the HIC with either the recommended changes incorporated into the protocol or an explanation why they are not. PRC approvals with comments requiring a response must include the PRC meeting minutes, the PI's response to the PRC, and the final PRC approval. More information regarding submissions to the PRC can be found at http://medicine.yale.edu/cancer/research/trials/services/review.aspx

Protocols Involving the Department of Veterans Affairs, West Haven (WHVA): All investigators who are located at the WHVA and have an academic appointment at Yale must submit their research project to the Yale HIC for review even when the research is conducted exclusively at the WHVA. All studies that are conducted **exclusively** at the WHVA must obtain approval from the WHVA IRB (VA-

HSS) **prior** to submission of the research project to the HIC. For protocols conducted solely at the WHVA, the HIC accepts the WHVA application in lieu of the Yale application. See the document, "How Many Copies" on the HRPP forms website.

Protocols Utilizing Radiation:

Any protocol involving the use of ionizing radiation for research in humans that is not the standard of care must be reviewed and approved by the Yale New Haven Hospital Radiation Safety Committee (RSC) or the Radioactive Drug Research Committee (RDRC), before implementation. Human research protocols involving ionizing radiation that is not the standard of care must also be approved by the Yale University Radiation Safety Committee (YURSC) when the research is conducted at facilities owned by Yale University, such as the Yale University PET Center.

Approval from the RDRC is required prior to submitting the protocol to the HIC for review. However, the protocol may be submitted to the YNHH-RSC or the YURSC and the HIC simultaneously. The HIC will not issue final approval until proof of YNHH-RSC approval has been submitted to the HIC. See HRPP Policy 940, Radiation Safety Reviews at: http://www.yale.edu/hrpp/policies/index.html

Protocols Utilizing the Magnetic Resonance Research Center at the Anlyan Center:

Any research protocol involving humans and the use of equipment, supplies, or space in the Magnetic Resonance Research Center (MRRC) located in the TAC building, whether or not the scan is standard of care, should be reviewed and approved by the MRRC- Protocol Review Committee (MRRC-PRC) before the research can commence. Protocols that use magnetic resonance techniques at other facilities, such as Yale-New Haven Hospital's clinical facility, are not subject to review by the MRRC-PRC. Instructions for submitting protocols to the MRRC-PRC can be found at http://mrrc.yale.edu/users/index.aspx and the required "MRRC Proposal for Use of MRRC Resources" can be found at http://mrrc.yale.edu/search.aspx?q=proposal+for+use&x=0&y=0&site=YSM_Bioimaging_MRRC.

Protocols Utilizing the Yale University School of Medicine/Yale-New Haven Hospital Cancer Data Repository (CaDR):

Investigators who are not faculty members of the Department of Pathology who wish to access data that are maintained within the Cancer Data Repository (Tumor Registry) (CaDR) for research purposes are required to obtain HIC approval of the research protocol prior to initiating any requests to access the data. Investigators must also complete and submit the *Yale University School of Medicine/Yale New Haven Hospital Cancer Data Repository Request for Information Form* along with the protocol submission. The Principal Investigator will be required to submit a copy of the HIC approval and the CaDR form that has been signed and stamped by the HIC to the Pathology Informatics Program when requesting the data. For more information see http://www.yalepath.org/CaDR/data.htm

The CaDR form requirement does not pertain to requests by investigators to conduct activities considered preparatory to research.

Protocols Utilizing the Department of Laboratory Medicine

The hospital laboratories may be asked to participate in research studies in several ways: 1) by performing laboratory tests on subject samples, on animal samples, or on other materials, such as solutions or devices; 2) to "spin and save" samples for research studies; 3) to provide excess clinical samples (with or without individual identifiers) to researchers; or 4) to provide test result data. For more information on procedures for initiating such research, and for more about the Department's role in

research see http://medicine.yale.edu/labmed/research/testing/index.aspx. Note departmental timeframes for processing requests.

Protocols Utilizing Yale New Haven Hospital and Yale University Diagnostic Radiology

In an effort to streamline the process for imaging services on YNHH equipment and to ensure appropriate agreement of imaging protocols with clinical trial protocols, a combined YNHH and Yale University Diagnostic Radiology form is now required. Although HIC approval will not be contingent on approval of the YDRCTO application at this point in time, this form is required for imaging services performed on YNHH Diagnostic Radiology hospital equipment. Forms can be found at http://radiology.yale.edu/research/ClinTrials.aspx and should be submitted to the Yale Diagnostic Radiology Clinical Trials Office listed on the form.

2. Probable Duration of Project: The duration of the project must be a defined period of time and cannot be indefinite. **NO** research activities can commence prior to receiving IRB approval.

3. Research Type/Phase: (Check all that apply)

a) **Study Type**: Indicate the type of study being proposed. Yale investigators who are the Principal Investigator of a multi-center study must also indicate this on the form and be aware that there are specific responsibilities unique to this designation. It is the responsibility of the PI to implement a system in which data are monitored and adverse events are evaluated and reported from each site to the appropriate site monitor, DSMB, other investigators and IRB(s). It is also the responsibility of the PI to maintain copies of appropriate IRB documents from the IRB of each study site.

b) **Study Phase:** Indicate the phase of the study.
Pilot Studies are usually small preparatory investigations that comprise a very small number of subjects and are not intended to directly investigate or test the research hypotheses of interest..

According to the FDA:

Phase I includes the initial introduction of an investigational new drug into humans. These studies are closely monitored and may be conducted in patients, but are often conducted in healthy volunteer subjects, as they are not designed to provide benefit. These studies are designed to determine the metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness.

Phase II includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition. This phase of testing also helps determine the common short-term side effects and risks associated with the drug.

Phase III studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained (Phase II), and are intended to gather the additional large scale information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug.

Phase IV studies, also known as post-marketing studies, are designed to delineate additional information including the drug's risks, benefits, and optimal use once the FDA approval has been granted.

4. **Areas of Research**

This section attempts to collect specific attributes about each protocol that are used by the University for research administration reporting and monitoring purposes. Please check all that apply.

Clinical Research: The NIH defines categories of human clinical research using a three-part definition as summarized below. Clinical research is research in which it is necessary to know the identity of the patient from whom the cells, tissue, specimens or data are derived.

- **Patient-Oriented Research**: Research conducted with human subjects (or material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects or their identifiable data. Excluded from this definition are in-vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) research on mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, (d) development of new technologies.

- **Epidemiologic and Behavioral Research:** Clinical research in this area is divided into five categories: (a) research on the identification and understanding of risk and protective factors associated with the onset and course of illness, and with health conditions; (b) research on the effects of illness or physical condition on behavioral and social functioning; (c) treatment outcomes research; (d) research on health promotion and disease prevention (i.e., behavioral interventions); and (e) research on institutional and organizational influences on health.

- **Outcomes Research and Health Services Research:** Clinical research in this area is done to understand the results of health care practices and interventions. It is necessary to know the identity of the patient from whom the cells, tissue, specimens or data are derived, in order to correlate the impact of care or interventions on the health outcomes of patients and populations.

- **Translational Research #1 ("Bench-to-Bedside"):** The process of applying discoveries generated during research in the laboratory, and in preclinical studies, to the development of trials and studies in humans. Included in this category is some research using animal models that represent the final steps immediately prior to the development of human protocols or FDA filings. It also includes the development of technological modifications needed to translate laboratory techniques into use in humans and the validation of these techniques in humans.

- **Translational Research #2 ("Bedside-to-Practice")**: Research aimed at enhancing the adoption of best practices in the community. It includes investigation of the effectiveness of interventions in real-world settings and the transfer of evidence from randomized controlled trials into practice.

- **Interdisciplinary Research:** A mode of research by teams or individuals that integrates information, data, techniques, tools, perspectives, concepts, and/or theories from two or more disciplines or bodies of specialized knowledge to advance fundamental understanding or to solve problems whose solutions are beyond the scope of a single discipline or area of research practice.

- **Community-Based Research:** Broadly defined, community-based research takes place in community settings and brings together researchers and community partners with the purpose of

solving a pressing community problem or effecting change in the community. This may or may not include community-based participatory research (CBPR), a collaborative process that begins with a research topic of importance to the community and involves community members in the design and implementation of the research projects.

5. Trials requiring registration with ClinicalTrials.gov include:
   - **Trials** that are required to be publicly registered in accordance with the International Committee of Medical Journal Editors (ICMJE)
   - **Trials of Drugs and Biologics**: Controlled clinical investigations, other than Phase I investigations, of a product subject to FDA regulation
   - **Trials of Devices**: Controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, and pediatric post market surveillance

   For more information see http://medicine.yale.edu/ycci/researchers/ors/registerstudy.aspx

6. This question is provided as a courtesy to the Yale Medical Group and helps to ensure that research trials rendering clinical services use proper billing methods. Determine whether or not the study includes a billable service as defined by the Billable Service Definition. If you answer "yes", please register this study in the IDX/GE system at http://medicine.yale.edu/ymg/systems/ppm/index.aspx

7. This question is provided as a courtesy to Yale New Haven Hospital (YNHH), to ensure appropriate credentialing for research interventions. If you answered "no" to question 7a, or "yes" to question 7b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

SECTION III: FUNDING, TRAINING AND PROTOCOL-RELATED CONFLICT OF INTEREST

1. **Funding Source:** Identify all funding source(s) for this study and whether the study is funded by internal funds such as departmental funds or CTSA funding. Investigators are advised to indicate the department from which they are paid a salary if there is no other identified funding source. Indicating that there is no funding is not acceptable.

   It is necessary to identify whether the study is funded or supported by an external funding source such as a grant from a federal or private agency, contract from a pharmaceutical company or other entity, or a sub-contract from another university or research organization.

   Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grant-funded). If the funding source associated with a protocol is "pending" at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note "Pending" in the appropriate section of the protocol application, provide the M/C# and Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

Important Note: If using more than one funding source for this study, list **all** funding sources.

IRB Review fees are charged for projects funded by Industry or Other For-Profit Sponsors. Provide the Name and Address of the Sponsor Representative to whom the invoice should be sent. ***Note: the PI's home department will be billed if this information is not provided.***

2. **Research Team**: Indicate the name, degrees, title and affiliation and NetID of the PI, co-investigators/collaborators, and all study personnel, using the chart provided on the form. List all individuals who are ***engaged*** in the research, meaning, in general, that the individuals, for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research. See OHRP guidance at http://www.hhs.gov/ohrp/policy/engage08.html for more information.
    - The ***Principal Investigator*** is the one individual responsible for directing the research project. The principal investigator must ensure the proper conduct of the project or program. Yale policy, as outlined in the faculty handbook, requires that only those who have the requisite training and skill, as well as the appropriate relationship to Yale, may normally serve as the principal investigator or project director. The policy states that only full-time faculty with an appointment as assistant professor, associate professor, professor, research scientist/scholar, or senior research scientist/scholar may serve the role. Exceptions require the approval of the Provost, or where appropriate, the Dean of the relevant professional school, or the Human Subject Protection Administrator of the Yale-New Haven Hospital. For further information on who can serve as a PI see http://www.yale.edu/provost/html/facultyhb.html
      To obtain the form needed to request permission to serve as a PI see http://www.yale.edu/hrpp/forms-templates/biomedical.html .
      Students, fellows, post-doctoral appointees or other trainees may serve as principal investigator when under the oversight of a designated faculty advisor. The faculty advisor must sign the HIC application attesting appropriate oversight of the student/trainee researcher.
      Associate Research Scientists may work under the oversight of a designated faculty advisor, or request to serve as PI by completing the Request for Permission to Serve as PI Form at http://www.yale.edu/hrpp/forms-templates/biomedical.html.
    - The ***Co-Investigator/Collaborator*** is an individual working with the PI in the scientific development or execution in a substantive, measurable way, whether or not salary or compensation is received. The co-investigator (collaborator) may be employed by or be affiliated with Yale or another organization participating in the project under a collaboration agreement.
    - ***Study Personnel*** are individuals involved in the design, conduct, and/or the analysis of identifiable data for the research, or are otherwise engaged in the research. The definition does not usually extend to include persons performing only clinical activities. For example it usually is unnecessary to list as study personnel a nurse who is drawing blood from a subject as part of the subject's clinical care. However, if the nurse is obtaining consent or acting as an authoritative representative of the investigators for the research protocol, then it is necessary to list him/her as study personnel. It also does not extend to individuals analyzing de-identified data (see note below).

- ***Consultant***: an individual who provides professional advice or services. Individuals who will be **analyzing de-identified data only** should be included in the research plan or statistical analysis section of the protocol as consultants, and not listed on the chart as co-investigators or study personnel.

Under the column heading **Affiliation,** it is important to indicate the name of the institution that each research team member represents or where they hold their primary appointment (i.e., who pays their salary). Depending upon the role of the individual or institution, it may be necessary to obtain local approval from that institution's IRB. (See Section II.a and II.b above.)
NetIDs are required for all Yale personnel listed on the study, so the IRB can access accurate training information.

3. **Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act Training (HIPAA):** All investigators and study personnel listed on the protocol as members of the research team are required to complete basic HSPT, and to complete a continuing education course in human research protections every three years. The basic HSPT requirement can be met by completing the Yale web-based program or the CITI basic human research protection course, both available through the Yale training and certification website, http://www.yale.edu/training/ or by completing the NIH program at http://phrp.nihtraining.com/users/login.php . The continuing education requirement can be met by attending any Human Research Protection Program educational session, or by completing any one of the Yale human research modules or any one of the CITI continuing education modules available through the training and certification website, http://www.yale.edu/training/. Training in the use of the Coeus electronic submission system does not meet the continuing education requirement.

   All School of Medicine and School of Nursing investigators and research staff, and all School of Public Health investigators working on a School of Medicine or School of Nursing protocol are required to also complete HIPAA training. The HIPAA training requirement can be met by completing the Yale web-based HIPAA training program at http://learn.med.yale.edu/hipaatraining/ or reading the Researcher's Guide to HIPAA Privacy at http://www.yale.edu/hrpp/forms-templates/hipaa.html and returning the last page signed as an attestation that the guidance has been reviewed. If an individual has completed either training requirement(s) at another institution or through a different non-Yale training course, a copy of the certification must be submitted to the HIC and may satisfy the University requirements. All investigators and study personnel must complete these training requirements prior to participating in research activities.

Note: The HIC will reject a protocol submission if the Principal Investigator has not completed required training, and will remove from the protocol any research personnel who have not completed the required training. An amendment to add personnel will need to be submitted when training is complete.

SECTION IV: PRINCIPAL INVESTIGATOR/FACULTY ADVISOR AGREEMENT

Carefully read this entire statement prior to signing. The principal investigator of the research project must sign the certification statement.

Faculty Advisor. If the principal investigator is a student, resident, fellow, or other trainee, the Yale IRB requires that a faculty advisor be appointed to oversee the conduct of human research. The faculty advisor must meet the Yale University policy requirements for serving as the principal investigator of an HIC application and sign the certification statement. For further information on who can serve as a principal investigator see http://www.yale.edu/provost/html/facultyhb.html .

The **Department Chair's Assurance Statement** must be signed and completed by the Chair of the department where the principal investigator and co-investigators hold their primary appointment and/or from which departmental resources are used to support the research project.

When the PI is **solely** affiliated with Yale-New Haven Hospital and not the School of Medicine, Public Health or Nursing, it is necessary to obtain the signature of the YNHH Human Subjects Protection Administrator (Ms. Stuart Warner, J.D.). The administrator will attest to the qualifications of the PI and affirm that there are no known undisclosed COIs either with the institution or the investigator and that the investigator can serve as PI (see COI section above). Stuart Warner can be contacted at (203) 688-2291 or stuart.warner@ynhh.org.

Applications will **not** be accepted by the HIC office without the required review and signatures described above.

SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aims of the study, or the hypotheses to be tested.

2. **Background:** Describe the background information that led to the plan for this project. Please provide references that support the expectation of obtaining useful scientific data. When available, previous work in animal and/or human studies should be included.

3. **Research Plan:** Provide an orderly scientific description of the intended procedures as they directly affect the subjects. Include the number and estimated length of hospitalizations, length of time for various procedures and the frequency of repetition, doses and routes of administration of drugs and the amounts of blood to be drawn and plans for follow-up. Describe the setting in which the research will take place. The use of published and widely accepted survey or assessment instruments or tools need only be identified in the protocol and the instruments themselves need not be submitted since the HIC retains a library of these instruments. However, the use of original surveys and instruments must be approved for use by the Committee and such instruments must be submitted for review. Investigators should take care to distinguish clearly in all protocol documents any procedures that are experimental and those that are part of subjects' standard clinical care.

   4. Genetic Testing: If genetic testing is included in the protocol, the research plan must include information describing the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome-wide association studies, or animal studies are planned; the plan for the collection of material or the conditions under which material will be received; the types of information about the donor/individual contributors that will be entered into a database; the methods to uphold confidentiality; the conditions or procedures for sharing of materials and/or distributing for future research projects; whether widespread sharing of

materials is planned; when and under what conditions will materials be stripped of all identifiers; whether donor-subjects can withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials; how requests to withdraw materials will be handled (e.g., material no longer identified: that is, anonymized) or material destroyed); provisions for protection of participant privacy; and the methods for the security of storage and sharing of materials.

5. Subject Population(s): Provide a detailed description of the characteristics of the subject population(s), including the anticipated number, age range and health status. The selection of subjects must be equitable within the context of the research question. Generally speaking, the subject selection should reflect a reasonable cross-section of the population that is being studied. In research that requires a more restricted population, the rationale for this need should be fully justified. Investigators must also provide scientific justification for the specific exclusion of underrepresented populations such as women, children, or minorities.

6. Subject Classifications: Investigators must note in this section of the application all the classes of subjects that will be **specifically targeted** for enrollment in the study, including healthy control subjects. Identification of all the vulnerable populations and justification for their involvement must be noted.

Federal regulations require that additional safeguards be in place for research involving populations that are, or may be, considered vulnerable. Such populations include, but are not limited to, children, wards, prisoners, pregnant women, fetuses, mentally disabled, or decisionally impaired persons (either temporarily or permanently disabled), students, employees or economically or educationally disadvantaged persons. When some or all prospective subjects are likely to be vulnerable to coercion or undue influence, as may be likely with most of the populations cited above, additional safeguards must be incorporated into the protocol to protect the rights and welfare of these subjects. Investigators should also be cognizant that a person may become vulnerable under certain circumstances (as when in great pain or emotionally distressed) and that such vulnerability may be transient, may fluctuate, or become progressively more serious over time.

When vulnerable populations or subjects are expected to be enrolled, adequate provisions for evaluating the subject's capacity or non-capacity to provide consent/assent must be addressed in the protocol. Additional safeguards that will be used to protect the rights and welfare of vulnerable subjects must be specified in the protocol.
Investigators should familiarize themselves with HRPP guidance on conducting research with vulnerable populations. See subject classifications below for additional guidance. Also visit National Bioethics Advisory Commission's report on Research Involving Persons with Mental Disorders That May Affect Decision-Making Capacity http://bioethics.georgetown.edu/nbac/capacity/TOC.htm the National Institutes of Health (NIH), Office of Extramural Research Involving Individuals with Questionable Capacity to Consent http://grants.nih.gov/grants/policy/questionablecapacity.htm, and HRPP policies at http://www.yale.edu/hrpp/policies/index.html#VulnerablePops

Decisionally Impaired Persons
Where research is conducted using human subjects who suffer from mentally disabling disorders or conditions that may affect their decision-making capacity, additional protections are required. The enrollment of these subjects must include the permission of a legally authorized representative or surrogate prior to the subject participating in the research. If there is a reasonable likelihood that a

significant fraction of the subject population could become incapacitated during the study and no longer be able to provide consent to continued participation, it is advisable to have subjects prepare an advance directive at the start of the study so a person of their choosing can consent to the subject's continued participation.
See Authorization and Advance Directive template located at http://www.yale.edu/hrpp/forms-templates/biomedical.html

When including individuals with limited decision making capacity, the investigator should consider the following:

- When potential subjects are capable of making informed decisions about participation, they may accept or decline participation without involvement of any third parties.
- Any potential or actual subject's objection (verbal or behavioral) to enrollment or to continued participation in a research protocol must be heeded.
- An investigator, acting with a level of care and sensitivity that will avoid the possibility or the appearance of coercion, may approach people who previously objected to ascertain whether they have changed their minds.
- For research protocols that present greater than minimal risk to subjects, the HIC may require that an independent, qualified professional assess the potential subject's capacity to provide consent. The protocol should describe who will conduct the assessment and the nature of the assessment. The HIC may permit investigators to use less formal procedures to assess potential subjects' capacity if there are good reasons for doing so.
- Persons who have been determined to lack capacity to consent should not be enrolled in research that is not likely to result in direct benefit to them unless the research presents no more than minimal risk or is likely to yield generalizable knowledge about the subject's disorder or condition.
- A person who has been determined to lack capacity to consent to participate in a research study must be notified of that determination before permission may be sought from his or her legally authorized representative or surrogate to enroll that person in the study. If permission is given to enroll such a person into the study, the potential subject must then be notified. Should the person object to participating, this objection should be heeded.
- For research protocols involving subjects who have fluctuating or limited decision-making capacity or prospective incapacity, investigators should establish and maintain ongoing communication with involved caregivers, consistent with the subject's autonomy and with medical confidentiality.

Children
Specific conditions are cited in the federal regulations regarding the inclusion of children into research. Children include all persons who have not attained the legal age to consent for themselves to treatments or procedures under the applicable law of the jurisdiction in which the research will be conducted. In Connecticut, this legal age is 18 years, except for children seeking treatment for substance abuse and reproductive health, or when the child is emancipated. Investigators should note that in the State of Connecticut, pregnancy does not qualify a child as being emancipated.

Parental permission and a child's assent are normally required for research involving children. Assent is defined as "a child's affirmative agreement to participate in research" and should be sought

in addition to parental permission when the child is sufficiently mature to understand the nature of his or her participation in a research study.

Wards

Children who are wards of the state or any other entity can be included in research that is approved by the IRB as minimal risk. They may also participate in research considered greater than minimal risk when the research has the potential to provide direct benefit to the ward. However, wards may not participate in research that is considered greater than minimal risk when there is no direct benefit to the ward unless such research is related to their status as wards OR conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are **not** wards. All research protocols designed to enroll children who are wards of the State of Connecticut must obtain approval from the Connecticut Department of Children and Families IRB. See http://www.ct.gov/dcf/cwp/view.asp?a=2555&q=314538.

Researchers must be careful when identifying the appropriate parental figures from whom parental permission must be obtained in order to enroll the child into the research. Foster parents can not provide consent for foster children to participate in research because they are not considered their legal guardians. However, the foster parent(s) may need to be consulted, as the research may require their commitment; for example, driving the child to and from research appointments. In this population, it is typically the protective service worker or state-appointed case worker who is the legal guardian or *in loco parentis* from whom parental permission must be obtained. The researcher should consult with the case worker in determining whether additional permissions from other parental figures, e.g., the biological parent may be necessary. Researchers should note that studies involving medical risks may require a medical history of the child from someone who has a thorough and reliable knowledge of the child's health.

In an effort to further protect the welfare of the child, the IRB shall require the appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian when it finds that the research presents greater than minimal risk with no prospect of direct benefit to the child.. An individual with appropriate background and expertise may serve as an advocate for more than one child. However, the advocate may not be associated in any way with the research (except in the role as advocate or member of the IRB) or the investigator(s) or be the potential subject's guardian and/or foster parent.

If the study is designed to enroll children who are wards of the state, the Subject Classifications section of the application must address the following:

1) How will wards be identified and recruited to participate in the research?
2) How will the permission for participation of the ward(s) of the state be obtained?
3) How will the investigator ensure that the appropriate person grants permission for each ward to participate in the research?
4) How will the investigator determine whether there has been a change in guardianship status during the course of the research and permission should be obtained from the new guardian?

Even if the study does not intentionally plan or expect to enroll wards of the state, if at any time during the course of research a research participant becomes a ward of the state, the PI must notify the IRB as soon as the investigators become aware of the change of status.

7.Inclusion/Exclusion Criteria: Describe the criteria for subject inclusion or exclusion and how eligibility of potential subjects will be determined, and by whom. Appropriate inclusion and exclusion criteria for research participants are essential. Criteria for inclusion may consist of any combination of biomedical and behavioral characteristics. Poorly specified inclusion/exclusion criteria can affect data analysis and result in inadvertent exclusion of eligible research subjects and an imbalance of, or inappropriate enrollment of, research subjects.

8. **Eligibility:** Describe how eligibility will be determined, and by whom.

9. **Risks:** Describe the reasonably foreseeable risks, discomforts, or inconveniences associated with the subject's participation in the research. Potential research risks include more than physical harm; risks may also include, for example, emotional or psychological harm, risk of social stigmatization, economic or legal risk. Risks identified in this section must be adequately represented in the consent forms and assent forms presented to the potential subjects.

10. **Minimizing Risks:** Describe how the above-mentioned risks can be minimized.

11. **Data and Safety Monitoring Plan:** Provide a Data and Safety Monitoring Plan (DSMP) that includes an explicit statement of overall risks (e.g., minimal, greater than minimal/moderate, or high), addresses attribution and grading of adverse events and describes procedures for monitoring the ongoing progress of the research and reporting adverse events. The Data and Safety Monitoring Plan should describe how the principal investigator intends to provide ongoing supervision and evaluation of the activities of the study including whether appropriate progress is being made. It should document the procedures and means to protect the welfare and safety of subjects and protect the integrity of the data.

The plan must include provisions for data review and performance of safety reviews, at a specified frequency, as well as the plan for reporting to the HIC and/or other internal or external organizations. When participating in a multi-site study, the Yale principal investigator must indicate how safety reports and/or reporting of serious adverse events from other sites will be provided to the Yale HIC. For more information, please see the HRPP website: http://www.yale.edu/hrpp/forms-templates/biomedical.html.

12. **Statistical Considerations:** Sample size estimations are warranted in all clinical studies for both ethical and scientific reasons. The ethical reasons pertain to the risks of enrolling either an inadequate number of subjects or more subjects than the minimum necessary to accomplish the research. In both instances, the risks include randomizing the care of subjects and/or exposing them to unnecessary risk/harm. Therefore, the HIC requires that all investigators justify the proposed sample size. This section should include:
    a) the number of patients expected to enter the study
    b) a statement about the statistical power of the study to test the major hypothesis and
    c) a summary of the plans for statistical analysis.

SECTION VI: RESEARCH INVOLVING DRUGS, BIOLOGICS, PLACEBOS OR DEVICES

Protocols using drugs, chemicals, hormones, other natural substances or devices must complete this section of the application form. If the section does not apply to this study, state N/A and deleted the rest of the section.

A. DRUGS and BIOLOGICS

Based upon the information provided in this section, items 1-4, the investigator should consider and present a justification for or against the need for submitting an Investigational New Drug (IND) application to the FDA. Investigators who inquire of the FDA as to whether or not an IND is required prior to submitting the protocol application should attach the FDA's determination to this application.

1. **Identification of Drug or Biologic:** State the name of the drug(s) or biologic(s) being used. Identify whether the drug(s) or biologic(s) has(have) FDA approval and if so, for what indication(s).

   a) **Use of an Investigational Drug, or Biologic:** An investigational new drug (IND) is defined as a new drug or biologic that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes [21 CFR 312.3]. This section **must** include:
   1) The IND [21CFR312.40] number assigned by the FDA
   2) The name of the holder of the IND
   3) If the drug is provided free of charge to subjects (by the Sponsor or other entity).

      i. **Exemption from IND Requirements**
      There are four IND exemption categories established by the FDA, as identified in the HIC application. The most frequently used is category 1, but investigators should be aware of the requirements for categories 2, 3 and 4 as listed in the Application and determine if the research use of the drug or biologic better fits into one of these categories. Check only the box for the appropriate category.

2. Background Information: Provide a description of the drug's previous use in humans, known risks associated with the drug, and data including any references addressing dosage(s), interval(s), route(s) of administration, and any other factors that might affect risks. Include data relating to the pre-clinical animal model studies in this section if this is the first time the drug is being administered to humans.

3. Source: Identify the source of the drug or biologic to be used. Indicate whether it will be provided to the subject at no cost.

4. Storage, Preparation and Use: Adequate control and storage of the drug or biologic to be used is required. Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity. Indicate the applicable Investigational Drug Service utilized. If the YNHH Investigational Drug Service (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.

5. Use of Placebo: Placebo can be defined as "an inactive substance or preparation used as a control in an experiment or test to determine the effectiveness of a medicinal drug." Placebos are most commonly

used in a control group to determine if a therapy is more effective than chance alone in the proposed study. In order for the HIC to approve the use of a placebo, it must first determine if the use of the placebo is safe and if there is an alternate treatment or standard of care which can be used as a control. Placebo use may be allowed when: there is no standard of care for the condition; standard of care is no better than placebo; standard treatment is placebo; there is doubt about the net therapeutic advantage of the standard of care; or the standard of care is unavailable. If any part of the study involves the use of placebo, include in this section a robust justification for the use of placebo which includes the following:

a) The safety and efficacy of other available therapies (if any).
b) The maximum total length of time a participant may receive placebo while in the study.
c) The greatest potential harm that may come to a participant as a result of not receiving effective therapy (immediate or delayed onset).
d) Procedures in place to safeguard participants receiving placebo.

6. **Use of Controlled Substances:** This question is asked in collaboration with Yale's Occupational and Environmental Health Services (OEHS) department to help ensure investigator compliance with Connecticut State law requiring an investigator to obtain a Laboratory Research License for use of a controlled substance in a non-therapeutic research study involving human subjects.
Examples include controlled substances used for basic imaging, observation or biochemical studies or other non-therapeutic purposes. To view a listing of controlled substances see http://www.deadiversion.usdoj.gov/schedules/index.html
For more information on this topic see http://www.yale.edu/oehs/consub.htm#

7. Continuation of Drug Therapy (if applicable): Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended? If so, describe the conditions under which continued access to study drug(s) may apply (e.g., how subjects become eligible, what costs are covered by the sponsor, the subject and/or his/her insurance company).
Also indicate the conditions for termination of the continued access (e.g., sponsor no longer provides the drug, the drug becomes commercially available, the sponsor, FDA, DSMB or HIC terminates the study, the subject no longer qualifies, or the investigator decides continued drug therapy is not in the patient/subject's best interest).
If continued access to the study drug(s) is not planned, then please justify why this is acceptable.

B. DEVICES
Based upon the information provided in this section, the investigator should consider and present a justification for or against the need for submitting an Investigational Device Exemption (IDE) application to the FDA. An IDE allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Pre-Market Approval (PMA) application or a Pre-Market Notification [510(k)] submission to the FDA. Investigational use also includes the clinical evaluation of certain modifications or new intended uses of legally marketed devices. All clinical evaluations of investigational devices, unless exempt, must have an approved IDE before the study is initiated.

Investigators who inquire of the FDA as to whether or not an IDE is required prior to submitting the protocol application should attach the FDA's determination to this application.

1. YNHH Review Procedures: Investigators intending the use of an investigational device or investigational procedure to be performed at YNHH (e.g., YNHH Operating Room or YNHH Heart and

Vascular Center) should follow the requirements stated in the HIC application and contact Gina D'Agostino at 203-688-5052 to initiate YNHH review procedures.

2. Identification of Device: State the name of the device being used. Identify whether the device has FDA approval and if so, for what indication(s).

3. Background Information: Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.

4. Source: Identify the source of the device, and whether or not it will be provided free of charge to subjects.

5. Risk Level of Device: Devices are categorized depending on the level of risk involved with their use. The PI is asked to assess the risk of the device as **Significant** or **Non-Significant** according to FDA definitions:

a) Significant Risk (SR) Device Study: A study of a device that presents a potential for serious risk to the health, safety, or welfare of a participant and 1) is intended as an implant; 2) is used in supporting or sustaining human life; or otherwise prevents impairment of human health; 3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or 4) otherwise presents a potential for serious risk to the health, safety, or welfare of a participant.

Significant Risk Devices require an Investigational Device Exemption (IDE) issued by the FDA. If this category applies, the PI must provide the following information:

a. the **IDE number** assigned by the FDA

b. the approval category of the IDE: **Category A** (experimental/investigational) or **Category B** (non-experimental/investigational)

c. the holder of the IDE

b) Non-Significant Risk (NSR) Device Study: A study of a device that does not meet the definition for a significant risk device and does not present a potential for serious risk to the health, safety, or welfare of participants. Note that if the HIC concurs with this determination, an IDE is not required.

6. Abbreviated IDE or Exemption from IDE Requirements: If any of these categories applies, complete the relevant category, and copy and paste it into the HIC application.

a.) Does the device fulfill the requirements for an **abbreviated IDE (21 CFR 812.2(b)(1))?**
(For this condition to be met, all answers related to this condition must be "Yes".)

- The device is not a banned device. ___ Yes ___ No
- The sponsor labeled the device in accordance with 21 CFR 812.5. ___ Yes ___ No
- The sponsor will obtain IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval. ___ Yes ___ No
- The sponsor will ensure that each investigator participating in an investigation of the device obtains from each subject under the investigator's care consent under 21 CFR 50 and documents it, unless documentation is waived. ___ Yes ___ No
- The sponsor will comply with the requirements of 21 CFR 812.46 with respect to monitoring investigations. ___ Yes ___ No
- The sponsor will maintain the records required under 21 CFR 812.140(b)(4) and (5) and make the reports required under 21 CFR §812.150(b) (1) through (3) and (5) through (10). ___ Yes ___ No
- The sponsor will ensure that participating investigators will maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and ___ Yes ___ No
- The sponsor will comply with the prohibitions in 21 CFR 812.7 against promotion and other practices. ___ Yes ___ No

b.) Does the device fulfill one of the **IDE exemption categories (21 CFR 812.2(c))?**

(For this condition to be met, only one main bulleted item must be answered "Yes".)

- The device, other than a transitional device (i.e., those devices previously regulated as new drugs), was in commercial distribution immediately before May 28, 1976, and will be used or investigated in accordance with the indications in labeling in effect at that time. ___ Yes ___ No
- The device, other than a transitional device, was introduced into commercial distribution on or after May 28, 1976, the FDA determined the device to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and the device will be used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence. ___ Yes ___ No
- The device is a diagnostic device, and the sponsor complies with applicable requirements in 21 CFR §809.10(c) and the testing (to be met, all of the following must be "Yes"):
    - Is non-invasive. ___ Yes ___ No
    - Does not require an invasive sampling procedure that presents significant risk. ___ Yes ___ No
    - Does not introduce energy into a subject. ___ Yes ___ No
    - Will not be used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic

product or procedure. ___ Yes ___ No

- The device is undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, and the testing is not for the purpose of determining safety or effectiveness and does not put participants at risk. ___ Yes ___ No
- The device is intended solely for veterinary use. ___ Yes ___ No
- The device is shipped solely for research on or with laboratory animals and labeled in accordance with 21 CFR §812.5(c). ___ Yes ___ No
- The device is a custom device as defined in 21 CFR §812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution. ___ Yes ___ No

7. Device Accountability: The principal investigator, or a named designee, is responsible for ensuring that an investigational device is used only in accordance with the research protocol approved by the HIC, and is required to maintain control of the investigational device through proper record-keeping, inventory, storage, distribution and disposal, as described in the HIC application.

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: State the number of individuals that are specifically targeted for enrollment into the protocol at Yale. If the number of subjects expected to sign consent for purposes of screening (determining eligibility) is likely to be different than the number expected to complete interventions, indicate both the number expected to sign consent and complete interventions. For multi-center studies, indicate the total number of subjects to be enrolled across all sites as well as the number enrolled at Yale. If different subject populations will participate, state the anticipated number in each group.

2-3. Recruitment Methods and Procedures: Indicate all recruitment methods that will be used. Describe how potential subjects will be identified, contacted and recruited into the research study, and by whom. Attach copies of recruitment materials that will be used, such as flyers, telephone and radio scripts, web advertisements or letters used to introduce the research to potential subjects. Federal agencies consider direct advertising to be the start of the informed consent process and thus must be conducted in a straight-forward and non-coercive manner. Advertisements should not feature monetary compensation as an introduction before describing the study purpose. The monetary compensation should not be enlarged, bolded, underlined, or otherwise emphasized. No claims should be made, either explicitly or implicitly, that the intervention is safe or effective.

Use of registries such as the YCCI subject recruitment registry must be indicated on the HIC application. The use of federally funded clinical trial registries (clinicaltrials.gov) is not considered by Yale to be a recruitment method requiring IRB approval. Therefore, copies of the information posted on clinicaltrials.gov need not be attached to the protocol being submitted to the IRB.

All advertisements must include the HIC number. Advertisements should be limited to 1) the purpose of the research and, in abbreviated summary form, the eligibility criteria that will be used to admit subjects into the study; 2) a straightforward and truthful description of the incentives to the subject for participation in the study; and 3) the location of the research and the person to contact for further information.

4. **Screening of Potential Subjects**. Indicate whether email or telephone correspondence will be used to screen potential subjects for eligibility prior to the potential subject coming to the research office. If identifiable health information will be collected and retained by the research team during the email or telephone conversations, check all applicable HIPAA identifiers to be collected.

Investigators are reminded that screening procedures that collect and store identifiable health information are subject to HIPAA requirements because the information becomes protected health information (PHI) once it "enters" Yale. Therefore, investigators should design screening procedures to avoid, or minimize, the collection and retention of PHI when possible. However, if it is necessary to collect PHI either because this information is required as part of the enrollment process or because the sponsor requires the retention of failed screen information, then the investigator may do so under a waiver of signed HIPAA authorization. Approval from the IRB is required prior to initiating the screening plan in the conduct of research. Investigators do not need to send a Request for Waiver of HIPAA Authorization for Research to the HIC for approval. The HIC will issue an approval based on the request made by the investigator in Section VII, Question 6 of the HIC protocol application.

Investigators interested in screening subjects through phone or e-mail should consider requesting verbal authorization by incorporating the following language into telephone/e-mail scripts used to screen potential subjects: "We will keep the information we just talked about in our files until you come in to screen for the study. If you qualify and choose to be part of the study, this information will become part of your study file. If you don't come in or if you don't qualify for the study, we will keep this information until [the duration can be modified but as a suggestion- the study is over] and then we will destroy it. We are required by law to keep this information confidential and we will not use it for any purpose other than to see if you qualify for this study and for research oversight."

Investigators who wish to retain screening information for the purposes of creating a recruitment database are encouraged to contact the HIC prior to retaining the information for future use. Investigators must have a repository protocol and appropriate consent documents approved by the HIC prior to using screening information for recruiting individuals for other future studies.

Sharing PHI with any person outside of the research team without the authorization of the subject, including sharing with the study sponsor, will require the investigator to account for the disclosure of the PHI. Investigators should account for the disclosure by using the Accounting of Disclosures Log found at http://www.yale.edu/hrpp/forms-templates/hipaa.html . Investigators are reminded that completed logs must be submitted to the HIPAA Privacy Office (hipaa@yale.edu or fax to 432-4033). Disclosures of de-identified data or limited data sets do not require an accounting for the disclosure.

5. Assessment of Current Health Provider Relationship for HIPAA Considerations:
State whether medical records will be accessed to identify potential subjects and indicate whether the principal investigator or other member of the research team has a direct clinical relationship with the

potential subjects. Researcher-clinicians are permitted to access the Protected Health Information (PHI) of their own patients, or patients of co-investigators listed on the protocol, for recruitment purposes. Absent this treating relationship with potential subjects, PHI **cannot** be accessed without subject authorization, or a waiver. See Section VII question 6 to request a HIPAA waiver. *For further information, see* http://www.yale.edu/hrpp/forms-templates/hipaa.html

6. **Request for Waiver of HIPAA Authorization**: Complete this section when requesting a waiver of HIPAA Authorization for either the entire study or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes. *(For further information, see the Yale HIPAA website at* http://hipaa.yale.edu/).

7. **Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), a separate authorization is required under the HIPAA Privacy Rule. HIPAA requires either a subject research authorization or an approved waiver of the authorization requirement for the use, disclosure or creation of PHI for research. If a researcher uses or collects health information from which the 18 HIPAA defined identifiers have been removed, then no authorization is required, meaning an authorization is not required for research collecting or using only "de-identified" data. In circumstances where samples will be banked and used for future research that is unspecified in the current study, a second Research Authorization Form specific to the banking aspect of the protocol is necessary.

Investigators must provide the HIPAA Research Authorization Form (RAF) or a Compound Consent and Authorization Form to the HIC for review. (See http://www.yale.edu/hrpp/forms-templates/biomedical.html)
If requesting a waiver of HIPAA research authorization, the information in question 6 must be completed. *(For further information, see the Yale HIPAA website at* http://hipaa.yale.edu/).

8. **Consent Personnel:** List all members of the research team who will be obtaining consent, permission and/or assent. These individuals must be personnel who have a thorough understanding of the methodology of the protocol and a comprehensive knowledge of the procedures of the protocol. These individuals must be capable of answering the possible questions raised by the potential subject regarding the study. All individuals listed here must also be listed as co-investigators or study personnel and complete the necessary human subject protection and HIPAA training prior to participating in the conduct of the study.

9. **Process of Obtaining Consent, Assent, Parental Permission, or Surrogate Permission:** Describe the setting and conditions under which consent, assent, parental permission, or surrogate permission will be obtained. Include steps taken to ensure subjects' independent decision-making.

No investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative or surrogate. An investigator shall seek such consent only under circumstances that

minimize the possibility of coercion or undue influence and provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate. The information that is given to the subject or the representative shall be in a language understandable to the subject or the representative. No informed consent, whether oral or written, may include any language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or release or appear to release the investigator, the sponsor, the institution or its agents from liability for negligence.

For research involving children, there are additional issues which need specific consideration. These include, but are not limited to, whether the child's assent will be obtained in the presence of the parent/guardian or separately, as well as obtaining consent after the child has reached the age of majority as may be necessary in conducting longitudinal studies. Although the IRB is granted the ultimate authority to determine what type of assent is required, researchers are in the best position to assess the capabilities of the potential subject population. This assessment may need to be made on a case-by-case basis. This section of the protocol should therefore contain a thorough description of the procedures that will be used to obtain parental permission and child assent. This description should include information such as:

- How the potential subjects' maturity will be assessed
- Who will obtain assent
- Where and when parental permission and child assent will be obtained (indicate whether the child will be alone or in the presence of his/her parents)
- The types of assent documents that will be used
- Whether signed assent will be requested of the child
- How the child's assent will be documented by the researcher
- How it will be determined whether subjects/parents understand the research and all interventions
- Justification of a waiver of parental permission or child assent, if such a waiver is requested

For studies that are longitudinal in nature, it is also necessary to indicate whether and how the investigator plans to obtain consent from subjects once they reach the age of majority.

Assent for Children. Assent is defined as "a child's affirmative agreement to participate in research," and should be sought in addition to parental permission when the child is sufficiently mature to understand the nature of his or her participation in a research study. While children are legally incapable of providing informed consent, they nevertheless may possess the ability to assent or dissent from participation. The assent process assures the elements of understanding and cooperation, and provides a feeling of inclusion on the part of the child. The process also illustrates the investigator's respect for the rights and dignity of the child in the context of research. In recognition of children's differing rates of intellectual and emotional development, federal regulations do not specify the age from which assent is required. They also do not state what form the assent process should take. Rather, these determinations are left to the judgment of the principal investigator and the IRB. In making such assessments, the principal investigator and the IRB are obligated to examine the ages, maturity and psychological state of the children involved. For guidelines in developing age appropriate assent forms, see Section V.

Parental Permission. Parents or court-appointed guardians are the legal decision makers for children in most situations. Parents or legal guardians can grant "permission" for children to

participate in research. The parental permission form is in essence a consent document and should follow all applicable requirements for informed consent.

Waiver of Parental Permission. The investigator may request, and the IRB may waive, the requirement to obtain parental permission under limited conditions. In Connecticut, a child gains majority at age 18. The regulations permit children, with IRB approval, to consent on their own behalf if the research involves a treatment for which a child's consent is permissible under applicable law (e.g., outpatient mental health care, pregnancy, treatment for venereal disease, or treatment for alcohol or drug dependence). When the permission of the parent(s) is not a reasonable requirement because it poses additional risk to the potential subject, or the parents' interests may not adequately reflect those of the child (for example, in research concerning neglected or abused children), parental permission can be waived. In this case, the researcher should propose in the application an alternative mechanism as to how the child's rights and welfare will be protected. The choice of an alternative mechanism depends on the nature and purpose of the research, the risk and anticipated benefit to the child, and their age, maturity, status and condition.

10. Evaluation of the Subject's Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent/assent to the research being proposed. As part of the consent/assent process, the individual obtaining the informed consent or assent must evaluate the potential subject's capacity to provide complete informed consent or assent. This is usually done through the evaluation of the questions raised by the potential subject and answers given to the questions asked of the subject. However, as the risk of a study increases or the benefits decrease, the potential vulnerability of the subject may increase-- thus requiring more stringent measures for evaluating the subject's capacity to provide consent/assent. The level of capacity required to provide consent/assent varies amongst study populations as well as the type and complexity of the study protocol. It may be necessary to take steps to enhance comprehension of the study subject in order to maximize the ability to provide informed consent/assent. This process should be tailored to the specific study population. As part of the consent/assent process, prospective subjects should be asked open-ended questions about the research because "yes" and "no" answers do not suffice to determine whether the subject recalls and understands what has been explained to him/her. Such questions include: "Can you tell me what will happen if you agree to take part in this study?" "How will this study help you?" and "What should you do if you want to stop being in this study? Can you leave this study once it begins?" For research in which the subject population includes individuals with limited decision-making capacity, it may be necessary to obtain consent from an appropriate representative. (See 11.e below).

11. Documentation of Consent/Assent: Specify the documents or forms that will be used to obtain consent/assent. Forms appended to the protocol for HIC review must be in the same format and language as those that will be given to subjects. Templates for the forms can be found at: http://www.yale.edu/hrpp/forms-templates/biomedical.html

a. **Adult Consent Form:** The consent form must be a clear and descriptive document that can stand alone in describing the essential elements of the study. It should be written at no greater than an 8th grade level of understanding. The consent document should contain the information a reasonable person would

want to know in order to decide whether or not they wish to participate in the research. As per 45 CFR 46.116 (a), an informed consent must include the following elements: (1) An invitation to participate; (2) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental; (3) A description of any reasonably foreseeable risks or discomforts to the subject; (4) A description of any benefits to the subject or to others which may reasonably be expected from their participation in the research; (5) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject; (6) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained; (7) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what compensation consists of, or where further information may be obtained; (8) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and (9)(i) A statement that participation is voluntary and the subject may discontinue participation at any time, and (ii) specifically the subject's refusal to participate will involve no penalty or loss of benefits or rights to which the subject is otherwise entitled. Additionally, an In Case of Injury section is required for all research posing greater than minimal risk to subjects. Investigators may choose to include this section for minimal risk studies. If used, the In Case of Injury section must include a statement that the subject does not forfeit his/her legal rights by signing the form; otherwise, this statement should be placed at the end of the Voluntary Participation section. The following statement can be used to satisfy this requirement; "You do not give up any of your legal rights by signing this form." If genetic testing will be included in the protocol, information regarding the testing, including the types of future research to be conducted using the materials must be outlined, including, as applicable, (1) any planned immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies, (2) the plan for the collection of material or the conditions under which material will be received, (3) the types of information about the donor/individual contributors that will be entered into a database, (4) the methods to uphold confidentiality, (5) the conditions or procedures for sharing of materials and/or distributing for future research projects, (6) whether widespread sharing of materials is planned, (7) when and under what conditions will materials be stripped of all identifiers, (8) whether donor-subjects can withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials, (9) how requests to withdraw materials will be handled (e.g., material no longer identified: that is, anonymized) or material destroyed, (10) provisions for protection of participant privacy, and (11) the methods for the security of storage and sharing of materials.

b. Parental Permission Form: The parental permission form is considered equal to the consent form and must include the same elements described in Section 4.a above. Investigators should modify the adult consent form template for use as a parental permission form. 45 CFR 46.402 defines Permission as "the agreement of parent(s) or guardian to the participation of their child in research." Parent is defined as "a child's biological or adoptive parent" and guardian as "an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care." Adequate provisions must be made for soliciting the permission of each child's parent(s) or guardian. Where parental permission is to be obtained, the IRB will determine whether the permission of one parent is sufficient for research to be conducted or whether both parents must give their permission (unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.)

c. Child Assent Form (ages 7-12 inclusive): The child assent form should include the same elements of the adult consent form described above; however, it should be written in language developmentally appropriate to the age of the children being recruited. In many circumstances an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs may not be appropriate and therefore may be omitted from the assent form.

d. Adolescent Assent Form (ages 13-17 inclusive): Given the developmental differences between "children" and "adolescents," a separate assent form is required for individuals between the ages of 13 and 17. This form must have the same elements of the adult consent form described above; however, it should be written in language developmentally appropriate to the age of the children being recruited. In most circumstances the form will closely parallel the adult permission form because the latter should be written at an 8th grade level of understanding. In many circumstances an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs may not apply and therefore may be omitted from the assent form.

e. **LAR (Legally Authorized Representative)/ Surrogate permission form**: 45 CFR 46.102 defines legally authorized representative as "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**."** A surrogate can be an individual who would normally provide consent for another person's medical care under prevailing, commonly accepted clinical practices. Informed consent must be sought from each prospective subject's LAR or surrogate. This form must have the same elements of the adult consent form described above and be written to the LAR/surrogate.

f. Adult Assent Form (for decisionally impaired subjects): For subjects who are deemed decisionally impaired, an adult assent form may be used to obtain the individual's agreement to participate in the research project. This form must have the same elements of the adult consent form described above; however, it should be written in language developmentally appropriate to the population being recruited.

g. **Information Sheet:** The information sheet is intended to give subjects sufficient information regarding their involvement in the proposed research study. This sheet will usually be required in situations in which a waiver of written and signed consent is granted by the HIC. This sheet can also be used as an outline for describing research procedures to young children, who are incapable of providing written assent.

h. Compound Authorization and Consent Form: In an effort to streamline the consent and authorization process, the HIC has developed a template that combines the HIPAA research authorization and consent forms. This combined form is designed to incorporate and satisfy the elements required of both forms. This form can be used instead of the separate HIPAA RAF and consent forms.

12. Non-English-Speaking Subjects: Explain what provisions are in place to ensure comprehension of the research when involving non-English-speaking subjects. If non-English-speaking subjects will be recruited, it is necessary to develop and submit consent (and recruitment) materials in the language(s) that will be used by the subjects. Submit translated copies of all consent materials to the HIC for approval before such subjects are recruited. Whenever possible, documentation should take the form of a written consent document that embodies all the elements necessary for legally effective informed consent.

Otherwise, where the oral presentation of informed consent information is used with subjects who do not speak (or cannot read) English, the IRB may approve an alternate method which provides for (i) the oral presentation of the research and the short form written document in a language readily understandable by the subjects. Investigators are reminded that a family member of a potential subject can **not** be used as the translator for that individual because he or she may have a conflicting interest(s) relating to the study and may not be capable of fully explaining the study's risks and benefits to the potential subject. The Yale-New Haven Hospital Interpreter Service may be available for investigators conducting clinical trials to use to accomplish the consent process. For more information on the alternate consent method and consenting non-English speaking persons, see the Inclusion of Non-English Speaking Individuals guidance at: http://www.yale.edu/hrpp/policies/index.html#ICF

13. A. Waiver of Consent: In certain circumstances, the HIC may grant a waiver of consent or a waiver of signed consent, for either recruitment only, or for the entire

study.If the research requires a waiver of consent, or a waiver of signed consent, the following must apply:

For a Waiver of Consent (45 CFR 46.116(d)), an IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in the regulations, or waive the requirements to obtain informed consent provided the IRB finds and documents that: (1) The research involves no more than minimal risk to the subjects; (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) The research could not practicably be carried out without the waiver or alteration; and (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

B. Waiver of Signed Consent: For a Waiver of Signed Consent (45 CFR 46.117 (c)), the HIC may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either: (1) that the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality, **or** (2) the research (or a specific part of the research activities, such as recruitment) presents no more than minimal risk of harm to subjects **and** involves no procedures for which written consent is normally required outside of the research context. In cases in which the documentation requirement is waived, the HIC will usually require the investigator to provide subjects with a written statement regarding the research (Information Sheet).

SECTION VIII: PROTECTION OF RESEARCH SUBJECTS

Confidentiality and Security of Data: 45 CFR 46.111 indicates that human subject research can be approved when "there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data." The HIC requires the investigator to explain how privacy and confidentiality of information obtained during the recruitment, screening and conduct of the research will be maintained. Acceptable measures taken to protect the privacy and confidentiality of the data obtained during a study can include some or several of the following depending on whether the data is identifiable, and the sensitivity of the data:

- Moveable electronic media used to collect or store the data is equipped with encryption software recommended by the University (PGP).
- Identifiable research data, including recruitment and screening information and code keys, are stored on a database located on a secure Yale-ITS network, which is backed-up nightly.
- Subject identifiers and the means to link the subject names and codes with the research data are stored in separate locations within the database and with distinct access controls.
- Access to the database is password protected and each research team member is required to have a unique ID and password to gain access to the database.
- Identifiable data which is collected electronically on (*state what media types will be used to store and collect data, e.g., laptop, jump-drive, CD etc*) is stored temporarily on the device until the identifiable data can be uploaded to the secure database.
- Research computers are set to lock the screensaver after 15 minutes of inactivity requiring a password to unlock the screen.
- Identified data sets will not be sent through e-mail or as an attachment.
- Hard copy data is stored under lock and key.

- The PI and other members of the research team work with coded or de-identified data when using moveable device(s) to perform data analysis.
- Alternate collection method: Moveable media devices are used to collect research data, however, the data collected in this manner is either de-identified or collected using the subject's unique code."

A Certificate of Confidentiality (CoC) is issued by the National Institutes of Health (NIH), the US Food and Drug Administration (FDA), the Center for Disease Control and Prevention (CDC), or the Department of Health and Human Services (DHHS) to protect subjects' privacy and ensure the confidentiality of their study data and participation in a study. The Certificate is designed to prevent researchers from having to involuntarily disclose, in any federal, state or local civil, criminal, administrative, legislative, or other proceedings, names and other identifying information about any individual who participates as a research subject. This protection is afforded by the Public Health Service Act §301(d), 42 U.S.C. §241(d). It does not protect against voluntary disclosures by the researcher, but those disclosures must be specified in the informed consent form. A researcher may not rely on the Certificate to withhold data if the participant consents in writing to the disclosure. A copy of the CoC should be forwarded to the HIC office upon receipt by the Principal Investigator from the issuing agency.

For more information, please see the HRPP website:
http://www.yale.edu/hrpp/policies/index.html, policy 400, PR 2, and
http://www.yale.edu/hrpp/forms-templates/index.html.
The policy also gives examples of language that can be used in consent documents to explain the CoC to subjects. The forms website gives instructions for submission to NIH and the FDA.

SECTION IX: POTENTIAL BENEFITS

Identify any benefits that are reasonably expected to result from the research, either to subjects or to society at large. Payment of subjects is considered separately (See Section X.2) and is not considered a benefit in this context. It should not be noted as one in the consent document. In order for a research project to be considered ethically sound, the project must have a benefit, either to the individual directly or to society through the knowledge which will be gained. Direct benefits to subjects may include improvement in a condition or availability of investigational treatment the subject may not be eligible for outside the study. The benefit to society at large can be considered as the possibility of knowledge gained from the study to assist in developing possible treatment options.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** For studies offering investigational treatment, describe standard treatment alternatives which are available outside of the research. In some circumstances where there is no treatment alternative, comfort care may be an option. Some categories of non-treatment investigational research may also require a section outlining alternatives to participation which includes not participating. For example, a study that provides screening for a particular illness or condition should state whether testing is available outside of the research.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to the subjects and the conditions for receiving this compensation. Payments may take the

form of direct monetary payment for time and effort, payment in the form of a gift, gift card or reimbursement for costs such as travel, parking, childcare, etc. Payments should be reasonable in relation to the subject's time, effort and task in the research study. Payment must not be so large as to cause an undue influence on subjects. The payment plan must be clearly described in the consent forms. If payment will be prorated for subjects who do not complete the study, this should be clearly explained. If payment is conditional on completing the study, this should be clearly explained.

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research. If it is possible that the subject's insurance, health plan benefits, or other third party payers will not cover research procedures or tests, this should be indicated. Clearly describe the parts of the research visits (drugs, tests, procedures, etc.) that will be provided at no cost to the subjects. Investigators must ensure that the Yale Grants and Contracts Administration's approved budget, the study protocol(s), and the consent form are consistent and explicit relative to whether the subject or the sponsor is responsible for costs incurred as a result of participation in the study. Investigators should not agree, without prior approval from the Yale Grants and Contracts Administration, to sponsor terms that indicate the sponsor will pay for study costs only if the subject's insurance carrier will not.

4. **In Case of Injury:** This section is required for any protocol that involves more than minimal risk. The HIC or the Investigator may also require it for some minimal risk protocols.

   Describe what medical treatment will be available should a research-related injury occurs. Also indicate where the treatment will be given, and who will provide the treatment. A point of contact (including a phone number) of a physician with a full and unrestricted Connecticut license must be provided in the consent form if there is the potential of physical or psychological injury. Include in the description whether there are any limits to the treatment being provided, who will pay for treatment, and how it will be accessed by subjects (e.g., by calling the point of contact). This section should also indicate whether compensation such as recompense for lost wages and pain and suffering is available.

   If the sponsor of the study is a commercial, for-profit entity and the study is not an oncology or an HIV study, the principal investigator should not agree, without prior approval from the Yale Grants and Contracts Administration, to contract terms that indicate that the sponsor is not responsible to pay for treatment for injuries that occur as a result of participation in the study. The Investigator should further not agree, without approval from the Grants and Contracts Administration, to any contract terms that indicate that the sponsor will pay for treatment of injuries only if the subject's insurance carrier will not.