

GUIDANCE FOR INVESTIGATORS

THE HUMAN INVESTIGATION COMMITTEE



**Yale University
School of Medicine**

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CONTENTS

A.	INTRODUCTION	p. 4
1.	GUIDELINES FOR PREPARATION OF PROTOCOLS FOR REVIEW BY THE HUMAN INVESTIGATION COMMITTEE (HIC)	p. 4
2.	PURPOSE OF HIC REVIEW.....	p. 5
B.	GENERAL GUIDELINES	p. 5
1.	ORDER OF PROCEDURE.....	p. 5
2.	CONSULTATION WITH PRIMARY REVIEWER.....	p. 7
C.	PREPARATION OF PROTOCOLS	p. 7
1.	FACE SHEET.....	p. 8
2.	DESCRIPTION OF STUDY.....	p. 9
3.	HUMAN SUBJECTS.....	p.12
4.	CONSENT FORMS.....	p.17
D.	ADMINISTRATIVE PROCEDURES	p.24
1.	DUPLICATION OF PROTOCOLS AND DELIVERY TO HIC.....	p.24
2.	ACTION BY HIC.....	p.24
3.	EXEMPTION FROM REVIEW.....	p.25
4.	EXPEDITED REVIEW	p.25
5.	INSTITUTIONAL ENDORSEMENT.....	p.26
6.	REAPPROVAL OF PREVIOUSLY APPROVED PROTOCOLS.....	p.26
7.	PROPOSED CHANGES IN PROTOCOLS AFTER APPROVAL.....	p.26

8.	WITHDRAWAL AND TERMINATION	p.28
9.	REPORTS OF ADVERSE EVENTS.....	p.29
10.	PROTOCOL-RELATED CONFLICT OF INTEREST.....	p.30
11.	EMERGENCY USE	p.33

E.	SPECIAL PROBLEMS IN RESEARCH	p.33
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1.	RESEARCH INVOLVING CHILDREN	p.33
2.	RESEARCH INVOLVING THE DECISIONALLY IMPAIRED.....	p.37
3.	FDA PROTOCOLS.....	p.39
4.	USE OF MEDICAL RECORDS AND ACCESS TO PATIENTS	p.40
5.	HIV ANTIBODY TESTING	p.45
6.	NIH-SPONSORED MULTICENTER CLINICAL TRIALS.....	p.45
7.	CERTIFICATE OF CONFIDENTIALITY.....	P.46

APPENDIX I p.49

APPENDIX II p.50

APPENDIX III..... p.52

APPENDIX IV..... p.53

A. INTRODUCTION

A1. GUIDELINES FOR PREPARATION OF PROTOCOLS FOR REVIEW BY THE HUMAN INVESTIGATION COMMITTEE (HIC)

These Guidelines incorporate the regulations for the protection of human subjects set forth in the Code of Federal Regulations at 45 CFR 46.

Research having the following attributes may not be initiated until it has been approved by the HIC:

- 1) Research involving human subjects done on the premises of Yale-New Haven Medical Center ("YNHMC")
- 2) Research in which access to the human subject involves any records maintained by faculty or staff of YNHMC
- 3) Research involving human subjects conducted by faculty, students, or employees of YNHMC no matter where it is done

Research having the attributes that create a requirement for HIC approval is ordinarily exempt from this requirement if the investigators are faculty or students of Yale School of Nursing and its Human Subjects Research Review Committee has approved the protocol; in some cases, however, HIC review and approval may be required.

The University adopts the following definitions of human subjects research set forth in 45 CFR 46.102:

Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains:

- (1) data through intervention or interaction with the individual, or
- (2) identifiable private information.

Human subjects research includes, but is not limited to, studies with tissues, fluids, or other material removed from a living human, as well as a wide range of medical, behavioral, biological and epidemiology studies. Investigators are encouraged to contact the HIC for guidance in determining whether a particular study is considered human subjects research.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for

research purposes. *Interaction* includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

The practice of medicine or behavioral therapy refers to a class of activities designed to enhance the well being (health) of individual patients. Investigational practice is defined as a therapeutic, diagnostic, or preventive procedure or modality performed or administered with the intent and reasonable prospect of yielding a direct health-related benefit to the patient and which differs from customary (routine or accepted) practice; for example, use of a drug or device in a manner that differs substantially from that approved by the Food and Drug Administration (FDA); use of a novel surgical, radiological, or psychiatric technique; and introduction of a new diagnostic laboratory test. Investigational practice is not research, but in general, when an investigational practice is employed, it should be preceded by evidence from animal and human research designed to determine whether the therapy is safe and effective.

Across all biomedical and behavioral disciplines, research encompasses the following:

- Research development, testing and evaluation
- Therapeutic, diagnostic or preventative procedure if different from customary practice
- Comparison of two or more diagnostic, therapeutic, or preventive maneuvers or modalities, even if both are standard
- Investigational drug or device trials

A2. PURPOSE OF HIC REVIEW

The HIC reviews each research plan and consent form in order to safeguard the rights and welfare of human subjects. To that end, it must determine that each protocol conforms to various ethical standards including; there is a reasonable balance of risks and anticipated benefits; there are adequate provisions for informed consent; and there are plans made for the equitable selection of subjects. The Committee also considers the scientific design because it is unethical to put humans at risk as subjects of badly designed research. HIC review also protects the interests of investigators by minimizing misunderstandings that could lead to litigation or termination of grants and contracts.

B. GENERAL GUIDELINES

B1. ORDER OF PROCEDURE

The HIC is divided into two sections. The HIC I meets on the first and third Wednesday of every month, while the HIC II meets on the second and fourth Wednesday. In the event there is a fifth Wednesday in any given month, that date is reserved and designated for a policy meeting. Occasional meeting dates are changed to avoid conflicts with major religious or governmental holidays. Protocols must reach the HIC office by 4:00 P.M. eight days before the meeting at which they are to be reviewed. Because of the number of research projects to be reviewed at each meeting, the HIC must adhere rigidly to this timetable. Generally, it takes about 5 to 7 weeks from the initial consultation with the primary reviewer to final approval. Since the Committee twice must review

some protocols, it is advisable to plan to submit the protocol in time to be reviewed at the meeting at least 3 weeks before the desired date of approval. The following timeline has been developed for planning purposes:

Step	Timeline	Action
1	At the onset of drafting the research protocol	<ul style="list-style-type: none"> ▪ Review the Calendar and deadline dates posted on the HIC website to determine the targeted submission date and meeting date to commence the protocol review process. http://info.med.yale.edu/hic/ ▪ Review the HIC Guidelines while developing the protocol. Utilize the prompts provided in the Informed Consent and/or Assent form templates to assist in the development of the consent documents. http://info.med.yale.edu/hic/forms/index.html#templates
2	Approximately 6 weeks before the targeted submission date	<ul style="list-style-type: none"> ▪ Complete the first draft of HIC application, protocol, and informed consent document.
3	Approximately 5 weeks before the targeted submission date	<ul style="list-style-type: none"> ▪ Identify a primary reviewer with research interests or background at least somewhat similar to your project. Verify that the primary reviewer sits on the Committee whose meeting date coincides with the targeted submission date. ▪ Contact the primary reviewer to determine if he or she will be available for your projected or targeted due date ▪ If your chosen primary reviewer is unable to review the project on a timely basis, ask him or her (or contact the HIC office) to suggest an alternate.
4	Approximately 4 weeks before the targeted submission date	<ul style="list-style-type: none"> ▪ Exchange drafts as necessary with the primary reviewer to ensure that the protocol is developed according to HIC specifications .
5	Approximately 2 weeks before the targeted submission date	<ul style="list-style-type: none"> ▪ Finalize application with primary reviewer and obtain the requisite signatures. ▪ Ensure that appropriate research personnel have completed the requisite human subjects protection training and have read the Protocol-Related Conflict of Interest policy.

6	At least 1 day before targeted submission date	<ul style="list-style-type: none"> ▪ Submit the protocol application prior to 4 p.m. to ensure that paperwork is accepted for meeting agenda submission.
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B2. CONSULTATION WITH PRIMARY REVIEWER

The HIC employs a primary reviewer system for all protocols including those that may qualify for expedited review. The primary reviewer is a committee member who will serve as an advisor throughout the preparation of the protocol. The Principal Investigator is responsible for identifying his/her own primary reviewer for all protocols. If the Investigator has difficulty locating a primary reviewer in a particular area of expertise, the HIC will assist in selecting one.

The primary reviewer will help the investigator understand these Guidelines and pertinent regulations. The primary reviewer is also in a position to identify, in advance, the kind of issues that the Committee is most likely to raise regarding the protocol and consent form. It will be to the investigator's advantage to address those issues before the protocol is submitted for review. In general, the greater number of these issues that can be resolved before submission, the fewer revisions the Committee is likely to require before approval and the faster the protocol will be approved. It should be noted that the primary reviewer's suggestions are not binding on the investigator, nor does this preliminary review ensure approval by the HIC.

Further, the primary reviewer serves as liaison between the investigator and the Committee at the time the protocol is reviewed. The primary reviewer, by virtue of her or his knowledge of the protocol, can provide information to the Committee to assist its decision making process.

The primary reviewer should be consulted sufficiently early to ensure time to make such changes as the primary reviewer may suggest without delaying submission of the protocol to the HIC. Any HIC member, other than a co-investigator, may serve as a primary reviewer. It is to the investigator's advantage to select a primary reviewer whose field of expertise is suitable to understand the proposed research. If the HIC member who is asked to be a primary reviewer cannot give early consideration to the task, the HIC staff will suggest another.

After the protocol is completed and before it is submitted to the HIC for review, the protocol must be signed by the primary reviewer, who thereby indicates that it is ready for submission. The protocol must also be signed by the Chairperson of all departments involved in the research. The HIC will not approve any protocol that does not have all the required signatures.

C. PREPARATION OF PROTOCOLS

The protocol consists of four parts:

- Part 1. THE FACE SHEET
- Part 2. DESCRIPTION OF STUDY
- Part 3. HUMAN SUBJECTS
- Part 4. CONSENT FORM

Part I, the face sheet, and Part 2, the description of the study, are prepared especially for the HIC, to summarize the essential details of the proposed study. The information can be abstracted from a grant proposal, and all sections must be completed. Part 3, Human Subjects, is required by both the HIC and NIH and some other granting agencies and is written so it may be used for both purposes. Continuation pages as provided by NIH, may be used. The consent form, Part 4, is essential for the HIC and is also required by some granting agencies.

All pages, including consent forms, should be numbered consecutively. Both sides of pages may be used.

It is essential that protocols and consent forms be prepared carefully, completely and according to these guidelines. They become part of the permanent records of the HIC and, therefore, are subject to inspection and review by various agencies such as NIH and FDA.

C1. FACE SHEET

The HIC # (protocol number) will be assigned by the HIC after the protocol has been delivered for review. All correspondence concerning a protocol must refer to this number, as it is the only way individual protocols are identified in the HIC files.

The investigator responsible for correspondence may be someone other than the principal investigator. The correspondent usually should be a faculty member -- someone who is not likely to leave before the research is completed. The correspondent name and contact information should be clearly marked in the space provided on the face sheet.

Be sure to obtain the signature of the departmental chairperson, (not section head), of each department in which the investigators are appointed. The signature of the department affords him or her an opportunity to know of each research study conducted in the department. It also provides an opportunity for those who so choose to approve the study or offer suggestions to the investigator. Where investigators from one department (e.g., psychiatry) wish to do research on patients of another department (e.g., pediatrics), the HIC requires the signatures of both.

The principal investigator should also sign the face sheet.

Real or apparent conflicts of interest may, if not properly managed, compromise the objectivity of research or the perceived objectivity of research. For this reason the University has developed procedures and policies that govern the disclosure and review of real and potential conflicts of interest by all Yale investigators, including those involved in human subjects research. These policies require that all investigators must file with the Provost's Committee on Conflict of Interest an annual disclosure statement which discloses all conflicts of interest related to their research and teaching activities. These forms are required of all investigators whose participation in a research project is such that they contribute significantly to the design, performance, analysis or interpretation of the research. Potential conflicts of interest are reviewed by the Conflict of Interest Committee; where necessary, this committee will recommend procedures to be implemented to eliminate or manage conflicts. All investigators listed on a protocol must have current Conflict of Interest forms (less than 1 year old) on file with the Provost's office. If an investigator has or may have a conflict of interest related to a specific protocol, this must be noted by indicating "yes" in the appropriate line on the face page of the protocol.

Any protocol requesting the use of human biological specimens obtained at YNHMC must also contain additional forms as described (Appendix II).

All boxes in the check-off section of the face sheet that apply to the particular research described in the protocol should be checked. The funding source of the research must be specified. If

research is to be funded only through departmental funds, this should be stated. **If the research may be supported in whole or in part by grant funds (federal or nonfederal), one copy of each grant application must be included with the other materials submitted.**

Federal Drug Administration (FDA) Information:

Investigators are required to indicate the number of the Investigational New Drug (IND) or an Investigational Devices (IDE). The HIC will apply the FDA regulations, 21 CFR 50, 56 and 812 when considering the research.

The FDA will categorize each IDE as an A or B. Medicare may pay for costs related to certain investigational devices that have an investigational device exemption (IDE) number and are categorized as a Category B. The information listed on the protocol application is shared with representatives from the Yale School of Medicine Clinical Compliance Office and the Legal Affairs and Risk Management Office at Yale New Haven Hospital. Therefore the IDE number and the Category A or Category B designation must be listed on the application.

Additional Approvals:

Review by committees other than the HIC may be required prior to commencing research activities. This review can be accomplished either before or after HIC review or it may be conducted concurrently. The HIC will, when appropriate, grant its approval contingent upon the approval by other required committees.

The Yale New Haven Hospital Radiation Safety Committee must approve research involving the use of FDA-approved radioisotopes. Plans to use non-FDA approved radioisotopes purely for research purposes must also be approved by the Yale New Haven Hospital Radioactive Drug Research Committee.

The Yale University Biosafety Committee must approve research involving Recombinant DNA or gene transfers. Additional review by other University and Hospital Committees may also be required for these studies and for other studies involving xenotransplantation or biohazards.

The Psychiatry Department Protocol Review Committee, (DPRC), must approve research funded by Department of Psychiatry grants which include provocative studies, studies with washout periods and those with placebo control groups.

The Cancer Center Protocol Review Committee, (PRC), must approve studies involving the use of Cancer Center personnel or resources.

If use of a clinical research center is required, its program director should be contacted regarding the requirements of the appropriate Clinical Research Committee.

C2. DESCRIPTION OF STUDY

This information may be extracted from a grant application or a cooperative group protocol. It should provide a succinct, but comprehensive, overview of the research sufficient to adequately review the science and the interventions with human subjects.

C2.1 Purpose. State briefly the purpose of the study; usually this will include the hypothesis, which is to be tested.

C2.2 Background. Describe relevant experimental or clinical findings, which led to the plan for this project. This must be succinct and comprehensible without reference to other material. A few pertinent references may be cited. In some cases, as in where earlier studies have produced

conflicting evidence, it will be necessary to cite these studies and explain how it was decided to rely on one side or the other. For studies designed to compare or evaluate therapies, there should be a statement of the relative advantages or disadvantages of alternative modes of therapy. This section should ordinarily be less than one page long; however, when necessary, it may be longer.

C2.3 Specific Location of Study. This should identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. When other institutions are involved, it may be necessary to secure the approval of their Institutional Review Boards.

C2.4 Probable Duration of Project. This should be the estimate for the entire study. HIC re-approval is required at least every year as long as the study is continued. In specific cases, more frequent re-approval may be required.

C2.5 Research Plan. This is an orderly scientific description of the intended procedures as they directly affect the subjects. There need not be a detailed account of techniques that do not directly affect the human subject (e.g., details of in vitro studies). Include number and estimated length of hospitalizations, length of time for various procedures and frequency of repetition, any manipulation that may cause discomfort or inconvenience, doses and routes of administration of drugs, amounts of blood to be drawn and plans for follow-up. The use of published and widely accepted survey instruments need only be identified in the protocol and the instruments themselves need not be submitted. However, the use of original instruments must be approved by the Committee and such instruments must be submitted for review.

C2.6 Data and Safety Monitoring Plan. All research protocols require an explicit plan for data and safety monitoring. The Plan should reflect the nature of the research, especially safety considerations for participants and concerns about unknown or unanticipated risks. When risks are considered minimal, a Plan could be as simple as monitoring of the data and performance of safety reviews, at specified frequency, by the principal investigator. Either the principal investigator or the HIC would be able to stop or modify the study.

When a protocol has more than minimal risks, and sometimes even if risks are thought to be minimal, a more complex Plan will be necessary. This may require the formation of an independent data and safety monitoring board or committee.

Adverse event reporting is a requisite for all Data and Safety Monitoring Plans. Serious unanticipated events must be reported to the HIC within 48 hours. Immediate reporting of serious anticipated events (i.e., those discussed in the protocol and consent form) is also required if the magnitude or frequency of the event is above expectations. If risks are minimal, a Plan could state that:

- 1) serious **unanticipated** adverse events will be reported immediately to the HIC (using HIC form 6A) any appropriate funding and regulatory agencies and the Research Subject Advocate (RSA) at the General Clinical Research Center if appropriate;
- 2) serious anticipated adverse events will be reported immediately to the HIC (and the RSA and others where required) whenever their magnitude or frequency **exceeds expectations**;
- 3) other adverse events will be reported to the HIC (and RSA if required) periodically or, at minimum, when reapproval of the protocol is sought.

Minimum requirements of a Plan are the following:

1. Assessment of risk for subjects participating in the research study.
2. Identify who will conduct the data and safety review and at what frequency the review will occur. Identify who has the power to stop or modify the study.
3. Provide for an assessment of adverse events to include grading and attribution. Adverse events include physical events and also other events such as loss of privacy or significant economic harm.
 - A. Grading (e.g., a graded scale, or serious vs. non-serious, etc., that is appropriate to the type of research)
 - B. Attribution (Is the event attributed to the research, not to the research, uncertain?)
4. Provide a plan for unanticipated adverse event reporting to the HIC, funding agency, and regulatory agency.
5. Provide a plan for anticipated adverse event reporting to the HIC, funding agency, and regulatory agency.

This is a subsection of the Research Plan that should be labeled and included within the Research Plan or Study Design section of the protocol. This same subsection must also appear in the Protection of Subjects section of the Human Subjects part of the protocol. It may appear in its entirety or only by the title, "Data and Safety Monitoring Plan", with reference to the Research Plan section.

Please note that there are specific data and safety monitoring plan requirements for research studies conducted at the Children's Clinical Research Center, the General Clinical Research Center and the Cancer Center. Please reference the center specific plans for further information at <http://info.med.yale.edu/hic/policy/index.html>.

C2.7 Statistical Considerations: Studies which cannot be expected to answer the scientific questions posed by the research, because of small numbers, low statistical power or other major flaws in research design, can provide no benefit to the patient and cannot justify even the smallest degree of subject inconvenience, let alone risk. Therefore, except for pilot studies, which are clearly designed to further the development of more extensive research protocols, 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.

C2.8 Economic Considerations. Describe any material inducements that will be offered to subjects in return for their participation: e.g., direct payment, free hospitalization, medical care, medication, food, tests, etc. Describe any schedule of payment to subjects based on their complete or partial participation. Identify whether early withdrawal from the study will result in a reduced payment or whether it makes a difference if it is the subject or the investigator who decides to terminate the subject's participation. Explain any bonus a subject may receive for completion of the study. These partial or bonus payments must also be explained in the consent form.

C3. HUMAN SUBJECTS

General Instructions: For your convenience this portion of the protocol is organized as required by NIH and some other Federal funding agencies. Because NIH now requires this section to be incorporated within the body of a grant or contract proposal, this material should be prepared as part of the grant application in such a way as to also form an integral part of the HIC research protocol. If you are not applying for a grant, this section must still be submitted for the HIC. For all protocols, instructions under these general headings must be followed:

C3.1 Subject Population: Provide a detailed description of the proposed involvement of human subjects. Describe the characteristics of the subject population, including their anticipated number, age range and health status. Identify the criteria for inclusion or exclusion of any sub-population. Explain the rationale for the involvement of special classes of subjects, such as fetuses, pregnant women, children, prisoners, institutionalized individuals, or others who are likely to be vulnerable.

List the specific inclusion and exclusion criteria. If women who could become pregnant are to be excluded, see Section C.3.D of these Guidelines.

C3.2 Source of Research Material: Identify the sources of research material obtained from individually identifiable living human subjects in the form of specimens, records, or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records, or data.

C3.3 Consent Procedures: Describe consent procedures to be followed, including how, where, and by whom informed consent will be obtained. Note that some funding agencies, including NIMH, require that the consent form be included in a grant application. The consent form should be appended to the protocol exactly as you plan to submit it to the funding agency and to the subject.

Oral consent: Written consent forms are generally required. However, in studies that present no more than minimal risk of harm to subjects and involve no procedures for which written consent is normally required in the context of medical practice, oral consent may be approved by the HIC. Written consent may also be waived by the HIC if the consent form is the only record linking the subject to research involving sensitive information and the primary risk of the research would be breach of confidentiality. If the investigator believes that oral consent is appropriate, he or she should put on the consent form the information to be presented to the subject and, in this section of the protocol, justify the request for waiver of the requirement for documentation of consent. If the HIC agrees that the nature of the research warrants oral consent, it will require that the information be presented to the subject as an information sheet.

Advertisements and materials designed to solicit subjects such as websites, TV ads, must be approved by the HIC. The HIC protocol number must appear on all such items.

No hospitalized patient should be approached to participate in research until his or her responsible physician has approved contact between the investigator and the patient. Investigators who believe that prior approval of the responsible physician is unnecessary for a particular protocol should provide their reasons for this in this section.

C3.4 Risks: There should be a description of all reasonably foreseeable risks, discomforts, or inconveniences to the subject; this description should reflect the information provided in Section III.B of the protocol. If there are no risks associated with participating in the study, state: "*There are no risks of physical injury.*"

Risks may include side effects of drugs, hazards of procedures, or dangers of withholding of a therapy of proven value. Potential research risks include more than physical harm; risks may also include emotional or psychological harm, social risk of stigmatization, economic or legal risk. Potential risks if genetic information becomes known to the subject or to others must also be considered. These risks may include:

- a. Access to or retention of benefits or entitlements (e.g., health insurance, life or disability insurance, educational opportunities, employment, etc.)
- b. Stigmatization: views of others, within or without the subject's family, about the subject; possibility of altered family relationships and interactions
- c. Psychological responses to information: altered self-concept; possible feelings of depression, guilt, anger, etc.
- d. Detection of biological relationships within a family: paternity, maternity, adoption

The magnitude of the risks and a description of the risks should be given in both the protocol and the consent form. The extent of the description of these risks may be extensive or may be brief, depending on the protocol. When possible, it is appropriate to cite statistical probability of risk occurrence. The subject should be told what will be done to minimize risks and counteract side effects and which, if any, side effects might be irreversible. In addition to the known risks of being in the study, there may be unforeseeable complications; the subject should be made aware of this fact.

Federal regulations require, for any research involving more than minimal risk an explanation as to whether any compensation and/or medical treatment is available if injury occurs and, if so, what it consists of, or where further information may be obtained. (See the Risk section under Part III D of the Guidelines). If a study entails minimal risk and if in the opinion of the investigator, there is the potential for physical injury, an "in case of injury" section should be incorporated into the protocol and consent form. The HIC requires that "*In case of injury*" provisions be addressed in the protocol and in the consent form for all studies conducted at the General Clinical Research Center (GCRC).

"*In case of injury*" provisions should include: (1) where and from whom medical therapy may be obtained (2) what therapy will consist of and its duration (3) who will pay for this therapy (4) whom to contact in case of injury and (5) what happens after the study ends or if the subject is dropped from the study because of progression of disease and/or other circumstances.

When appropriate given the nature of the research being conducted, the principal investigator may need to distinguish between treatment for injuries related to the investigational intervention versus routine medical care for complications or conditions associated or expected with the disease or disorder involved. The source of funds internal to Yale University, if any, to cover the costs of medical therapy for injuries should be specified. If none are available to the investigator, it is important that the subject understand what may be properly billed to him/herself or third party payer, including routine medical care that is normally billed to the subject even when it is performed in conjunction with a research study.

Additionally, because there is a responsibility to protect the subject and mitigate risks whenever possible, the principal investigator should attempt to obtain funding sources for treatment of injuries whenever possible.

When the study is sponsored by a commercial, for-profit entity, the principal investigator is required to attempt to secure from the sponsor a written commitment to pay for the costs of medical therapy. It is preferred that the sponsor's commitments not be that the sponsor's reimbursement begins where the subject's insurance carrier's coverage ends. A copy of the sponsor's written commitment (which may be in the research contract) must be sent to the Office of Grants and Contract Administration for inclusion into the formal agreement between the sponsor and the University.

C3.5 Protection of Subjects: Describe the procedures for protecting against or minimizing potential risks, including risks to confidentiality and assess their likely effectiveness. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Also, where appropriate, describe the provisions for monitoring the data collected to ensure the safety of subjects. For example, the subject might be withdrawn from the study or a corrective drug might be administered.

If data collected for research purposes have clinical significance for individuals in the study but the data will be analyzed at another institution, resulting in substantial delay in receipt of important clinical findings affecting the subject's welfare, the investigator should specify how he or she intends also to monitor the subject locally.

If women who might become pregnant are to be excluded, justify this exclusion in the protocol. Both the protocol and consent form must specify how this will be accomplished. The following information should also be included in the consent form. A pregnancy test (which one) will (or will not) be done as a screening procedure and if it is to be repeated, this should be specified. During the consent process the investigator will review with each woman her plans to avoid becoming pregnant. If -- in the judgment of the investigator -- the plans are inadequate, the woman either will be advised as to how to make them adequate or will be excluded from the study. Each woman should be informed that she is to notify the principal investigator promptly if she departs in any way from the plans she discussed at the outset with the investigator or if, in spite of adherence to these plans, she thinks she might be pregnant. (If applicable, describe procedures to be taken with minors when doing pregnancy tests.)

When appropriate, the subject should be assured that steps will be taken to assure confidentiality. This is particularly important in studies in which information will be recorded which, in the view of the subject, is sufficiently sensitive so that he or she would not wish persons other than the investigators to have access to it. In such cases, data may be marked only with a code number, and identifying information filed separately, with access to the code limited to responsible investigators. Whatever measures are taken to assure confidentiality should also be discussed in general terms in the consent form. Do not promise confidentiality in situations where it is unnecessary or where it may be presumed.

If videotapes are to be made for research purposes, a separate consent form should be used to cover this. YNHMC's standard videotape consent form may be used if modified to reflect the details of the protocol. It should state when the tape will be erased, that the subject has the right to demand erasure at any time, and the circumstances, if any, under which the tape might be used for purposes other than the research described in the protocol -- e.g., educational purposes.

C3.6 Data and Safety Monitoring Plan. (May restate or reference to the DSMP segment outlined in the Description of Study section of the protocol.) All research protocols require an explicit plan for data and safety monitoring. The Plan should reflect the nature of the research, especially safety considerations for participants and concerns about unknown or unanticipated risks. When risks are considered minimal, a Plan could be as simple as monitoring of

the data and performance of safety reviews, at specified frequency, by the principal investigator.. Either the principal investigator or the HIC would be able to stop or modify the study.

When a protocol has more than minimal risks, and sometimes even if risks are thought to be minimal, a more complex Plan will be necessary. This may require the formation of an independent data and safety monitoring board or committee.

Adverse event reporting is a requisite for all Data and Safety Monitoring Plans. Serious unanticipated events must be reported to the HIC within 48 hours. Immediate reporting of serious anticipated events (i.e., those discussed in the protocol and consent form) is also required if the magnitude or frequency of the event is above expectations. If risks are minimal, a Plan could state that:

1. serious **unanticipated** adverse events will be reported immediately to the HIC (using HIC form 6A) and any appropriate funding and regulatory agencies;
2. serious anticipated adverse events will be reported immediately to the HIC (and others) whenever their magnitude or frequency **exceeds expectations**;
3. other adverse events will be reported to the HIC periodically or, at minimum, when reapproval of the protocol is sought.

Minimum requirements of a Plan are the following:

1. Assessment of risk for subjects participating in the research study.
2. Identify who will conduct the data and safety review and at what frequency the review will occur. Identify who has the power to stop or modify the study.
3. Provide for an assessment of adverse events to include grading and attribution. Adverse events include physical events and also other events such as loss of privacy or significant economic harm.
 - Grading (e.g., a graded scale, or serious vs. non-serious, etc., that is appropriate to the type of research)
 - Attribution (Is the event attributed to the research, not to the research, uncertain?)
4. Provide a plan for unanticipated adverse event reporting to the HIC, funding agency, and regulatory agency.
5. Provide a plan for anticipated adverse event reporting to the HIC, funding agency, and regulatory agency.

This is a subsection of the Research Plan that should be labeled and included within the Research Plan or Study Design section of the protocol. This same subsection must also appear in the Protection of Subjects section of the Human Subjects part of the protocol. It may appear in its entirety or only by the title, "Data and Safety Monitoring Plan", with reference to the Research Plan section.

Please note that there are specific data and safety monitoring plan requirements for research studies conducted at the Children's Clinical Research Center, the General Clinical Research Center

and the Cancer Center. Please reference the center specific plans for further information at <http://info.med.yale.edu/hic/policy/index.html>.

C3.7 Confidentiality: Describe the provisions to protect the privacy and confidentiality of subjects participating in the research study, including how any identifiable information that is obtained in connection with the study will remain confidential and will be disclosed only with the subject's permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. Further describe the disposition of information obtained during a study. When a study is of a diagnostic or therapeutic modality, information is very often entered in the subject's medical record, discussed with the subject, and transmitted to anyone else whom the subject designates. If the intent of a study is not directly related to diagnosis or therapy of a particular subject, he or she has the right to decide whether or not such information shall be entered into the medical record or transmitted directly to the private physician.

Some particularly sensitive research (e.g., involving drug or alcohol abuse) may require a federal confidentiality certificate, which affords protection of the investigator's records against subpoena. Further information on [Certificates of Confidentiality](#) is available on the HIC website and in section E7 of these guidelines.

When subjects will be tested for reportable diseases, such as HIV or Hepatitis testing the protocol must clearly reflect these limits to confidentiality. "The requirements for reporting infectious disease to the Connecticut Department of Public Health includes positive HIV results. The report must include the subject's name or a coded version of the name."

Limits on confidentiality, such as inspection of medical records by the HIC or agents of the FDA and the industrial sponsor in studies involving investigational drugs and devices, should also be explained.

C3.8 Potential benefits: Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and in relation to the importance of the knowledge that may reasonably be expected to result.

If a test article (investigational new drug, device or biologic) is involved, name the test article and state whether the 30-day interval between submission of applicant certification to the Food and Drug Administration and its response has elapsed or has been waived and/or whether use of the test article has been withheld or restricted by the Food and Drug Administration.

C3.9 Risk-Benefit Ratio: This section should consist of the investigator's explanation of how he or she concluded that the risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result from the research.

C4. CONSENT FORMS

C4.1 General Principles

The National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research highlighted in *The Belmont Report* the concept of respect for persons as a basic ethical principle of human subject research. The practical expression of this concept is the informed

consent process, which is codified in the informed consent form. The consent form serves a dual role: as an informational and reference document for subjects, as well as a symbol of the process through which consent is obtained.

The consent form should be a statement addressed to the subject that gives reasonable information about the study, its procedures, benefits, risks and alternatives, to enable him or her to make an intelligent decision about participation. The consent form should be worded in the second person and written in language that the prospective subject can be expected to understand. It should be concise, literate and be proofread carefully for errors in spelling and grammar. The HIC has developed an [informed consent form template](#) that contains information on the key aspects of informed consent, suggested wording, and required formatting elements. Use of this template is strongly encouraged; however, the HIC acknowledges that this form may not be appropriate for all research. Investigators should use their discretion in modifying or deviating from the informed consent template.

The consent form must not sound coercive. It may not include any language through which a subject is made to waive or to appear to waive any legal rights or to release the institution or its agents from liability for negligence.

All subjects invited to participate in a research protocol must give voluntary, prospective informed consent. For these purposes, control subjects – including normal volunteers – are always viewed in the same way as other subjects. Even if the research plan is to treat control subjects with standard accepted diagnostic and therapeutic maneuvers, consent will be required if data are to be collected for research purposes.

If a procedure is performed solely for purposes of identifying a population of research subjects, or for screening purposes, consent is required. In this case, investigators may wish to present prospective subjects with a consent form describing only the screening procedure. This document need not contain detailed information about the entire study, but should instead inform subjects about the screening procedures. A separate consent form may then be presented to those who are found to be suitable. In such situations, while soliciting consent for screening or eligibility procedures, the investigator should make available the consent form subjects will be asked to sign if they prove to be suitable subjects for further study.

If there are two or more consent forms, please label each clearly as to which subject population is addressed.

C4.2 Secondary and Third Party Research Subjects

Pursuant to 45 CFR 46.116, the HIC requires researchers to obtain legally effective informed consent from all research subjects. Federal regulations define human research subjects as individuals about whom an investigator conducting research collects (1) data through interaction or intervention, or (2) private identifiable information. Individuals who are not primary subjects in a research study, but *about whom* the study seeks identifiable private information, are commonly referred to as “secondary” or “third-party” subjects.

Private information includes information

- About behavior that occurs in a context in which an individual can reasonably expect that no observation is taking place;

- Which has been provided for specific purposes by an individual, and that the individual can reasonably expect will not be made public; and
- That is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator).

Examples where informed consent from the secondary subject would be required include asking a subject's caregiver to fill out quality-of-life or other questionnaires relating to the subject's condition and care, questions to a caregiver about the *caregiver's condition*, or creating a pedigree based on the presence or absence of a phenotypic characteristic.

The HIC has the authority to waive informed consent pursuant to 45 CFR Section 46.116(d) and will consider such requests for waiver of consent for secondary subjects when reviewing the protocol application. This regulation permits the HIC to approve a consent procedure which does not include, or which alters, some or all of the key elements of informed consent (See Part C4.B) or waive the requirement to obtain informed consent provided that the HIC finds and documents the following:

- (1) Research involves no more than minimal risk to 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

Investigators seeking a waiver of informed consent are encouraged to address these four criteria in their applications, thereby facilitating HIC evaluation of the request.

C4.3 Preparation of Consent Form

General Instructions: THE MOST COMMON REASON FOR DELAY OF APPROVAL OF A PROTOCOL IS AN IMPROPERLY PREPARED CONSENT FORM – EITHER INCOMPLETE INFORMATION OR COERCIVE, JARGONISTIC, OR OVERLY TECHNICAL LANGUAGE. The primary reviewer is available to help write the consent form. In addition, the HIC has created an [Informed Consent Checklist](#) to aid investigators in determining whether the consent form meets current standards and requirements.

As required by federal regulations¹, each of the following points must be covered on all consent forms except in cases where the point is irrelevant to the proposal:

Invitation to Participate and Description of Project: The subject must be clearly *invited* to participate in the study. To “request” participation does not convey so clearly that the subject has a choice.

Example: *You are invited to participate in a research study of...*

After the invitation the following paragraph should appear, modified as appropriate. For example, if no therapy is involved in the protocol, there is no need to mention alternatives. In some cases the entire paragraph may be unnecessary; e.g., very simple protocols involving collection of single specimens of blood or urine.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed judgment. This consent form provides you with detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Purpose: The purpose of the study should be expressed in lay terms, at a level that can readily be understood by the subject population. It should be clear to the subject that this is a research study.

The nature of some studies requires that the full purpose not be revealed to the subject until the study is completed. Such deliberate withholding of information is permitted only if the subject is informed that this is the case and agrees. This must be clearly stated in the consent form, along with the plan for when and how the complete information will be shared with the subject. Research based on deception or incomplete disclosure should be thoroughly justified and discussed with the primary reviewer.

Selection of Subjects: The consent form should explain briefly why the prospective subject is eligible to participate in the research.

Procedures: The subject must be informed exactly what participation will involve, with particular attention to the way he or she will experience the research. This may include description of the length and frequency of hospitalizations; number, length, and frequency of visits with the research team; types of medication; types and numbers of tests; or amount of blood to be withdrawn (in terms a lay person could understand, such as teaspoons, tablespoons, ounces, or milliliters). It is also important to describe common research terminology, such as “randomization,” “placebo control,” “single” or “double blind” and “crossover studies” in suitable lay language.

There are situations where the difference between clinically indicated and experimental interventions must be explained for subjects in the “Procedures” section of the consent form. These sections should contain a clear statement regarding which procedures are experimental and which procedures are standard of care.

If the research involves non-invasive procedures such as questionnaires, interviews or focus groups, subjects should be clearly informed of the types of question they will be asked.

Risks and inconveniences: There should be a description of all reasonably foreseeable risks, discomforts, or inconveniences to the subject; this description should reflect the information provided in Section 3B of the protocol. Risks may include side effects of drugs, hazards of procedures, or dangers of withholding a therapy of proven value. Potential research risks include more than physical harm; risks may also include emotional or psychological harm, social risk of stigmatization, economic or legal risk. When possible, it is appropriate to cite statistical probability of risk occurrence. The subject should be told what will be done to minimize risks and counteract side effects and which, if any, side effects might be irreversible. In addition to the known risks of being in the study, there may be unforeseeable complications; the subject should be made aware of this fact.

In single or double blind studies, the consent form must also contain the information that the key to the codes will be kept in the Pharmacy Department, where there is 24-hour service. In an emergency, telephoning the Pharmacy Department may identify the medications being taken as part of the study. The principal investigator must provide the subject with an identification bracelet or

wallet card which includes the information that he or she is participating in a blinded study, the HIC number of the study, the name and phone number of the investigator, the subject's code number in the study, and the message that in an emergency the code may be broken and information about the drug may be obtained by contacting the YNHH Pharmacy (provide its phone number) at any time of day or night.

In studies involving investigational drugs, it may be desirable to state on the consent form that, in an emergency, information about the drugs may be obtained by contacting the study pharmacy. When appropriate, the subject should also be informed that he or she would be provided with a card identifying the subject as being in a study involving an investigational drug. The card should include the name of the investigational drug, the HIC number of the study, the name and phone number of the investigator and a phone number that may be called at any hour of day or night for further information about the drug. Ordinarily, this will be the number of the YNHH Pharmacy.

All plans to involve the YNHH Pharmacy in the conduct of a protocol must be cleared in advance with the Pharmacy.

Benefits: This section should describe any benefits that may be reasonably expected to result from the research. These benefits may be expected to accrue to the subject, to the population the subject represents, or to society at large. However, expected benefits should not be guaranteed or overstated. Research, by definition, is not designed to provide direct health-related benefits to subjects. For some studies, it may be appropriate to state that subjects will receive no direct benefit from their participation.

Payment to subjects is *not* considered a research benefit, and should not be listed in the Benefits section of the consent form.

Economic Considerations: The information presented in Part II on Economic Considerations should be presented here in appropriate language. The net financial consequences of participation in the project should be made clear. Using terms as specific as the protocol will permit, identify the amount the subject (or the third-party payer) will be expected to pay as a consequence of the subject's participation in the protocol. Subjects and third-party payers generally should not be expected to pay for procedures performed purely for research purposes. Additionally, please describe any payment that will be made to subjects.

Treatment Alternatives/Alternatives: For studies offering treatment, the consent form should identify the subjects' alternatives to participation in the protocol and should offer a discussion of their relative advantages and disadvantages. In some cases it may be appropriate to provide a statement of the nature of the alternatives—(e.g., surgery, radiation therapy). However, it is usually not necessary to provide a full account of their risks and benefits in the consent form. In some cases it may be appropriate to state that one reasonable alternative to the prospective subject is to choose against accepting any therapy.

Some categories of non-treatment research may also require a section outlining alternatives to participation. For example, a study that provides screening for a particular illness or condition should state whether testing is available outside of the research. In this case, the section should be labeled "Alternatives" rather than "Alternative Treatments."

Confidentiality: Steps taken to assure confidentiality should be explained in the consent form. Limits on confidentiality, such as inspection of medical records by the HIC or agents of the FDA and the industrial sponsor in studies involving investigational drugs and devices, should also be explained.

The subject should be informed about the disposition of information obtained during a study. When a study is of a diagnostic or therapeutic modality, information is very often entered in the subject's medical record, discussed with the subject, and transmitted to anyone else whom the subject designates. If the intent of a study is not directly related to diagnosis or therapy of a particular subject, he or she has the right to decide whether or not such information shall be entered into the medical record or transmitted directly to the private physician. Positive HIV antibody test results will be recorded in the medical records of those who have such records (see Section E.5 of these Guidelines).

Some particularly sensitive research (e.g., involving drug or alcohol abuse) may require a federal confidentiality certificate, which affords protection of the investigator's records against subpoena. Further information on [Certificates of Confidentiality](#) is available on the HIC website.

When subjects will be tested for reportable diseases, such as HIV or Hepatitis, the consent form must clearly reflect these limits to confidentiality. For example, a consent form for subjects who are tested for HIV should state, "The requirements for reporting infectious disease to the Connecticut Department of Public Health includes positive HIV results. The report must include the subject's name or a coded version of the name."

Compensation and medical therapy: Federal regulations require, for any research involving more than minimal risk, an explanation as to whether any compensation and/or medical treatment is available if injury occurs and, if so, what it consists of, or where further information may be obtained. (See the Risk section under Part 3.D of the Guidelines). If a study entails a minimal risk of physical injury, the HIC requires that "*In case of injury*" provisions be addressed in the protocol and in the consent form.

"*In case of injury*" provisions should include: (1) where and from whom medical therapy may be obtained (2) what therapy will consist of and its duration (3) who will pay for this therapy (4) whom to contact in case of injury and (5) what happens after the study ends or if the subject is dropped from the study because of progression of disease and/or other circumstances.

When appropriate given the nature of the research being conducted, the principal investigator may need to distinguish between treatment for injuries related to the investigational intervention versus routine medical care for complications or conditions associated or expected with the disease or disorder involved. It is important that the subject understand what may be properly billed to him/herself or his/her insurance carrier, such as routine medical care that is normally billed to the subject even when it is performed in conjunction with a research study.

Federal regulations also require that the consent form not include any exculpatory language through which the subject is made to waive or appear to waive his or her legal rights or to release the University, hospital, or a sponsor from liability for negligence.

The following sample language is provided to assist principal investigators in meeting their responsibilities to clearly and fully disclose to subjects provisions provided in case of injury. These are only guidelines and should not be used as substitutes for the principal investigator's careful assessment of the specifics of each unique study.

C4.3(A) For protocols sponsored by a commercial (for-profit) entity in which the sponsor has agreed to provide reimbursement for medical therapy, state in the consent form in language appropriate for the proposed subject population:

If you are injured as a direct result of your participation in this research study, the medical staff at the Yale New Haven Hospital [or enter appropriate site] will provide immediate emergency

care, short-term hospitalization and/or short-term outpatient care to you. The sponsor, [enter name], will pay for the cost of this treatment (if applicable, add, "if your insurance carrier does not pay for it").

Additionally, you should know that there are no plans to compensate you for physical or mental disability, lost wages or any other losses or damages occurring over the long term or if an injury becomes apparent after your participation in the study has ended. However, by agreeing to participate in this research study, you are not waiving or giving up any legal rights to seek compensation. If you believe you have been injured, please contact [Enter name of principal investigator] at [Enter phone number] immediately.

C4.3(B) For protocols sponsored by a commercial (for-profit) entity in which the sponsor will not provide reimbursement for medical therapy, state in the consent form in language appropriate for the proposed subject population:

If you are injured as a direct result of your participation in this research study, the medical staff at the Yale New Haven Hospital will provide immediate emergency care, short-term hospitalization and/or short-term outpatient care to you. However, you or your insurance carrier will be billed for the cost of this treatment.

Additionally, you should know that there are no plans to compensate you for physical or mental disability, lost wages, or any other losses or damages occurring over the long term or if an injury becomes apparent after your participation in the study has ended. However, by agreeing to participate in this research study, you are not waiving or giving up any legal rights to seek compensation. If you believe that you have been injured, please contact [Enter name of principal investigator] at [Enter phone number] immediately.

C4.3(C) For protocols sponsored by not-for-profit entities or governmental agencies in which no funds are provided for reimbursement of medical therapy, the language in paragraph (B) above is appropriate.

C4.4(D) For protocols sponsored by not-for-profit entities or governmental agencies in which funds are provided for reimbursement of medical therapy, the language in paragraph A is appropriate along with an explicit explanation as to any limitations and/or constraints associated with the funding provided.

Voluntary Participation: Subjects should be informed that they are free to decide whether or not to participate, and also free to withdraw from the study at any time unless the nature of the investigation, once commenced, precludes this. They should be assured that if they prefer not to participate or decide to withdraw, they would still receive standard treatment, if such a statement is appropriate. There should also be assurance that a decision not to participate will not adversely prejudice future interactions with the institution. This is particularly important when a dependent relationship exists between the investigator and the subject, such as physician-patient, employer-employee, faculty-student, etc. If withdrawal or non-participation in the study would result in transfer of the patient to another service or institution, this must be made clear. The right to withdraw includes the right to require that stored tissue or body fluid specimens be destroyed, unless subjects are specifically informed in the consent form that the only option will be anonymization.

In some studies, abrupt withdrawal from a study may be dangerous to a subject. In such cases, this danger must be explained and it must be made clear that the subject should not withdraw without first discussing it with the investigator so that plans for safe and orderly withdrawal can be made.

Questions: Since subjects usually need time to decide about participation, it is generally appropriate to include the following statement: *"Before you sign this form, please ask any questions on any aspect of this study that is unclear to you. You may take as much time as necessary to think this over."* If the proposed procedures are complex or hazardous, patients should be encouraged to discuss them with their own physician or anyone else they wish before making a decision.

Authorization: This statement is included on the template consent form.

Signatures: Spaces are provided for the signature of the person who consents to participate in the study or someone else who consents on behalf of the individual who will be the subject of the study. There is a space also for the signature of the person who obtains the consent – who would be the principal investigator or his or her authorized representative. If the subject is a child old enough to understand, the child should indicate her or his assent by signing the consent form after the procedures have been explained.

Continuing Contact: Following the signatures on the consent form there is a standard statement of whom to contact in the event questions arise during the conduct of the research or the subject believes he or she has sustained a research-related injury. The name and telephone number of the principal investigator should be typed in the spaces provided. In addition, the Human Investigation Committee Office and telephone number should be specified as a contact regarding rights of subjects. The reasons for any proposed modification of the standard statement should be provided.

A signed copy of the consent form must be placed in the subject's hospital medical record, if applicable. If the subject has a medical record in YNHMC but the principal investigator does not wish to include the consent form therein, the reasons for this must be specified in the protocol. Examples of exceptions might include research irrelevant to the medical record or violations of confidentiality. In all cases, a copy showing the signatures must be given to the subject, and another must be retained in the investigator's files. These latter copies must be available for review in the event of an audit. Signed consent forms are not to be sent to funding or regulatory agencies or industrial sponsors.

When appropriate (as determined by the HIC), the following additional elements may be included in the consent form. Such elements include, but are not limited to:

A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant), which are either known or currently unforeseeable.

Anticipated circumstances under which the subject's participation may be terminated by the investigator.

A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

The approximate number of subjects involved in the study.

A specific estimate of costs to the subject that may result from participation in the research.

The consequences of the subject's decision to withdraw from the research and procedures for safe and orderly termination of participation by the subject

D. ADMINISTRATIVE PROCEDURES

D1. DUPLICATION OF PROTOCOLS AND DELIVERY TO HIC

When the protocol is complete and all the necessary signatures have been obtained on the face sheet, the original plus two (2) copies must be delivered to the HIC Office in time to make any applicable deadlines. For expedited review, the original plus two (2) copies are required. (*See Guidelines for Investigators, The Human Investigations Committee, Section A, 1*)

D2. ACTION BY HIC

The HIC assigns to each protocol a secondary reviewer who, with the primary reviewer, has the responsibility of studying it carefully and introducing its discussion at the HIC meeting. Copies of protocols are sent to all committee members for study. At the HIC meeting the committee decides

- (a) to approve the protocol as submitted,
- (b) to approve it subject to minor modification,
- (c) to defer its decision pending substantive change and resubmission to the entire committee, or
- (d) to disapprove the protocol.

The HIC conveys in writing to the investigator the committee's decision promptly after the meeting.

D2.1 If the protocol is approved, a copy of the protocol is signed and dated by the chairperson or his/her designee. The signed protocol is returned to the investigator, along with a letter which should convey her or his responsibilities to report adverse reactions, to request that modifications of the research plan be approved by the HIC, and to seek re-approval accordingly. In addition, the approved consent form will be initialed and dated, validating it for the period of approval. The investigator is responsible for using only the current, validated consent form for obtaining signatures from subjects.

It is the responsibility of the investigator to forward notification of approval to those funding agencies, which require it. If a CRC is to be used, the investigator should also send one copy of the approved protocol to the program director or administrative coordinator of the CRC.

D2.2 If the protocol is approved subject to minor modification, the investigator is sent a copy of the protocol and a letter describing the revisions requested. After the revisions are made, the investigator sends three (3) copies of the revised protocol to the HIC Office. If the revisions are satisfactory, the forms are signed indicating approval and one copy is returned to the investigator. Investigators who disagree with the requested revisions can present their reasons in writing to the HIC for full Committee review.

D2.3 When the decision on a protocol is deferred, a primary reviewer is usually designated to discuss the reasons with the investigator and help him or her develop a more acceptable study. After a deferred protocol has been revised, it is treated like a new protocol. After the primary reviewer and department have endorsed it, the original plus two (2) copies must be delivered for circulation to the HIC for discussion at its next meeting.

D3. EXEMPTION FROM REVIEW

Some protocols may be exempt from review. The HIC in accordance with applicable regulations (45 C.F.R. 46.101(b)) will determine which procedures are exempt from review. The investigator cannot make this determination. Criteria for "exempt research" are described in Appendix I to these Guidelines. An application form for a determination of "exempt research" status (**Request for Exemption from Review**) is available in the HIC Office or through the HIC Web site.

D4. EXPEDITED REVIEW

Expedited review procedures may be employed at the discretion of the HIC, as limited by applicable regulations (45 C.F.R. 46.110), for some protocols and amendments that present no more than minimal risk. A list of classes of research that are usually eligible for expedited review is included in Appendix I to these Guidelines. The list is taken from the Federal Register at 63 Fed. Res. 60364-60367 (November 9, 1998). An application form for expedited review (*Request for Expedited Review*) is available in the HIC Office. Investigators must consult with a primary reviewer and obtain her or his signature before submitting a protocol with a request for expedited review.

Expedited review is conducted by the chairperson or his/her designee, in consultation with other HIC members as necessary. For expedited review the original plus two (2) copies of a completed protocol must be submitted.

D5. INSTITUTIONAL ENDORSEMENT

Many funding agencies, including NIH, require certification by an authorized official of the institution that any research involving human subjects described in a grant application or contract proposal has been approved by the HIC. At the Yale-New Haven Medical Center such endorsements may be provided by the chairperson or his/her designee. If institutional endorsement is required, it is necessary to complete the appropriate form. (Form #16).

D6. REAPPROVAL OF PREVIOUSLY APPROVED PROTOCOLS

All protocols must be reapproved at least annually by the HIC until they are terminated. For some protocols more frequent reapproval will be required; in these cases, the intervals will be specified in the initial letter of approval. HIC will issue a reminder notice to investigators prior to the deadline for reapproval. However, it is the investigator's responsibility to request review and reapproval by the HIC. A form for the request will be included with the notice (**Request for Reapproval or Termination, HIC Form 5**). When the request for reapproval is submitted, the most recent consent form should be attached so that it can be initialed and validated until the next scheduled review (including cases in which no revision of the consent form is planned). The original and two (2) copies of the request for reapproval and of the consent form should be sent to the HIC Office.

The HIC employs a primary reviewer system, the purpose of which is to provide the investigator with a Committee member to serve as an advisor throughout the protocol preparation process. The Principal Investigator may identify his/her own primary reviewer for all protocols; or if

the investigator chooses not to select a primary reviewer the HIC will appoint one. **(Please see the list of HIC I and HIC II Committee members to select a primary reviewer, at <http://info.med.yale.edu/hic/committee>)**

The protocol will be reviewed and reapproved at a convened meeting of the full committee or pursuant to expedited review procedures, if appropriate. Reapproval may be made contingent upon any modifications considered necessary by the HIC. Investigators are required to complete the requested modifications within a reasonable period of time. If the HIC does not receive the requested modifications within 6-8 weeks of the HIC's request, the Principal Investigator will be sent a notice asking why a response has not been forthcoming and informing him/her that the protocol may be closed if there is no response. The Principal Investigator must inform the HIC of the status of the protocol after receiving an inquiry notice.

In an attempt to tighten controls over research using human subjects and to ensure that all HIC protocols meet current applicable standards, the principal investigator will usually be required to re-write active protocols after five years. Principal Investigators will be notified of this requirement after the fourth year.

The reapproval application form **(Request for Reapproval or Termination, HIC Form 5)** is available in the HIC Office or on the HIC web site at <http://info.med.yale.edu/hic>.

D7. PROPOSED CHANGES IN PROTOCOLS AFTER APPROVAL

Any changes to an approved protocol must be requested in writing and submitted to the HIC office for approval. The investigator should outline and justify the amendment requests in a cover letter. The changes must also be incorporated into a revised protocol and consent form(s). Three copies of the revised protocol and/or consent form should be submitted to the HIC, one (1) copy should note the changes in bolded text copy. Two (2) non-bolded copies should also be submitted.

Amendments are reviewed either at a convened meeting of the full committee or, if it qualifies, reviewed in accordance with expedited review procedures. HIC approval is required before implementing any changes to the research study. Investigators should be prepared to wait two to four weeks for amendment approval.

The HIC may require a principal investigator to rewrite a protocol or develop a separate protocol if the amendment is found to be an extensive modification of study design or purpose.

When amending protocols there may be certain amendments that are billable. Commercial, for-profit company initiated studies, may have IRB fees negotiated into their contracts. The company will be billed according to the negotiated IRB review schedule for any sponsor-initiated amendment and may be billed for any investigator-initiated amendment. Amendments are usually billed differentially, depending on whether they are major or minor.

7.1 Minor Amendments

A minor amendment is defined as a change that would not materially affect an assessment of the risks and benefits of the study or does not substantially change the specific aims or design of the study.

Some examples of a minor amendment include, but are not limited to:

- Advertisements
- An increase or decrease in subject enrollment
- Narrowing the range of inclusion criteria

- Broadening the range of exclusion criteria
- Changes in dosage form of a drug, provided the dose and method of administration stay the same
- Changes in subject payment
- Change in Title
- Administrative and clerical changes to improve clarity
- Adding or deleting investigators or others to the research team
- Adding or deleting study sites
- Lessening the number or volume of biological sample collections

7.1.1 Advertisements

When submitting an advertisement investigators should remember the following:

- Print advertisements and flyers in final format, including any graphics or photographs to be used.
- For advertisements that will be placed in media such as radio or television, submit all text, graphics, and other substantive materials.
- Clearly state that the project is a research study.
- Recruitment language should not be coercive and should not state or imply a guarantee of benefits beyond what is outlined in the consent form and protocol.
- Compensation should be stated but it should not be over-emphasized or be the focus of the advertisement to the point it appears coercive.

The following information should be included in an advertisement:

- HIC number,
- Purpose of the study,
- Brief description of eligibility for the study (e.g. age, specific disease, etc.)
- Location of the study and contact person/ name /telephone number.
- All advertisements should conform to commonly accepted standards of “good taste”.

7.1.2 Adding Investigators

When adding an investigator to the research team, that investigator must complete the required Human Subjects Protection Training at either <http://info.med.yale.edu/irbtraining> or <http://cme.nci.nih.gov/>. The investigator may not take part in the research until this training has been completed. If the investigator has taken the NIH training course or another IRB approved human subjects protection training program, he/she must provide proof of completion to the HIC by either faxing or mailing the completion to the HIC office so that the investigator’s human subject protection training profile can be updated.

Also when adding an investigator, the investigator must acknowledge in writing to the HIC that he/she has read the Conflict of Interest (COI) policy and state whether or not a conflict exists. If a conflict is found the investigator(s) must complete and submit the protocol-related COI disclosure form (<http://info.med.yale.edu/hic/forms/>).

The authorization page and the first page of the consent form must be revised and submitted if the Principal Investigator (PI), or the investigator to whom a subject is referred for research related problems, is being changed. When actively enrolling subjects, the consent form must be reviewed and approved by the HIC if the PI’s name and contact information is being amended and the information is referred to in the document.

7.2 Major Amendments

A major amendment is defined as any change, which materially affects an assessment of the risks and benefits of the study or substantially changes the specific aims or design of the study.

Some examples of a major amendment include, but are not limited to:

- Broadening of the range of inclusion criteria
- Narrowing of the range of exclusion criteria
- Changes in design or changes in administration method of a drug
- Substantially expanding the duration of exposure to the test material or intervention
- Adding serious risks or adverse events to the consent form so that they would be considered anticipated risks or events

D8. WITHDRAWAL AND TERMINATION

When a study is completed or withdrawn, the investigator should notify the HIC by submitting a **Request for Reapproval or Termination Form**. Include a brief summary of experience with the project and reasons for its termination or withdrawal. When a protocol is terminated, the investigator should provide an account of any existing continuing obligations to subjects.

A protocol that is not re-approved on or before the anniversary date has lapsed. The protocol will be terminated three months after the anniversary date if there has been no request for re-approval or no formal notification to the HIC that it is terminated. A final report from the Principal Investigator is required by the HIC for all terminated protocols.

D9. REPORTS OF ADVERSE EVENTS

Investigators are required by federal regulations, 21 CFR 56.108(b) and 45 CFR 46.103 (b)(5) to report to the HIC specific types of adverse events or any unexpected situation in which a subject or “others” are exposed to risk. Federal regulations further require the HIC to consider these adverse event reports at the time they are submitted and during the continuing review process.

Investigators are required to report:

- All problems involving risks to subjects that were unanticipated (in that they were not disclosed in the protocol and/or informed consent documents), such as occurrences of physical or psychological harm, or unexpected threats to privacy (e.g., lost records and breaches of confidentiality) or safety (e.g., contaminated IV solutions).
- Risk to “others”. An example would include a research assistant who inadvertently punctured a colleague with a needle used to extract a blood specimen from a research subject.
- Adverse consequences of investigational therapy should be reported only if they were either unanticipated in the consent form or if the original description in the protocol underestimated substantially their probability or magnitude. In addition, anticipated adverse consequences of research procedures must be reported if they are of sufficient magnitude to lead hospitalization or prolong hospitalization or require intervention to prevent hospitalization.

The FDA also provides the following definitions for reporting adverse events:

- Associated with the use of the drug when there is a reasonable possibility that the experience may have been caused by the drug.
- Disability: A substantial disruption of a person’s ability to conduct normal life functions. Life threatening adverse drug experience: Any adverse drug experience that in the view of the investigator places the subject at immediate risk of death from the reaction as it occurred,

i.e., it does not include a reaction, had it occurred in a more severe form, which might have caused death.

- Unexpected adverse drug experience: Any adverse experience, the specificity or severity of which is not consistent with the current investigator brochure or package insert, or not consistent with the risk information described in the general investigational plan or elsewhere in the current application.
- Serious adverse drug experience: Any adverse drug experience occurring at any dose that results in any of the following outcomes:
 - Death
 - A life-threatening adverse experience
 - Hospitalization or prolongation of existing hospitalization
 - A persistent or significant disability/incapacity.
 - A congenital anomaly or birth defect.
- Please note that there are specific reporting requirements and conditions for protocols utilizing the Yale Cancer Center, the General Clinical Research Center and the Children's Clinical Research Center. These requirements are noted in the centers' Data and Safety Monitoring Plans. Investigators are encouraged to reference the comprehensive plans for further guidance. They can be found at <http://info.med.yale.edu/hic/policy/index.html> .
- All reportable adverse events as specified in the data and safety monitoring plan of the individual protocol.

Investigators must report serious and unanticipated adverse events to the HIC within 48 hours of learning of the event using the appropriate form. The name of the subject experiencing the adverse event and/or other information that may directly identify the subject should not be included in the report. The HIC discourages the inclusion of this type of identifying information in the report. The forms can be found at <http://info.med.yale.edu/hic/forms/index.html>. Investigators must analyze adverse events in terms of their relationship to the study protocol, as well as risks to human subjects. Risks must be minimized to the greatest extent possible. Investigators must also consider whether changes in the protocol are necessary to reduce or eliminate the risk. Finally, investigators must consider whether changes are required in the consent form to better inform and protect the rights of human subjects.

Upon receipt of a report of an adverse event, the HIC will consider factors such as the seriousness of the event, whether the event is described in the study protocol and consent form and whether the event occurred at a location for which the Yale School of Medicine is the managing site. The HIC may determine that further investigation of the event is required. In some cases investigators may be required to discontinue a study pending the outcome of HIC review of the adverse event. The HIC is required to ensure the reporting to the Department of Health and Human Services or to the Food and Drug Administration (if either agency has jurisdiction) "unanticipated problems involving risks to subjects or others." In many studies, investigators have additional obligations to report adverse incidents to funding agencies such as the National Institutes of Health, or industrial sponsors. In all instances, the PI will receive an acknowledgement of the HIC evaluation in writing and will inform the PI if further action is required.

D10. PROTOCOL-RELATED CONFLICT OF INTEREST

Introduction:

All members of the Yale University research community should be sensitive to the potential impacts of financial interests and/or non-financial relationships with commercial sponsors or other external entities on the conduct of research and the participation and protection of human research subjects. In compliance with federal guidance and University policy, the HIC considers such relationships and determines whether they might influence or appear to influence the outcome of a research project involving human subjects, the objectivity of the investigator during the performance of such a project, or the investigator's interactions with research subjects who participate in the project. Accordingly, the HIC solicits and reviews relevant information regarding the financial interests of all investigators and key study personnel participating in a protocol involving human research subjects prior to approving or re-approving that protocol.

Definitions:

“Key study personnel” means those persons involved in the design, conduct, and/or the data analysis of the research involving human subjects.

“Financial interests” that may be considered to be conflicts include, but are not limited to, the following: ownership of stocks, bonds, options, patent or royalty interests, receipt of consulting, honoraria or speaking fees, salary, subject accrual rewards and/or penalties, loans, lectureships, memberships on boards of directors or scientific advisory boards.

Role of Investigators and Key Study Personnel:

For all protocols submitted to the HIC, including new protocols and those submitted for reapproval, each participating investigator and key study person must read the Protocol-Related Conflict of Interest policy and answer the screening questions posted on the HIC website. *{Enter hyperlink}*. Investigators and key study personnel being added onto research teams of previously approved protocols must also read the policy and answer the screening questions.

The screening questions assist in evaluating whether the investigator or key study person has a reportable interest. The questions ask whether any investigator or key study person has a financial interest as defined above. The questions also inquire whether the investigator or key study person may have other non-financial interests in or relationships with the company /sponsor that may require disclosure to the human subjects considering participating in the research project. Finally the financial interests of the investigator or key study person include those of his/her spouse, dependent children or domestic partner.

Each participating investigator and key study person who answers “no” to all of the screening questions listed on the website must sign the Protocol for Research Application Form or the Request for Reapproval Form in the space noted on the form as “COI signature”. His/her signature indicates that no actual or perceived COI exists. Individuals who answer “yes” to any of the screening questions are required to complete and sign a Protocol-Related COI Disclosure Form and submit it to the HIC as part of the application package or request for reapproval.
<http://info.med.yale.edu/hic/forms/index.html>

The investigator and/or department chairperson is also responsible for disclosing conflicts of interest in research between the institution and the sponsor as well. Examples include “Enrollment bonuses”, incentives, significant ownership in companies, and post study or other rewards that can be considered compensation within the research arrangement itself.

Investigators and key study personnel affiliated with Yale are reminded of their separate obligation to complete the annual disclosure form required by the University Policy on Conflict of Interest and Conflict of Commitment.

The Role of the HIC:

The HIC is the primary authority at the Yale School of Medicine responsible for ensuring that human research subjects are protected in accordance with federal regulations, University policies, and ethical principles. One of the primary responsibilities of the HIC is to ensure that human research subjects receive all information needed to provide informed consent. The HIC's consideration of investigators' financial interests is intended to ensure 1) that the informed consent process provides the subjects with the facts necessary to make a knowledgeable and sound decision as to whether they wish to participate in the study, and 2) that no conflict exists that would otherwise compromise the protection of human subjects.

The HIC's consideration of investigators' financial interests as they relate to human subject research complements, but does not supplant, the deliberations of the Provost's Committee on Conflict of Interest (the "COI Committee"), which is responsible for reviewing the financial disclosures of all faculty members in accordance with the University Policy of Conflict of Interest and Conflict of Commitment.

Before the HIC meeting at which a protocol is scheduled for consideration, the HIC Chair will review the Protocol Related COI Form, if one is submitted, to determine if there are related actual or potential conflicts. The Chair will evaluate such conflicts and, if necessary, provide a summary to the Committee.

The HIC acknowledges that existing policies for the Public Health Service (PHS) and the Food and Drug Administration (FDA) provide threshold amount guidance as to when an investigator is required to disclose a financial interest. The standard for PHS is \$10,000 or 5% ownership in an enterprise, while the FDA standard is \$25,000. The HIC also acknowledges that current and pending federal guidance is not consistent on this issue and is frequently silent. Therefore, investigators are required to disclose their financial interests, regardless of amount, in general categories.

The HIC Chair will consider whether the interest is so minute that it constitutes a *de minimis* exception, which precludes it from committee deliberation. The Committee will consider established financial thresholds when evaluating studies that are unsponsored or sponsored by entities that do not have established guidelines for financial disclosure. The Committee will determine (1) whether the conflict is permissible in the context of the protocol, and, if so, (2) whether the conflict warrants disclosure to potential subjects as part of the informed consent process. The disclosure of a financial or managerial interest will require the investigator to add an "**Institutional and Investigator Interest in the Protocol**" section to the protocol's consent form. The language included in this section should inform the subject of the investigator/key study person's personal financial interest in the sponsoring company or other interested entity and that it is believed (appropriate review committees believe) that this interest would not adversely effect the safety of subjects enrolled.

Example: "Dr[*Enter name of PI*], the principal investigator of this study at Yale, receives payments from the study sponsor, [*enter name of sponsor*], for lectures about [*name disease*] and its therapy".

Notification

The HIC Chair will notify the principal investigator in writing of any protocol interest that requires disclosure.

Referral to the Provost's Committee on Conflict of Interest

The HIC Chair will share relevant information with the Provost's Committee on Conflict of Interest (the "COI Committee"), which may make additional findings and recommendations

regarding actual and potential conflicts of interest. The COI Committee will also have access to the HIC's records regarding protocol-related conflicts of interest.

Confidentiality and Record Retention

In the Protocol-Related COI process, the confidentiality of investigators and key study persons will be respected. Financial disclosure forms will be kept in confidential files, and information will be shared only on a need-to-know basis.

D11. EMERGENCY USE

Federal regulations for the protection of human subjects do not permit research activities to be started, even in emergency, without prior HIC review and approval. Nothing in these regulations, however, limits or interferes with the authority of a physician to provide any emergency medical treatment for patients who need such care for therapeutic purposes.

Whenever emergency treatment that may otherwise be considered research is initiated without prior HIC review and approval, the patient may not be considered to be a research subject. Such emergency treatment may not be claimed as research, nor may the outcome of such care be included in any report of a research activity.

If the emergency treatment involves the use of drugs, devices, or biologics that are considered to be investigational by the Food and Drug Administration (FDA), then it is necessary to meet the applicable FDA requirements.

Investigators are required to submit a report to the Committee on the emergency use of any investigational drug, device or biologic within five (5) working days. See Emergency Use form.

E. SPECIAL PROBLEMS IN RESEARCH

Sections 1 and 2 provide guidelines for the conduct of research involving two of the "special populations," (those having "limited capacities to consent"), children and those individuals who are decisionally impaired.

There are also Federal Regulations for research involving pregnant women, fetuses, in vitro fertilization, gene transfer and prisoners. Further information may be obtained on these regulations at the HIC Office. Special considerations are described in the Committee's separate **Worksheets on Prisoners, Children, Pregnant Women and Fetuses.**

E1. RESEARCH INVOLVING CHILDREN

Federal Regulations (45 C.F.R. 46.408, et seq.) set forth special requirements for research involving children. Protocols in which children are to be involved as subjects must include the following information in addition to that required in the general guidelines:

Human Subjects (Section 3)

A. **Subject Population:** There should be a statement of the number of subjects and their age range.

B. **Risks:** For protocols involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects, both of the following are required:

- 1) The risk must be justified by the anticipated benefit to the subjects, and
- 2) The relation of the anticipated benefit to the risk must be at least as favorable to the subjects as that presented by available alternative approaches.

Protocols involving greater than minimal risk and no prospect of direct benefit to individuals subjects should be justified by all of the following:

- 1) The risk must represent a minor increase over minimal risk
- 2) The intervention or procedure must present experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations, and
- 3) The intervention or procedure must be likely to yield generalizable knowledge about the subjects' disorder or condition, which is of vital importance for the understanding or amelioration of the disorder or condition.

Protocols involving greater than minor increases over minimal risk and no prospect of direct benefit cannot be approved by the Human Investigation Committee. The Human Investigation Committee must forward such protocols to Secretary, DHHS, for review.

C. **Consent/Assent Procedures:** The protocol should contain procedures for obtaining (1) the permission of the parent(s) or guardian(s) of the child and (2) the assent of the child (when it is determined that the children are capable of providing assent). Children include all persons who have not attained the legal age for consent to treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted.

Permission of the Parent(s) or Guardian(s). HIC may approve procedures requiring only one parent or guardian to give permission for a child to participate in research if the research involves:

- (1) No greater than minimal risk or
- (2) Greater than minimal risk and presenting the prospect of direct benefit to individual subjects.

Both parents must give their permission for the child's participation in research involving greater than minimal risk and no prospect of direct benefit to individual subjects unless one parent is deceased, unknown, incompetent, or not reasonably available, or if only one parent has legal responsibility for the care and custody of the child.

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 minor subject 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.

It was noted in a recent report to Congress that many institutions follow a "common policy of obtaining assent from children aged 7 and older."⁽¹⁾ While many children under the age of 7 may not be sufficiently mature to assent to participate in research, young research participants exhibit a broad range of cognitive abilities. Assessing children's maturity based solely on chronological age may not provide an accurate picture of their capacity to understand the research or to give assent. An alternate standard proposed by the American Academy of Pediatrics recommends that assent "should usually be obtained from any child with an *intellectual* age of 7 years or more"⁽²⁾ (emphasis added). The HIC supports this approach, finding that an assessment of children's intellectual or developmental ages will more accurately predict whether they can comprehend and appreciate what it means to be in a research study.

***Assent for Participation in Research Offering Direct Benefit.* The mere absence of an objection by a child should not be construed as assent.⁽³⁾ However, if the HIC determines that the research offers the possibility of a direct benefit that is important to the child's health or well being and is available only in the context of research, the assent of the child is not necessary.⁽⁴⁾ In such circumstances, it is still expected that investigators will fully inform subjects about the research, and parental permission is required. The principal investigator and the HIC will determine whether subjects should also be given an age-appropriate Information Sheet that explains the nature of their participation.**

Although minors are viewed as having diminished autonomy by federal regulations and State law, the HIC recognizes that children develop increasing authority to make decisions about their lives as they age and mature. Particularly with older adolescents, investigators conducting research should be sensitive to subjects who actively dissent to experimental treatment. When the research involves the provision of experimental therapies for life-threatening diseases such as cancer, difficult decisions must be made when the child does not wish to participate. Resolution of conflicts about accepted medical therapies usually involve family, physicians, and hospital-based or other social services. These mechanisms are also appropriate in the setting of research with experimental therapies.

***Procedures for Obtaining Assent.* The crafting of an assent process should be viewed as a collaborative effort between investigator and Committee. Although the HIC is granted ultimate authority to determine what type of assent is required, researchers are often in the best position to assess the capabilities of their potential subject population. This assessment may even need to be made on a case-by-case basis. The [HIC Protocol Application Form](#) should therefore contain a thorough description of the proposed procedures that will be used to obtain parental permission and child assent. This description should include information such as:**

- How potential subjects' maturity will be assessed;

⁽¹⁾ <http://ohrp.osophs.dhhs.gov/reports/ohrp5-02.pdf>

⁽²⁾ <http://www.aap.org/policy/00655.html>

⁽³⁾ 45 CFR 46.402(b)

⁽⁴⁾ 45 CFR 46.408(a)

- Who will obtain assent;
- Where and when parental permission and child assent will be obtained;
- What types of assent documents will be used;
- Whether signed assent will be requested;
- How the child's assent will be documented by the researcher;
- How it will be determined whether subjects/parents understand the research;
- Justification of a waiver of parental permission or child assent, if such a waiver is requested.

Copies of all parental permission and assent forms should be appended to the protocol, in the same format that they will be given to subjects.

Parental Permission. In accordance with the principle of autonomy presented in the Belmont Report, current regulations tend to avoid the term “consent” when one person grants approval for another to enroll in research. Parents or legal guardians therefore grant “permission” for children to participate in research. Connecticut law recognizes parents or court-appointed guardians as legal decision makers for children in most situations. The parental permission form is in essence a consent document and should follow all applicable requirements for informed consent as outlined in the HIC guidelines. The form should be labeled as a “Parental Permission Form,” and should be written to address the parent of a child who might enroll in the study.

Waiver of Parental Permission. The HIC 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 HIC 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).
- If a subject under the age of 18 is legally emancipated, he or she may consent to participate in research without the permission of a parent or guardian.
- When the permission of parents 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). In this case, the researcher should propose an alternative mechanism in the application and explain 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.

Infants and Young Children. If the child is under the age of 7, or found intellectually unable to provide assent, only a parental permission form is required.

Writing the Assent Form for Children. If the subject's intellectual capabilities fall within the range of a normal 7-12 year-old, a [child assent form](#) is required in addition to the parental permission form. The form should be brief and study specific, and should explain the research procedures, risks and benefits in language that is appropriate to the child's maturity. The assent form should have a simple format that is easy to read and when possible, should be limited to one to two pages. The use of larger type, simple schema, and pictures can facilitate the child's understanding of the text. The HIC understands that the writing of a good assent form is an art and that there is more than one correct approach to creating a document that is easily understood by the child and includes all of the pertinent information. The HIC has developed a suggested assent form template to be used by investigators as a guide; however, use of this template is not

required. Investigators are encouraged to develop assent forms that they feel will most effectively present information about the research to subjects.

The assent form does not replace a thoughtful discussion with the child regarding participation in the research. The assent process, or discussion with the child, is more important than the document. Investigators should remember that the assent process should take into account, in both oral and written communication, the child's experience and level of understanding. Ultimately, the assent process should illustrate respect for the child and convey the essential information the child requires, in a manner the child can understand, in order to make a decision about participating in the research.

Writing the Adolescent Assent Form. **If the subject is 13-17 years of age, and has age-appropriate cognition and understanding, an adolescent assent form is required in addition to a parental permission form for non-therapeutic studies. The adolescent assent form may follow the format provided for adult consent but is required to contain simple language written at the appropriate educational level of the youngest prospective subject in the adolescent age range. In some research projects, it may be necessary to utilize two assent forms written to accommodate subjects at either end of the age range. The Adolescent Assent Form must contain all required elements of informed consent, and may essentially mirror the parental permission form in its content and format.**

Documentation of Assent and Information Sheets. **Investigators must state in their HIC submission how children's assent to participate in research will be documented. In many cases, this will simply involve the child and investigator both signing the assent form. There may be other instances, however, when signed assent is inappropriate. If the research involves young children, children with poor literacy, or treatment for an illness, investigators may choose to use the assent form as an information sheet.**

The information sheet is essentially the same document as the assent form, but with the signature page removed. The HIC assent templates are structured so that the subject's signature is requested on a page separate from the rest of the document. In this way, an assent form can be converted into an information sheet simply by detaching the last page. The information sheet can be used solely to inform subjects about the research, or also to solicit a verbal agreement to participate. When information sheets are to be used in place of signed assent, it is the investigator's responsibility to document subject's verbal agreement in the study record. The HIC recognizes that it may be impossible to predict in the Protocol Application Form whether all subjects will be capable of providing signed assent. It is sufficient for investigators to state that this determination will be made on an individual basis.

Confidentiality. **Assent forms and parental permission forms should be written in parallel fashion in order to maintain consistency between guaranteed elements of privacy and confidentiality. For example, investigators should not promise in the parental permission form that the child's research data will be shared with the parent if the assent form assures the child that no one besides the researcher will have access to the material. Similarly, any limits to the child's privacy, or the confidentiality of his or her data, should be clearly stated in both forms.**

E2. RESEARCH INVOLVING THE DECISIONALLY IMPAIRED

Where research is conducted using human subjects who suffer from mental disorders that may affect their decision-making capacity, additional protections are needed. (45 C.F.R 46.111(b)).

The National Bioethics Advisory Commission recently issued a report on *Research Involving Persons with Mental Disorders That May Affect Decision-making Capacity* (December 1998). Although not regulation, the recommendations set forth in that report should be carefully reviewed if an investigator is considering research involving such a population. Some additional requirements or considerations discussed in the report include:

Study Design and Selection of Subjects

- Research protocols should not target persons with mental disorders as subjects when such research can be done with other subjects.
- Investigators should provide HIC with a thorough justification of the research design they will use, including a description of procedures designed to minimize risks to subjects.
- Studies that are designed to provoke symptoms, to withdraw subjects rapidly from therapies, to use placebo controls, or otherwise to expose subjects to risks that may be inappropriate will be subject to heightened scrutiny.
- Investigators should provide HIC with a thorough evaluation of the risks and potential benefits to the human subjects involved in the proposed protocol. The evaluation of risks includes the nature, probability, and magnitude of any harms or discomforts to the subjects. The evaluation of benefits should distinguish possible direct medical benefits to the subject from other types of benefits.

Consent

- No person who has the capacity for consent may be enrolled in a study without his or her informed consent.
- 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 to enrollment or to continued participation in a research protocol must be heeded in all circumstances.
- 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, the Committee may require that an independent, qualified professional assess the potential subject's capacity to consent. The protocol should describe who will conduct the assessment and the nature of the assessment. An HIC should 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 which is not likely to result in direct benefit to them unless the research presents no more than minimal risk.
- 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 to enroll that person in the study. If permission is given to

enroll such a person in 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 subjects' autonomy and with medical confidentiality.

The special concerns raised by the decisionally impaired population will be considered by HIC in its review. *See Worksheet on Studies Involving the Decisionally Impaired*.

E3. FDA PROTOCOLS

In addition to the requirements imposed by NIH, which form the basis of these Guidelines, the Food and Drug Administration also has regulations involving HIC review, informed consent and protection of human subjects. These regulations apply to all studies of test articles where the results will be submitted to the FDA. Most of the provisions are identical to those in the NIH regulations discussed in the general sections of these Guidelines, but there are some additional requirements specific to the FDA.

FDA regulations refer to those items that they regulate (drugs, medical devices, biological, radiopharmaceuticals, food additives, and so on) as "test articles." It is frequently difficult for investigators to determine whether FDA regulations apply to their plans to use or study an "article." When in doubt, consult the HIC. In general, any plan to use an "article" that has not been approved by FDA for commercial distribution for use in humans will be covered by FDA regulations. In such cases, the industrial sponsor (or occasionally the individual "sponsor investigator") of the "article" has the obligation to file with FDA a "Notice of Claimed Investigational Exemption for a New Drug" (IND) or, in the case of devices, an IDE (Investigational Device Exemption). In some cases, use of "articles" for either research or practice purposes may be covered by FDA regulations even though FDA has approved commercial distribution of the "article." For example, use of an approved drug for an indication or in a population not mentioned on the FDA-approved package label may be subject to FDA regulation. This would be the case if data were being developed in connection with the new use of the "article" to support an application to the FDA for a change in the package label. Physicians who plan to use "articles" in ways that differ substantially from those identified on the package label should contact the firm that distributes the "article" in order to learn whether it wants the physician to develop data that might be used to support an application to the FDA for a change in labeling. If so, the industrial sponsor will usually choose to file an IND (or IDE) and all FDA regulations will be applicable. Even if FDA regulations are not applicable, research involving investigational practices must conform to HIC Guidelines. For emergency use of investigational drugs, biologics or devices outside the research context, see the discussion in *Emergency Use*.

E3.1 Consent Form:

Subjects must be informed that their medical records may be subject to review by the HIC, agents of the FDA and, in some cases, by agents of the industrial sponsor. All consent forms must be dated as well as signed.

E3.2 Special requirements:

E3.2(a) When there is an industrial sponsor, a letter of indemnification is required (*See* discussion in Guidelines on Part II of Protocol).

E3.2(b) Drug company reporting forms are to be modified so that no names, initials or other identifiers are used. Separate research protocol numbers should be used to identify individual subjects and only the investigators should have the means to link the code numbers to identifiable patients.

E3.2(c) The Medical Board at Yale-New Haven Hospital has approved a program of investigational drug use for all non-FDA approved drugs and FDA approved drugs used for a new indication, in a new dosage or dosage form, and/or by a new method, route, or duration of administration. Investigational drugs shall be used only under the direct supervision of the principal investigator, who shall be a member of the medical or dental staff. The Pharmacy, already the center for drug procurement, storage and inventory control, dosage formulation and packaging, distribution and drug information services, serves as the central coordinating center for investigational drugs.

All investigational drugs must be stored centrally by the Pharmacy. The inventory supply shall be received in care of the Pharmacy for the investigator. A policy exemption to central storage may be requested from the Pharmacy and Therapeutics Committee.

All investigational drugs must be dispensed by the Pharmacy, which will dispense them only upon receipt of an order or prescription written and signed by the principal investigator or his or designee as indicated in the study protocol. Exemptions from this policy must be approved through the Pharmacy and Therapeutics Committee.

Requests for further information detailing the policies and procedures of the Medical Center's investigational drug program should be directed to the Pharmacy.

E3.3 Inspections:

Various federal agencies such as the FDA, the NCI and others have the authority to inspect medical records of patients or subjects involved in research studies in which these agencies have an interest. Because of the serious legal questions involved in federal access to information unrelated to research, investigators should call the Counsel for Medicolegal Affairs before showing medical records to any inspectors.

Investigators working on FDA-regulated studies are strongly encouraged to keep all data, notes, and consent forms as "research records" that are separate from the medical records. When FDA personnel arrive to inspect records they may, in the interests of protecting the patient's privacy, be given these records rather than the medical charts.

E4. USE OF MEDICAL RECORDS AND ACCESS TO PATIENTS

The guidelines for research involving record reviews and for access to patients and/or their families are related to such factors as the sensitivity of the information to be obtained, whether the information obtained by the investigator will include the names or other identifiers of patients, the relationship of the investigator to the potential subjects and the relationship of the investigator to the Yale-New Haven Hospital or Yale School of Medicine. In general, before planning any research involving medical records, the investigator should contact the custodian of the records -- e.g., Director of Medical Records, private physician -- for advice as to whether the research plans will be feasible in that particular system.

The HIC should review all requests for access to medical records for **research** purposes. In many cases a special short form (Either a Request for an Exemption from Review Form or a Form

12: Request for Approval of Medical Record Review) can be utilized. Please consult the HIC for advice.

Chart reviews may be considered exempt **ONLY if the data is existing at the time the research is proposed and no patient/subject identifiers are retained** by the investigator. The HIC must grant an exemption **in writing** before an investigator may make claim that a research activity is exempt from review and begin the research project. This exemption cannot be applied to activities involving the prospective collection of such materials.

If identifiers must be kept, the project is **not exempt** and must be submitted for HIC review using Form 12.

If a study is not deemed to be exempt, it may be reviewed by an expedited review procedure if the following two criteria are met:

- (1) The activity must present no more than minimal risk to subjects **AND**
- (2) The protocol procedures must be listed as one of the categories in the regulations' list of procedures that qualify for an expedited review process. (Link to guidelines.)

The final decision on whether an expedited review process may be used rests with the HIC Chair or his/her designee.

Definitions:

Medical Records: The documents containing information recorded about a patient's condition and treatment, including the traditional medical record, out-patient medical record and emergency room record. (Psychiatric records and drug abuse records are discussed separately in Section 2).

Hospital Records: Documents for administrative purposes kept by the hospital about individual patients but not included in the medical records, such as operating room logs, surgical audit records and the like.

Hospital Medical Staff: Physicians with privileges at Yale-New Haven Hospital, residents and interns.

Authorized Individuals: The hospital medical staff, members of the faculty of the Yale University School of Medicine and the School of Nursing and their students and post-doctoral fellows with faculty sponsors.

Non-authorized Individuals: Any other persons, whether or not they are affiliated with Yale.

Responsible Physician: The physician in charge of the care of the patient.

4.1 Medical or Hospital Records:

Individual informed consent for record review may not be necessary if the research is exempt from HIC review under the federal regulations (45 CFR 46.101(b) 4) or if the HIC waives the informed consent requirement in accordance with applicable federal regulations (45 CFR 46.116 (d).)

*In order to exempt research involving the collection of data, documents, or records from HIC review, these sources must be **existing at the time the research is proposed and recorded by the investigator in such a manner that subjects cannot be identified, directly or indirectly or through identifiers linked to the subject.***

If a request for record review is not exempt from IRB review, in some circumstances, the HIC has the authority based on federal regulations to waive the requirement to obtain informed consent from subjects and/or the requirement to have subjects sign a consent document. The regulations provide specific criteria that the HIC must consider before making a decision to waive either informed consent or documentation of informed consent.

The final decision about whether a record review is exempt from HIC review or whether the requirement to obtain informed consent and/or the requirement to have subjects sign a consent document may be waived is made by the HIC.

The following information should be considered when preparing protocols for HIC review. When appropriate, this information should be incorporated into the protocol.

- a) Authorized individuals who are identified, as investigators on HIC-approved protocols are entitled to use records, documents and specimens as described in the protocol. Students and non-authorized individuals that are principal investigators must have faculty sponsors.
- b) When the principal investigator is a non-authorized individual, the faculty sponsor must sign a statement in which he or she accepts responsibility for confidentiality of the records.
- c) Purpose of the review should be stated clearly. *Please include the objective (hypothesis) of the research study and a brief background for the study.*
- d) Criteria for inclusion should be described. *Please include the rationale for the use of the selected subject population, archive or material and plans for recruitment and consent of participants if appropriate.*
- e) Duration of the study should be stated. *Please state how long you plan to implement the study, including data analysis activities.*
- f) Please inform the HIC whether or not the Principal Investigator has a doctor/patient relationship with the subjects of the records and if so, what the nature of the relationship is. *Please read the "Access to Patients" section and be sure to incorporate these guidelines, if planning any contact with patients/subjects.*
- g) Please let the HIC know whether any names or identifying information will be recorded. If so, a plan for maintaining confidentiality of the records needs to be described. *Please indicate the steps to be taken to protect the privacy and/or confidentiality of participants and/or to maintain anonymity of research data.*
- h) Funding Source (or funding requested source). *Please attach copies of any grant applications.*

4.2 Psychiatric, Drug and Alcohol Records:

Yale-New Haven Hospital and Yale University School of Medicine regulations severely restrict access to psychiatric records or records concerned with drug or alcohol abuse. These regulations apply to information about treatment for drug or alcohol related problems even when substance abuse is not the reason for the hospital admission. It is the responsibility of a principal investigator who wishes access to such records to know what these regulations are and to draft the protocol in compliance with them; specific advice may be obtained by contacting the hospital counsel.

Psychiatric records are kept in the patient care unit and not in the medical records department. In addition to all other requirements for access to such records, even for researchers who are members of the medical staff other than psychiatrists, access to them is entirely within the Unit Chief's discretion even if a protocol has been approved by the HIC. Only in extremely unusual circumstances will access to such records be approved by the HIC for non-authorized investigators.

4.3 In-patient Records:

Any authorized individual who is an investigator on the study has access to patients' charts once the protocol has been approved by the HIC. The responsible physician in charge of the patient must be asked if he or she has any objections to review of the chart. These charts are, of course, on the patient's unit and are needed for documentation of the care of the patient. They may never be removed from the unit for research purposes. All investigators should arrange to see charts at a time causing the least amount of inconvenience to the nursing and medical staff members caring for the patient.

Investigators should be prepared to identify themselves, the protocol title and HIC number and HIC approval date, to the nurse or clerk who is asked for the chart.

Any investigator who hires persons who are not otherwise associated with the Medical Center to assist in in-patient chart reviews must give these persons letters of identification signed by the principal investigator. The letters should state who they are, the title, HIC number and approval date of the protocol, and the name and telephone number of the principal investigator.

Non-authorized individuals will rarely be granted HIC approval to serve as principal investigators on protocols that involve reviewing current medical records.

4.4 Access to Patients:

(a) Out-patients or former patients or their families

- 1) HIC approval is required even for medical staff members to contact patients for research purposes.
- 2) Authorized investigators, including members of the medical staff who had no role in treatment of the patient and whom the patient does not know, will, in general, be asked to state in the protocol that permission to contact the patient will be obtained from the patient's responsible physician before contact. Any proposals to do otherwise must be justified in the protocol.
- 3) Any student of the Yale School of Medicine or Yale-New Haven Hospital may be asked to have the patient's responsible physician co-sign any letter to the patient inviting participation in research. In some cases, the co-signature of a medical staff member or other faculty member will be accepted in lieu of the signature of the responsible physician on such a letter, but this should be discussed with the HIC primary reviewer before submission of the protocol to the HIC.

4) If the investigator is known to the patient or the family, or would be recognized by the patient as having had legitimate access to information from which the patient's name had been obtained, then the investigator may contact the patient directly, with no co-signature on the letter, once HIC approval is obtained.

5) The initial letter should be sent to the patient or the family explaining the purpose of the research and stating how they will be contacted to be invited to participate (for example, by telephone).

6) In some cases where particularly sensitive information will be obtained in an interview, the HIC may require the investigator to send a postcard with the letter that the patient or family member may return indicating a willingness to be interviewed. In these situations, if the postcard is not returned, no follow-up calls may be made.

7) In some cases involving particularly sensitive information, even if the investigator is a medical staff member who has had prior contact with the patient, the HIC may require that the patient's current physician or the current chief of the service make initial contact with the patient and request permission for the investigator to contact the patient.

8) In general, the HIC will not approve patient contact by non-authorized individuals. However, if such research is approved, in addition to the requirements for authorized individuals there may be, depending upon the nature of the research, some or all of the following additional requirements:

a) Written agreement to assume responsibility, as required for access to records, by a member of the medical staff, must be submitted with the protocol.

b) Agreement from the patient's physician must be obtained by the non-authorized investigator and retained with the research records.

c) A non-authorized individual may not contact a patient without having the member of the medical staff assuming responsibility for the study co-sign the letter or make initial telephone contact with the patient.

(b) In-patient or family interview contacts for research purposes

1) Anyone who is not involved in the care of the patient must obtain oral approval of the patient's responsible physician to contact the patient or his/her family.

2) If an investigator hires people who do not otherwise have a medical center ID card to interview patients, it is the responsibility of the investigator to furnish these persons with a letter of introduction to the nurse on the floor who will allow access to the patient. This letter should contain the following: the identify of the interviewer, the identity of the faculty member for whom the interviewer is working, the name and telephone number of the principal investigator on the protocol, the HIC number of the approved protocol, and a statement that approval has been obtained from the responsible physician for the interview.

E5. HIV ANTIBODY TESTING

HIV antibody testing to determine eligibility for participation in protocols will be approved by the HIC if:

1. A satisfactory explanation is provided as to why such testing is necessary. In general, testing designed to protect the health of subjects -- as in certain vaccine trials -- will be approved. Occasionally the HIC will approve testing designed to protect investigators and staff members -- e.g., to protect laboratory workers as when large numbers of blood specimens are to be handled by inexperienced personnel.
2. A satisfactory statement is provided as to which prospective subjects will be tested.
3. Appropriate plans are made and described to safeguard confidentiality.
4. Informed consent for HIV antibody testing will be documented on a consent form (or incorporated in a general consent form for the protocol) which includes:
 - a. Explanations of items 1-3 above;
 - b. A statement that subjects will be informed of results (They should be advised that if they do not want to know the results they should refuse to be in the study.), that counseling will be offered to those having positive results at the time they receive their results, that results will be given only orally in a face-to-face discussion with an investigator (not by telephone or mail), and (for those having medical records) that the results will be entered in the medical record; and
 - c. A statement of the social risks of having a positive HIV antibody test. This should include at least a statement of potential limitations in one's employability, insurability, freedom to travel to some other countries, and so on.
5. No results of tests should be recorded in any identifiable records intended to be seen by persons other than investigators and those persons duly authorized by Yale-New Haven Hospital to read medical records. For example, results are not to be entered into research records designed to be reviewed by agents of drug companies or the Food and Drug Administration.
6. Any of the preceding provisions may be waived by the HIC at the request of the investigators, but only based upon the HIC's decision that there is good cause to do so.

E6. NIH-SPONSORED MULTICENTER CLINICAL TRIALS

Effective November, 1992 the National Institutes of Health (NIH) implemented a new policy governing the conduct of NIH sponsored multicenter clinical trials. The policy requires the following:

- A. The HIC must receive a copy of the NIH-approved sample informed consent document and the full NIH-approved protocol as a condition for review and approval of the clinical trial.
- B. Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the HIC.
- C. For trials sponsored by the National Cancer Institute, investigators must forward copies of such HIC approved changes, with their justifications, to the appropriate Cooperative Group headquarters.

E7. CERTIFICATE OF CONFIDENTIALITY

What is a Certificate of Confidentiality?

A Certificate of Confidentiality is issued to protect subjects' privacy and ensure the confidentiality of their data. The Certificate prevents researchers from having to release identifying information about human research subjects in any Federal, State or local civil, criminal, administrative, legislative, or other proceedings. This protection is afforded by the Public Health Service Act §301(d), 42 U.S.C. §241(d).

When is a Certificate required?

Any person engaged or intending to engage in research that will collect "sensitive" information should apply for a Certificate. Sensitive information consists of (but is not restricted to):

- Information regarding sexual practices or preferences;
- Information regarding the use of alcohol, illegal drugs or other addictive products;
- Information concerning illegal behavior;
- Information that can be destructive to the subject's financial standing, employability or reputation within the community or might lead to social disgrace or prejudice;
- Information regarding the subject's psychological state or mental health;
- And genetic information or tissues samples.

A Certificate protects in perpetuity information collected during a distinct period of time (the duration of the study). It is the responsibility of the researcher to ensure that the Certificate remains valid. If a study's duration needs to be extended, and data collection will continue past the expiration date of the Certificate, the researcher must submit a written request to the appropriate agency for an extension of the Certificate expiration date. NIH and other agencies request that this proposal be submitted at least 3 months prior to the expiration date. Extension applications should include a rationale for the extension request, a revised estimate of the study duration, the most recent HIC approval of the study, and a copy of the approved consent form which states a Certificate has been obtained.

How do I apply for a Certificate?

Applications should be made after the HIC has reviewed and approved the study. Certificates of Confidentiality are issued by agencies within the Department of Health and Human Services (such as the Centers for Disease Control and Prevention, Food and Drug Administration, or National Institutes of Health), and researchers should apply to the particular agency involved in the funding or regulation of the study.

A Certificate application must be signed by the Principal Investigator of the study and the authorized institutional official. The designated institutional official for the Yale University School of Medicine is Rebecca Balentine, Assistant Director Grant and Contract Administration.

Contact information for Certificate of Confidentiality applications is available at:
<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/cert-con.htm>

Please Note: For multi-site protocols, the coordinating center is strongly encouraged to apply for a Certificate to cover all sites. The coordinating institution must retain on file the IRB approvals from all sites and make them available upon request to the NIH. All consent forms from all sites should include appropriate language regarding the Certificate.

HIC requirements relating to Certificates of Confidentiality

Please note that the Certificate application and approval process may take up to three months. The HIC will not withhold approving research until the investigator has obtained a Certificate. Therefore it is possible that a research study may begin to enroll subjects without the protection provided by the Certificate. In these instances it is imperative to inform potential subjects that their records may not be protected until such time that the Certificate has been acquired.

Investigators must clarify in protocols, consent forms and during the consent process that a Certificate of Confidentiality has either been applied for or acquired. The consent form must also explain the protections offered by the Certificate, and any conditions of or limitations to these protections.

Suggested wording for the consent form to assure that subjects are fully aware of this circumstance is below.

“If you decide to take part in this research study, you will be required to answer some questions about your drug use. You will also be asked to tell the researchers about problems you may be having that are related to your drug use. The researcher has applied for/obtained a Certificate of Confidentiality (COC) issued by the Department of Health and Human Services (DHHS). The COC will protect the investigators from being forced to release any information in which you are identified, even under a subpoena. This protection, however, will not apply until the researcher has obtained the COC, which may take a few months. The investigator will inform you when the COC has been obtained.”

“The protection offered by the COC does not stop the researchers from voluntarily reporting information about suspected or know sexual or physical abuse of a child or older person, or a subject’s threats of violence to self or others. If any member of the research team is given such information, he or she will make a report to the appropriate authorities.”

Once the Certificate has been obtained the researcher must inform all subjects enrolled before the COC that it has now been obtained.

Researchers planning to collect sensitive information must obtain a Certificate of Confidentiality within 6 months of the study being approved by the HIC. Failure to do so may result in the temporary suspension of enrollment.

For additional information on Certificates of Confidentiality please see <http://grants2.nih.gov/grants/policy/coc/index.htm>

Investigators are encouraged to consider the need for Certificate of Confidentiality when designing their research studies. It should be noted that studies may be designed without the need for a Certificate of Confidentiality. In some instances pre-screening procedures may be utilized outside of the protocol screening process, i.e. urinalysis in conjunction with hospital admission to determine illicit or illegal drug use.

APPENDIX I

EXEMPTION FROM REVIEW

(45 C.F.R. 46.101(b))

Certain research activities may be exempt from review by the HIC. This decision must be made by the HIC; not the principal investigator. Research may be exempt from review when the only involvement of human subjects in the research falls into one of the following categories:

- Research conducted in established or commonly accepted educational settings, involving normal educational practices such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
- Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.
- Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not otherwise exempt if: (i) The human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
- Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
- Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.
- Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

APPENDIX II

EXPEDITED REVIEW

45 C.F.R. 46.110

63 Federal Register 60364-60367 (November 9, 1998)

The expedited review process may be appropriate for research involving no more than minimal risk when the only involvement of human subjects in the research falls into one of the following categories listed below.

The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial status, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are not greater than minimal.

All protocols submitted for expedited review must be evaluated and signed by a primary reviewer.

- Research on drugs or devices for which an investigational new drug exemption or an investigational device exemption is not required.
- Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows: (a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or (b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.
- Prospective collection of biological specimens for research purposes for noninvasive means such as: (a) Hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.
- Collection of data from subjects 18 years of age or older using noninvasive procedures routinely employed in clinical practice. This includes the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve the input of matter or significant amounts of energy into the subject or an invasion of the subject's privacy. It also includes such procedures as weighing, testing sensory acuity, electrocardiography, electroencephalography, thermography, detection of naturally-occurring radioactivity, diagnostic ultrasound, electroretinography, magnetic resonance imaging (MRI), functional MRI (fMRI) without contrast material and magnetic resonance spectroscopy (MRS) with no IV injections. It does not include exposure to electromagnetic radiation outside the visible range (for example, x-rays,

microwaves). Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.

- Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).
- Collection of data from voice, video, digital, or image recordings made for research purposes.
- Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

In addition, under certain circumstances, expedited review may be appropriate for the continuing review of research previously approved by the convened Committee:

- Research where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects.
- Research where no subjects have been enrolled and no additional risks have been identified.
- Research where the remaining research activities are limited to data analysis.
- Research not conducted under an investigational new drug application or investigational device exemption where the research does not otherwise qualify for exemption but the Committee has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

In addition, expedited review is appropriate for minor changes proposed for previously approved research during the period (one year or less) for which approval is authorized.

APPENDIX III

HUMAN BIOLOGICAL MATERIALS (Tissue, Blood, Fluids, etc)

- A. The HIC requires that the forms noted below accompany all protocol applications utilizing human specimens or human biological materials. The forms must be completed and signed by the principal investigator
- Requests for Research Use of Human Specimens Form
http://info.med.yale.edu/hic/forms/forms/Form_15.pdf
 - Summary Sheet for Pathology Department Tissue and /or Information
<http://info.med.yale.edu/hic/forms/forms/form14.pdf>
- B. Origin of Samples

1. Samples requested from Department of Pathology:

Investigators planning to obtain or use samples of tissue which originated from procedures performed in the operating room, or which otherwise are handled by the Department of Pathology (surgical pathology, cytology, and autopsy) must consult with a contact pathologist from the Department of Pathology for use of tissue obtained through the Tissue Bank of the Program for Critical Technologies. The appropriate contact is the Director of the Tissue Bank (or designee).

The contact will help assess the needs of the investigator, and will sign the Summary Sheet for Pathology Department Tissue and/or Information after satisfactory arrangements have been made that protect patient diagnosis and confidentiality. If any tissue will be supplied to an investigator directly from the operating room, a letter of support from the Director of Surgical Pathology must also be obtained. The form (and letter if required) must be submitted with the protocol for review.

2. Samples requested from other departments or sections:

Investigators who request use of human samples obtained from other clinical departments must contact appropriate personnel within the relevant department, such that accurate descriptions of procedures and contact people are included in the protocol.

3. Samples collected solely for research or as additional material during a medically-indicated procedure:

Many protocols in which samples are collected solely for research can simply describe the procedures and their risks. For the special instances where a sample would be sent to the Department of Pathology if it were collected for clinical reasons, care should be taken to contact a pathologist for advice and instruction on how to handle specimen allocation. The form must be signed and submitted in such instances. The protocol and consent documents must clearly state if a pathologic diagnosis will be rendered.

APPENDIX IV

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

Title of Study: *[Insert title of the study.]*

Principal Investigator: *[Insert name.]*

Funding Source: *[Insert name of company or agency.]*

[If the study involves different consent forms for different populations, identify the population group as the subtitle of the study.]

Invitation to Participate and Description of Project

Suggested Text:

You are invited to participate in a research study designed to look at *[state what the study is designed to discover or establish.]* You have been asked to participate because *[explain briefly why the prospective subject is eligible to participate]*. *[If appropriate, state the approximate number of subjects or research sites involved in the study.]*

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed judgment. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

Suggested Text:

If you agree to participate in this study, you will be asked to *[describe the study procedures clearly, in roughly chronological order.]*

Guidelines:

- *Describe the procedures using lay language, short sentences and short paragraphs. The use of subheadings may help to organize this section and improve readability.*
- *Define and explain medical and scientific terms in ordinary language (for example, the amount of blood to be drawn should be given in terms of teaspoons, tablespoons, ounces)*

or milliliters). A medical or scientific term, drug name, etc. may be used throughout the consent form once it has been explained in lay language.

- Distinguish clearly between any procedures that are experimental and those that are part of subjects' standard clinical care.

Specify the subject's assignment to study groups, length of time for participation in each procedure, the total length of time for participation, frequency of procedures, location of the procedures to be done, etc.

- For research involving randomization of subjects into different groups, specify (and explain) the randomization procedures.
- For research involving the use of placebo, clearly define the term placebo.
- For research involving interviews, surveys, questionnaires, etc., clearly describe the content of the instruments. It may also be helpful to provide a representative sample of the types of questions subjects will be asked.
- For research involving review of subjects' medical record, the consent form should explain what types of information will be collected, and why.
- For research involving genetic or related testing, the consent form should describe the scope of the research that will be performed with subjects' DNA or tissue (e.g., cancer, aging, mental health, etc.) Alternatively, investigators may request completely unrestricted or open-ended current or future use of banked samples. If such a request is made in the application, the consent form should state in easily understood, plain language the wide scope of use that is being proposed.
- When relevant, any plans to return information to subjects, to medical records, to primary care physicians, or others must be made explicit in the consent form.

Risks and Inconveniences

Guidelines:

- Identify all reasonably foreseeable risks, discomforts or inconveniences associated with the study, and describe how they will be managed.
- When relevant, risks to pregnant women or to a fetus should be explicitly stated.
- In addition to physiological risks/discomforts, describe any psychological, social, legal or financial risks that might result from participating in the research.
- Risks should be listed in hierarchical order, from most likely to least likely to occur.
- Where such information is available, the consent form should state the likelihood of risks occurring. For example, "most subjects in a similar study had headaches and felt nauseous," or "10 out of 100 people who took drug X felt dizzy."
- If appropriate (e.g., if the research involves an experimental intervention or therapy), please include the following statement: "Participation in this study may involve risks that are currently not known."
- Include only those risks that are associated with the research. Risks associated with standard clinical procedures that would be done whether or not the patient is in the study should not be listed.

- *For studies involving investigational drugs or devices, the consent form should describe a means whereby information about the drug or device may be obtained in emergency situations.*
- *For research involving genetic or related testing, subjects must be informed of any risks associated with the genetic information that may result. Such risks could include reduced access to or retention of benefits or entitlements (e.g., insurance, educational opportunities, employment, etc.); stigmatization; psychological distress in response to information; or detection of biological relationships within a family.*

Benefits

Guidelines:

- *Describe any benefits that can be reasonably expected to result from the research. Please note that benefits include those that accrue directly to the subject (e.g., improved health outcomes), to the population the subject represents (e.g., a better understanding of the subject's condition that may lead to new treatments), or to society at large (e.g., general advancement of scientific knowledge).*
- *If there is no likelihood that subjects will benefit directly from their participation, this should be stated.*
- *Financial rewards for participating in research are not considered a benefit, and should not be included in this section.*
- *Please note that, by definition, the benefits of research are unproven. Therefore, subjects should be told that participation "may," rather than "will" yield benefit.*

Economic Considerations

Guidelines:

- *Describe any compensation that will be made to subjects (including direct monetary payment, payment in the form of a gift, or reimbursement for costs such as travel, parking, childcare, etc.), and the conditions for receiving this compensation.*
- *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.*
- *Clearly describe the subject's costs associated with participation in the research. If it is possible that research procedures or tests will not be covered by the subject's insurance, health plan benefits, or other third party payers, this should be indicated.*
- *Clearly describe the parts of the research (drugs, tests, procedures, etc.) that will be provided at no cost to the subjects.*
- *Subjects may be offered an estimate of the charges they will be expected to cover.*

Treatment Alternatives/Alternatives

(Note: This paragraph is a required element of informed consent for all research involving treatment or therapeutic intervention. Certain non-treatment protocols may also require an “Alternatives” section detailing appropriate treatment or procedures that are available outside of the research. Investigators may also choose to state that the only alternative is to decline participation in the study. If the “Alternative Treatments” section does not apply to your study, you may omit this entry and delete the heading.)

Guidelines:

- *Describe any appropriate alternative therapeutic, diagnostic or preventive procedures that should be considered before the subject decides whether or not to participate in the study.*
- *Please note that alternatives are not limited to curative procedures. For chronic or terminally ill subjects, alternatives may include procedures for symptom management, improving the ability to function, or palliative care.*

Confidentiality

Suggested Text:

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. [*Describe the methods used to safeguard the confidentiality of subjects’ data (e.g., coding data or samples with numbers, storing research materials in locked cabinets, password-protecting data stored on a computer, etc.)*] When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

Representatives from the Yale Human Investigation Committee may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

Guidelines:

- *Please state how long subjects’ data will be kept before it is destroyed or de-identified.*
- *If information will be released to any other party for any reason, identify the person/agency to whom the information will be furnished, the nature of the information, and the purpose of the disclosure. Examples include legal reporting requirements for child or elder abuse, or identification of reportable infectious diseases.*
- *When the research records may be subject to inspection by FDA, a funding agency, or an industrial sponsor, the following must be included: “Authorized representatives of the*

Food and Drug Administration (FDA) [or a funding agency, such as the National Institutes of Health] and the manufacturer of the [drug/device] being tested [insert name of company] may need to review records of individual subjects. As a result, they may see your name; but they are bound by rules of confidentiality not to reveal your identity to others.”

- *If the research involves audio or videotaping, describe the subject’s right to review or edit the tapes, and indicate when they will be erased.*

In Case of Injury

(Note: This paragraph is a required element of informed consent for all research presenting greater than minimal risk. It should also be used for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws). If the “In Case of Injury” section does not apply to your study, please omit this entry and delete the heading.)

Suggested Text:

If you are injured as a result of your participation in this study, [indicate whether treatment will be made available, and who will be responsible for its cost.]

Guidelines:

- *For studies sponsored by for-profit entities, the sponsor is encouraged to provide funds for the treatment of injuries sustained as a direct result of participation in the research. Per HIC policy, sponsors should not agree to cover only those expenses not paid for by the subject’s insurance.*
- *Yale School of Medicine and Yale-New Haven Hospital do not provide funds for the treatment of research-related injury. If the study is sponsored by a non-profit entity (e.g., investigator’s own funds, federal funding, or a private non-profit organization), the following paragraph should be used: “If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.”*

Voluntary Participation and Withdrawal

Suggested Text:

You are free to choose not to participate and if you do become a subject you are free to withdraw from this study at any time during its course. If you choose not to participate or if you withdraw it will not harm your relationship with your own doctors or with Yale-New Haven hospital. [If applicable: “We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment.”]

The researchers may withdraw you from participating in the research if necessary. [Describe the conditions under which a subject might be withdrawn from the research (e.g., progression of disease/poor response to treatment, development of serious side effects, or subject non-compliance)].

Guidelines:

- *Subjects should be informed whether they will have the ability to withdraw their data from the research once it is collected, unlike tissue samples, which often can be withdrawn and destroyed, data derived as part of the research usually will not be covered by an option for withdrawal. If data or samples will be unable to be withdrawn (for example, if they have been anonymized), subjects should be apprised of this fact in the consent form.*
- *If there are medical needs required by the subject upon withdrawal, these should be stated. Any follow-up procedures or assessments accompanying the withdrawal should be clearly explained.*

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Authorization

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name of Subject: _____

Signature: _____

Relationship: _____

Date: _____

Signature of Principal Investigator

Date

or

Signature of Person Obtaining Consent

Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator [include name and full telephone number]. If you have any questions concerning your rights as a research subject, you may contact the Human Investigation Committee at (203) 785-4688.

***THIS FORM IS NOT VALID UNLESS THE FOLLOWING BOX
HAS BEEN COMPLETED IN THE HIC OFFICE***

<p>THIS FORM IS VALID ONLY UNTIL: _____</p> <p>HIC PROTOCOL #: _____</p>
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INITIALED:

ⁱ (45 C.F.R. 46.116)