# Standard Operating Procedures

## September 4, 2013

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Appendices

VHA Handbook 1200.05, Requirements for the Protection of Human Subjects in Research

VHA Handbook 1058.01, Research Compliance Reporting Requirements
Section 1: Committee for the Protection of Human Subjects (CPHS)

NOTE: Throughout the CPHS Standard Operating Procedures (SOP), an asterisk (*) indicates a reference to specific requirements from the human research protection program of the Department of Veterans Affairs (VA). Please refer to the appropriate VHA Handbook whenever an asterisk is encountered.

This document is subject to revision as needed and is reviewed at least annually.

1. Policy

Dartmouth College (College) has established an Institutional Review Board (IRB) called the Committee for the Protection of Human Subjects (CPHS) to ensure the protection of participants in human research conducted under the auspices of the College. Human research not eligible for exemption and conducted under the auspices of the College is reviewed and approved by the CPHS prior to the initiation of the research.

The CPHS applies the ethical principles described in the Belmont Report and other international codes of ethics such as the Declaration of Helsinki to the conduct of human research conducted under the auspices of the College to ensure the ethically appropriate protection of research participants. These principles are respect for persons, beneficence and its corollary non-maleficence, and justice.

The following standard operating procedures (SOP) describe the authority, role, and procedures of the CPHS.

1.1 Definitions

Common Rule. The Common Rule refers to the “Federal Policy for the Protection of Human Subjects” adopted by a number of federal agencies. Although the Common Rule is codified by each agency separately, the text is largely identical to U.S. Department of Health and Human Services (DHHS) regulations in 45 CFR 46 Subpart A. For the purposes of this document, references to the Common Rule will cite the DHHS regulations.

Human Research means any activity that meets the definition of “research” and involves “human subjects” as defined by either the Common Rule or U.S. Food and Drug Administration (FDA) regulations.

Human Subject. A human subject as defined by the Common Rule is a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or through identifiable private information, 45 CFR 46.102(f).
a. Intervention means both physical procedures by which data are gathered, such as venipuncture, and manipulations of the subject or the subject’s environment that are performed for research purposes.

b. Interaction means communication or interpersonal contact between investigator and subject.

c. Private information means 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).

d. Identifiable information means information that is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information).

For research covered by FDA regulations, 21 CFR 50 and 56, human subject means an individual who is or becomes a participant in a clinical investigation (as defined below), either as a recipient of the test article or as a control. A subject may be healthy or may have a medical condition or disease. In the case of a medical device, a human subject also includes any individual whose biospecimen is used or tested with an investigational device.

Note: The terms “subject” and “participant” are used interchangeably in this document and have the same definition.

Research. The Common Rule defines research as a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalized knowledge.

For the purposes of these SOP, a “systematic investigation” is an activity that involves a prospective plan that incorporates data collection, either quantitative or qualitative, and data analysis to answer a question. Investigations designed to develop or contribute to generalizable knowledge are those intended to draw valid scientific conclusions, to gain knowledge that may apply to populations outside of the specific study population, or to inform policy.

Research as defined by FDA regulations means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the FDA under these sections of the Federal Food, Drug, and Cosmetic Act, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations. [21 CFR 50.3(c), 21 CFR 56.102(c)]
a. Experiments that must meet the requirements for prior submission to the FDA under section 505(i) of the Federal Food, Drug, and Cosmetic Act means any use of a drug other than the use of an approved drug in the course of medical practice. [21 CFR 312.3(b)]

b. Experiments that must meet the requirements for prior submission to the FDA under section 520(g) of the Federal Food, Drug, and Cosmetic Act means any activity that evaluates the safety or effectiveness of a device. [21 CFR 812.2(a)]

c. Any activity in which results are being submitted to or held for inspection by the FDA as part of an application for a research or marketing permit is considered to be FDA-regulated research. [21 CFR 50.3(c), 21 CFR 56.102(c)]

Research does not include activities connected with learning research methodologies for classroom credit, quality improvement, case studies or series reports, program evaluation, public health surveillance activities, or journalistic activities including the production of documentaries. Case series are expected to be limited in number, and if not, are considered research.

**Test Article.** A test article is a drug, device, or other article including a biological product used in clinical investigations involving human subjects or their specimens.

**Institutional Review Board (IRB).** An IRB is a board designated by an institution to review, approve the initiation of, and conduct periodic review of research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The IRB may be assigned other review functions as deemed appropriate by the institution.

**Committee for the Protection of Human Subjects (CPHS).** The Committee for the Protection of Human Subjects (CPHS) is the name of the Institutional Review Board (IRB) at Dartmouth College. The names and acronyms are interchangeable.

**Institutional Official (IO).** The Vice Provost for Dartmouth College serves as the Institutional Official for carrying out the College’s human research protections program. The IO is responsible for ensuring that the CPHS at the College has the resources and support necessary to comply with federal regulations that govern human subjects research. The IO is legally authorized to represent the institution, is the signatory official for Assurances, and assumes the obligations of the institution’s Assurance.

**Research under the Auspices of the College.** Research under the auspices of the institution includes research conducted at this institution, conducted by or under the direction of any employee or agent of this institution (including students, as well as faculty appointees and the professional staff employed by affiliated institutions) in connection with his or her institutional responsibilities, conducted by or under the direction of any employee or agent of this institution using any property or facility of this
institution, or involving the use of this institution's non-public information to identify or contact human subjects. The CPHS makes regulatory determinations as required under applicable law as it applies to research activities.

**Engagement in Research at the College:** Whether a Dartmouth investigator is engaged in research is reviewed by the CPHS staff on a case-by-case basis, relying on the OHRP Guidance and the circumstances.

**Principal Investigator (PI):** The local director of the study. Used in this document only when an action can solely be done by the Principal Investigator. For multi-site studies, the overall director of the study is referred to as the “lead PI”.

**Investigator:** A member of the research team.

**Clinical Trial or Study:** Any investigation in human subjects intended to discover or verify the clinical, pharmacological, or other pharmacodynamic effects of an investigational product(s), to identify any adverse reactions to investigational product(s), and to study absorption, distribution, metabolism, and excretion of investigational product(s) with the object of ascertaining its safety and efficacy.

### 1.1 CPHS Authority

The College authorizes the CPHS:

- a. To approve, require modifications to secure approval, or disapprove research activities overseen and conducted under the auspices of the College;

- b. To suspend or terminate approval of research not being conducted in accordance with the requirements of the CPHS or that has been associated with unexpected serious harm to participants;

- c. To observe, or have a third party observe, the consent process; and

- d. To observe, or have a third party observe, the conduct of the research.

Research that has been reviewed and approved by the CPHS may be subject to review and disapproval by officials of the institution. Those officials may NOT approve research if it has not been reviewed and approved by the CPHS or if it has been disapproved by the CPHS. College officials may add requirements, conditions, or other modifications to secure CPHS approval or approval by another College committee. Modifications to previously approved research proposals or consent forms should be reviewed and approved by the CPHS before initiating the changes or modifications. The CPHS Analyst in consultation with the CPHS Chair or Director makes the determination whether the changes require Full Committee review or Expedited review.
1.3 Number of Committees

There are currently four Committees that comprise the CPHS. The Committees are:

a. CPHS Committees A, C & D: These committees are comprised of members with appropriate expertise to review all types of studies. Based on the availability of complete study information, a particular study may be assigned to any committee. When the study application documents are ready for Committee review, the study is added to the next agenda for either CPHS A, CPHS C or CPHS D, whichever meets next. CPHS D meets the first Thursday of each month. CPHS A meets the third Thursday of each month. CPHS C meets the fourth Thursday of each month.

b. CPHS Committee B: This committee handles special requests to review a study when a deadline exists that is not accommodated by standing CPHS meetings, such as a situation when review is needed to provide study participation as a medical treatment option to a potential subject and for certain time sensitive categories of research.

The Institutional Official, the CPHS Director, and the CPHS Chairs review the CPHS operational activities regularly and make a determination as to the appropriate number of committees that are needed for the institution. This determination will be based on the evaluation of the performance of CPHS as described in Section 1.14.4.

1.4 Roles and Responsibilities

1.4.1 Chairs of the CPHS

The Dartmouth College Institutional Official (IO; Vice Provost for Research), in consultation with and approval by the CPHS members and the CPHS Director, appoints the Chairs and may appoint Vice-Chairs of the CPHS to serve for renewable three-year terms. Any change in appointment, including reappointment or removal, requires written notification to the Chair or Vice-Chair.

The CPHS Chairs should be respected individuals from within the College, fully capable of managing the CPHS and the matters brought before it with fairness and impartiality. The task of making the CPHS a respected part of the institutional community falls primarily on the shoulders of the Chairs. The CPHS must be perceived to be fair, impartial, and immune to pressure by the institution’s administration, the investigators whose studies are brought before the CPHS, and other professional and nonprofessional sources of potential influence.

The Chair’s term of service is three years, and the IO periodically reviews and discusses the Chair’s performance with the Chair. The IO may remove a Chair from his or her position. A Chair, who is also a committee member, is chosen for his or her expertise and experience as well as on the basis of peer recommendations.
1.4.1.1 Responsibilities of a Chair

Reviews each research study presented to the Committee at a convened meeting and directs the proceedings and discussion of the Committee.

Is expected to have an in-depth understanding of ethical issues, state law, institutional policy and federal regulations, as applicable, and may attend national meetings.

Is a voting member of the Committee.

Reviews proposed studies through the "expedited" procedure and may be the reviewer for "external' review.

May be involved in the process for allowing the CPHS to be the IRB of Record for another site.

The Chair reviews reported serious Adverse Events, protocol deviations, and eligibility exceptions.

Is involved with identifying and investigating issues of serious or continuing noncompliance.

The Chairperson will recuse him or herself from review or involvement if a conflict of interest exists.

1.4.2 Vice Chair of the CPHS

The Vice Chair serves as the Chair of the CPHS in the absence of the Chair and has the same qualifications, authority, and duties as the Chair.

1.4.3 CPHS Delegated Duties

The Chair, in consultation with the CPHS Director, may designate one or more other CPHS members, including the CPHS Analysts, to perform various duties, including reviews, signing documents, and other CPHS operational and review functions.

Delegated Duties may include the following activities:

a. Serve as designees of the CPHS Chair for expedited review of new or continuing studies, or modifications of continuing studies. The reviewer should be experienced and have appropriate expertise.

b. Sign formal CPHS correspondence in consideration of logistical and operational concerns, including foreseeable absences from work, as well as when specifically designated authority has been received for expedited review processes.

c. Review and approve modifications requiring only simple concurrence by investigators, i.e. "Specific Minor Revisions", when the initial review by the convened CPHS resulted in the request for specific minor revisions prior to approval.
d. Conduct an inquiry. A subcommittee consisting of CPHS members, and non-members if appropriate, may conduct an inquiry into allegations or reports of non-compliance. The subcommittee may act on behalf of the CPHS, including in any of the following activities:

   i. Review of the study(s) in question;
   ii. Review of a FDA audit report, if applicable;
   iii. Review of any other relevant documentation, including consent forms, case report forms, and subject files as they relate to the execution of the study;
   iv. Interview research personnel if necessary;
   v. Prepare either a written or oral report of findings to present to the full CPHS at its next meeting;
   vi. Recommend a response by the CPHS.

e. Conduct on-site review. Determination of the review interval and the need for additional oversight is made by the CPHS on a study-by-study basis. For example, if an investigator who is performing particularly risky research, or if an investigator who has recently had a study suspended by the CPHS due to regulatory concerns, an on-site review by a CPHS subcommittee may occur, or re-approval may be subject to review or audit after a few months of enrollment or after enrollment of the first several subjects.

1.5 CPHS Membership

1.5.1 Composition

a. The CPHS has at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.

b. The CPHS is sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including considerations of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.

c. In addition to possessing the professional competence necessary to review specific research activities, the CPHS is able to ascertain the acceptability of proposed research in terms of institutional policies, applicable law, and standards of professional conduct and practice. The CPHS includes individuals knowledgeable and having experience in these various areas.

d. When studies involve vulnerable populations, the review process includes one or more individuals who are knowledgeable about or experienced in working with these populations, either as members of the CPHS or as consultants (see Section 5.3).
e. Nondiscriminatory efforts are made to ensure that the CPHS does not consist entirely of men or entirely of women, including consideration by the institution of qualified persons of both sexes, so long as no selection is made to the CPHS on the basis of gender. The CPHS does not consist entirely of members of one profession.

f. The CPHS includes at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

g. The CPHS includes at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

h. One member may satisfy more than one representative membership category.

i. The CPHS Director and Analysts may be voting members of the CPHS.

j. The CVs of CPHS members are kept on file in the CPHS Office.

Members are drawn primarily from disciplines active in human subjects research. They may come from College faculty at the School of Medicine, in Arts & Sciences, or from the Thayer School of Engineering. They may represent affiliated VA facilities. Members are also selected from the administrative officials at the College and Dartmouth-Hitchcock Medical Center (DHMC), as well as from residents of the surrounding communities. All members, especially community members, are considered to represent the perspective of research participants.

The CPHS membership includes at least two representatives from each affiliated VA facility. The VA facility appoints representative members to the CPHS and maintains authority over the assignment. The VA facility consults with the CPHS about any determinations to remove its appointed members from the committee.

Representatives for vulnerable populations are identified in the CPHS database of member expertise. When reviewing a study involving vulnerable populations, reference is made to the roster and CPHS database as needed in order to ensure appropriate expertise for the review process. If the Committee does not contain the expertise necessary for representing the rights and welfare of a vulnerable population, a consultant is arranged. Similarly, a consultant is obtained for assistance when particular cultural knowledge is needed for the review of a study.

1.5.2 Appointment of Members to the CPHS

A variety of sources nominate CPHS members, including previous and current Committee members, affiliated entities, department chairs, colleagues, administrators, and public organizations. Consideration is given to race, gender, expertise, and cultural backgrounds. People with active licensure in various clinical disciplines are sought.
Both a background knowledge of and current familiarity with affiliated institutional concerns (e.g., the VA) help to ensure local research context is considered during the review process. Representation of community attitudes and experience with international issues are valued.

The CPHS Director discusses volunteering to serve on the Committee and reliable availability with newly identified nominees. When a nominee agrees to serve on the CPHS, a copy of his or her CV is requested. The CPHS Director reviews the nominee’s CV and any other relevant correspondence.

After review of his or her education, training, experience, and other characteristics that might add diversity to the CPHS, each member receives an appointment to the CPHS from the IO.

A CPHS member’s term of service is 3 years. Members may renew their membership. Periodically, the Director evaluates the membership roster and updates the membership as needed to meet the review needs of the research community in the following areas: scientific expertise, community representation, representation of or advocacy for vulnerable populations, and institutional affiliation. If a member fails to contribute regularly to the CPHS review process or fails to satisfy one or more of the following criteria, that member may be asked to resign. In this event the CPHS Director and Chairs agree to request the member’s resignation.

- a. Reliable attendance at meetings
- b. Timely reviews
- c. Preparation for meetings
- d. Availability for expedited reviews
- e. Responsiveness to CPHS staff and investigator questions
- f. Ability to balance competing considerations to achieve the goals of CPHS review

The CPHS Chairs and Director, in consultation with the CPHS office staff, continually review the performance of CPHS members using the above-listed criteria. The results of this review process are communicated to members by letter every eighteen months. One such letter accompanies each member’s reappointment letter for any new three year term.

1.5.3 Alternate members

The appointment of alternate members occurs in the same way as for other CPHS members. The role of the alternate member is to serve as a voting member of the
CPHS when a regular member is unavailable to attend a convened meeting. When an alternate member substitutes for a regular member, the alternate member receives and reviews the same documents prior to the CPHS meeting that the regular members receive. The alternate’s expertise and perspective are considered comparable to the expertise and perspective of the member for whom they are currently acting as alternate. Appointed alternate members are assigned to attend meetings depending upon the availability of primary members and the expertise required to review the studies on the agenda. The alternate member is not counted as a voting member unless a primary member for whom they are substituting is absent. Alternate members may also serve as consultants to the CPHS as circumstances require.

The CPHS meeting minutes document the members in attendance at each meeting who participate by voting. *

1.5.4 CPHS Member Conflict of Interest

No member or consultant may review a research project in which the member or consultant has a conflict of interest (COI) except to provide information as requested by the Committee. It is the responsibility of each CPHS voting member to disclose the existence of a COI in the study under review and recuse him or herself from the vote. In the event a member declares a COI involving a study under review at a CPHS meeting, the Chair requests that the member leave the meeting temporarily during the discussion and vote on the study, unless the member voluntarily does so. It is the responsibility of each CPHS member to evaluate any comments on the study by a member who declares a COI with the potential effects of the COI in mind.*

Committee members and consultants may have the following conflicts of interest when reviewing research:

a. The member or consultant is involved in the design, conduct, analysis, or reporting of the research.

b. An immediate family member of the member or consultant is involved in the design, conduct, analysis, or reporting of the research.

c. Another relationship of the member or an immediate family member to the research that may create or be perceived to create a conflict of interest.

d. The member or an individual in his or her immediate family holds significant financial interests in the research being reviewed. Significant financial interests include:

i. Ownership interest, stock options, or other equity interest in and compensation from a publicly traded entity related to the research unless it is:
   1. Less than $5,000 in total when aggregated for the immediate family.
   2. Value will not be materially affected by the outcome of the research.
   3. Less than 5% interest in any single entity.
ii. Any ownership interest, stock options, or other equity interest in or compensation of more than $5000 from a privately held entity related to the research when aggregated for the immediate family.

iii. Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright, or licensing agreement.

iv. Board or other executive relationship related to the research, regardless of compensation.

v. Reimbursed or sponsored travel by an entity related to the research except from government agencies, an institution of higher education, an academic teaching hospital, a medical center, or a research institute affiliated with an institution of higher education.

The CPHS Chair reminds members of the COI Policy at each convened meeting, including that they should recuse themselves from the vote on any study in which they have a COI. CPHS members with a conflicting interest are excluded from the quorum. The minutes record recusals by members.

If the status of a CPHS member changes and a COI results during the course of a study, the CPHS member declares the existence of the conflict prior to next review of the study. The member is then recused from the review and vote.

### 1.5.5 Use of Consultants

#### 1.5.5.1 Internal Consultants

CPHS staff or any CPHS member may request internal consultant review for any study. An internal consultant is an individual who is affiliated with the College.

Consultants may be asked to provide their expertise or special cultural insights regarding a specific issue, or to provide an overall review and assessment of a research project.

For studies that require Full Committee review, the CPHS staff or any CPHS member may request internal consultant review prior to a meeting of the convened CPHS, or the Committee may determine, upon review of a study, that internal consultant review is necessary.

Once an internal consultant is identified, CPHS staff provides the consultant with relevant study documents as well as a list of any specific concerns.

#### 1.5.5.2 External Consultants

An external consultant is an individual who is not affiliated with the College. Out of respect for the investigator’s intellectual property and to avoid professional conflicts, the
Principal Investigator (PI) will be informed of a request for external consultant review and provided an opportunity to identify individuals, if any, he or she does not wish to review the study.

The CPHS Chair, members, and staff may consult with the appropriate department chair to identify an external consultant with the required expertise, giving consideration to the PI’s wishes.

Once a consultant has been identified, CPHS staff contacts this individual to request his or her services and obtain a written confidentiality agreement.

CPHS staff provides the consultant with a written request to serve as a consultant, relevant study documents, and a list of specific issues to consider. If the consultant discloses a financial or other interest in the research, the CPHS Chair and CPHS staff will identify an alternate consultant as described above.

1.5.5.3 Consultant’s Responsibilities

A consultant is requested to provide his or her comments to the CPHS in writing provided the consultant has no conflicts of interest pertaining to the study being reviewed. Consultants are asked about conflicts of interest prior to an invitation to provide comments to the CPHS. Comments may be delivered to the CPHS staff or presented to the CPHS by the consultant in-person.

For research requiring full Committee review, consultant comments are distributed to the CPHS members prior to the scheduled meeting.

If a consultant is asked to attend a convened CPHS meeting, the consultant may not vote or count towards quorum.

The consultant’s written comments are retained by CPHS as part of the study file.

Before the CPHS staff assigns studies to a consultant for review, the CPHS staff makes an initial assessment whether there is a COI on the part of a CPHS consultant. When requesting a consultant to review a study, the CPHS staff will provide each CPHS consultant with guidance on conflicts of interest. Consultants are responsible for determining whether they have a COI with a study they are asked to review and are expected to notify the CPHS staff if a COI exists with respect to the study.

Ad hoc or informal consultations are requested and conducted as described above. All consultations are conducted in a manner that respects intellectual property and protects the investigator’s reputation.

1.5.6 Duties of CPHS Members
The CPHS staff distributes to members the meeting agenda, studies, proposed consent forms, and other relevant documents prior to the convened meetings at which the research is scheduled for discussion. Members typically receive the materials one week before each meeting in order to participate fully in the review of each proposed study. CPHS members treat study documents and supporting materials as confidential. Copies of study documents and supporting materials are returned to the CPHS staff at the conclusion of the meeting. The CPHS staff adds any review notes to the study file and destroys duplicate documents.

1.5.6.1 Attendance Requirements

Members should attend the meetings for which they are scheduled and are expected to attend nine of twelve meetings annually absent extraordinary circumstances. If a member is unable to attend a scheduled meeting, they should inform the CPHS staff. If the inability to attend will be prolonged, a request for an alternate to be assigned may be made to the Chair or the Director.

If a CPHS member is to be absent for an extended period of time, such as for a sabbatical, he or she notifies the CPHS in advance so that an appropriate replacement can be obtained. The replacement can be temporary, for the period of absence, or permanent if the member is not returning to the CPHS. An alternate may serve during the regular member’s absence.

1.5.7 Liability Coverage for CPHS Members

The College provides liability coverage under its insurance programs for CPHS members acting in good faith in the performance of their CPHS duties. The College also provides liability coverage for the community representatives who are CPHS members.

1.5.8 Review of CPHS Member Performance

The CPHS Chairs and Director periodically review member performance at least every eighteen months. Members who do not support the activities of the CPHS are asked to resign. Typically this review occurs halfway during the member’s term of service and again at reappointment, which coincides with the beginning of the academic and fiscal year for Dartmouth College on July 1. Nevertheless it may occur at any time during the appointment period, especially if a member is no longer actively engaging in and supporting CPHS activities.

The evaluation criteria include availability to serve as a reviewer, attend meetings, and respond with timely and proficient reviews. The CPHS Director and Chair may discuss the results of any performance assessment directly with the member whose performance was evaluated or communicate those results in writing.

1.6 CPHS Office
The CPHS Office is staffed by a number of permanent full-time employees, with the knowledge, skills and abilities appropriate to their respective roles. Additional support may be provided on a temporary “as needed” basis. The following resources are provided by the College to the CPHS to support its review, compliance, and record-keeping responsibilities:

**CPHS Director:** Directs the Office of CPHS, including compliance with applicable regulations, guidelines, and standards. The CPHS Director reports to the Vice Provost for Research. (1 FTE)

**CPHS Analysts:** Responsible for reviewing and evaluating confidential information about research projects involving human subjects, plus preparing project documents to satisfy:

a. Institutional expectations for quality, accuracy, completeness;

b. Regulatory requirements and ethical standards prior to review by the CPHS.

The CPHS Analysts work directly with investigators and other members of the research community to resolve study-related ethical and regulatory problems. The CPHS Analysts report to the CPHS Director. (5 FTE)

**CPHS Coordinator:** Provides support and assistance to the Director by managing the CPHS Office. The CPHS Coordinator supervises administrative assistants, supports the operation of the CPHS databases and other filing systems, reconciles expenses with account statements, assists in producing annual budgets, orders supplies and equipment, handles payroll and other personnel matters, facilitates hiring processes, and maintains the efficiency of CPHS office functions and operations. The CPHS Coordinator reports to the CPHS Director. (1 FTE)

**CPHS Administrative Assistant:** Provides a variety of support activities to the CPHS staff, Chairs, and members that enhance the efficiency of and facilitate CPHS operations. The Administrative Assistant reliably and consistently performs CPHS operational procedures, maintains necessary record systems, supports CPHS meeting processes, and carries out CPHS office functions. The Administrative Assistant reports to the CPHS Coordinator. (3 FTE)

1.6.1 Selection, Supervision and Evaluation of CPHS Supporting Staff

**Selection Process:** A College search committee, in consultation with the CPHS Chairs, selected the CPHS Director from a national search.

The CPHS Analysts vary in seniority, both in IRB experience and length of employment by the CPHS. Identifying analyst candidates for an open position may involve a national search.
The administrative support staff, consisting of the CPHS Coordinator and Administrative Assistants, was hired through the processes supported by Human Resources at the College.

**Supervision:** In the CPHS Office, each person has individual areas of responsibility, and works independently, with minimal direct supervision. At the same time, maintaining the efficiency and productivity of the complicated routine operations requires a coordinated team effort. As a result, the staff members are held to high standards of teamwork, attention to detail, accuracy, reliability, ethical and regulatory analysis, initiative, efficiency, and commitment to serving research participants.

**Evaluation:** Employee performance evaluations are conducted annually in accordance with College policies and procedures. Balancing and re-assessing the needs of the staff and demands on the CPHS office is a continuing process.

### 1.6.2 CPHS Resources

The CPHS Office is located in offices provided by the College and is equipped with the necessary office space, meeting space, storage space, and other facilities to support the functions of the CPHS. The CPHS Director, in consultation with the CPHS Chairs and staff, regularly evaluates the adequacy of personnel and non-personnel resources for the CPHS and reports the results of these evaluations to the IO.

The College's Institutional Official is responsible for providing adequate resources to the CPHS, including appropriate meeting and office space, and staff for conducting the operations of the CPHS. The College makes available to the CPHS and its staff office equipment and supplies, including technical support, file cabinets, computers, internet access, and copy machines. The resources provided for the CPHS Office are reviewed during the College's annual budget process.

### 1.6.3 CPHS Quality Improvement Plan

The CPHS Director is responsible for producing regular reports on CPHS Office operations regarding the volume of review actions in various categories and interval analyses of the length of time each action requires. The CPHS Director, Chairs, and IO evaluate these reports, which are distributed to various institutional officials as appropriate to assist efforts to facilitate the efficiency and effectiveness of research administration.

### 1.7 Training / Ongoing Education of CPHS Members and CPHS Staff

A vital component of a comprehensive human research protection program is a continuing educational program for CPHS Chair and the CPHS members. The College is committed to providing on-going educational opportunities for CPHS members and CPHS staff related to ethical concerns about and regulatory and institutional requirements for the protection of human subjects.
1.7.1 CPHS Chairs and Committee Members

**New Member Qualifications:** Newly appointed members of the CPHS provide the CPHS staff with a copy of their Curriculum Vitae (CV). The CV is maintained on file in the CPHS Office.

**Initial Orientation and Education:** New committee members receive an initial educational program and written materials from the CPHS staff. New members also receive initial training on the ethical principles, regulatory requirements, and institutional policies related to human research protection, as well as continuing education, mentoring, and professional development opportunities. New members do not participate in a CPHS meeting until their orientation is complete. New CPHS chairs receive additional education about their leadership roles and responsibilities.

**Ongoing Education:** Through continuing education materials presented at CPHS meetings, CPHS members are made aware of the review requirements, new procedures, and other information relevant to the work of the Committees. CPHS members are also encouraged to attend national and regional conferences on issues related to human subjects protection. Funds are available for CPHS members to attend such conferences. On occasion the CPHS staff also provides training through locally produced presentations as well as through continuing access to the Collaborative IRB Training Initiative’s education modules.

For research conducted or funded by the VA, Department of Defense (DoD), or other federal agencies, members are informed or reminded by the CPHS staff of special regulatory requirements at the time of review. Examples of such requirements are those that apply to study populations such as active military, pregnant women, children, and prisoners.

**Educational Records:** The CPHS staff maintains education and professional development records for CPHS committee members.

1.7.2 CPHS Office Staff

CPHS office staff are encouraged and provided with financial support and protected time to pursue certification as IRB professionals.

The performance of the CPHS office staff are evaluated at least annually by the CPHS Director. Staff members receive initial training, continuing education, and professional development opportunities.
Office staff members are regularly provided with continuing education at CPHS meetings, staff meetings, and other continuing educational opportunities available at the College, Dartmouth-Hitchcock Medical Center, and affiliated VA facilities.

Office staff members may also attend a number of continuing education activities offered through federal agencies and private organizations. They routinely have opportunities to attend webinars, workshops, conferences, and retreats sponsored by the FDA, OHRP, PRIM&R, ASLME, and other organizations.

1.8  Reporting and Investigation of Allegations of Undue Influence

If a CPHS Chair, Director, member, or office staff member feels that an attempt has been made to unduly influence the CPHS, the individual should make a confidential report to a CPHS Chair, the Director of the CPHS, the Vice Provost for Research, or the Provost, depending on the circumstances. The official receiving the report will conduct a thorough investigation and corrective action will be taken to prevent additional occurrences.
Section 2: CPHS Review Processes

2.1 Policy

Projects determined to be human subjects research conducted under the auspices of Dartmouth College will be assigned to one of the following levels of review:

a. Exempt
b. Expedited Review
c. Full Committee Review

The CPHS ensures that the research meets required ethical and regulatory criteria for initial and continuing review and any modifications of approved research. The following sections describe the procedures for review of research by the CPHS.

2.2 Definitions

Minimal Risk. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. This definition is used in reference to a healthy individual in a safe environment.

Minor Change. A minor change is one that, in the judgment of the CPHS reviewer, makes no substantial alteration in:

a. The level of risks to subjects: A CPHS reviewer should not consider a the addition of a procedure that involves more than minimal risk to research participants to be a minor change.
b. The research design or methodology: A CPHS reviewer should not consider additional procedures that are not among the categories of research activities eligible for expedited review as a minor change. See section 2.5.1 for the categories of research activities eligible for expedited review.
c. The number of subjects enrolled in the research.
d. The qualifications of the research team.
e. The facilities available to support safe conduct of the research.
f. Any other factor that would warrant review of the proposed changes at a convened meeting of the CPHS.

Quorum. A quorum of the CPHS consists of a simple majority of the voting membership in attendance, including at least one member who is a non-scientist. If research involving an FDA-regulated article is involved, a licensed physician must be included in the quorum.
Suspension of CPHS approval. A suspension is a directive of the convened CPHS or other authorized individual (See Section 3.16) to temporarily stop some or all previously approved research activities. Suspended studies remain open and require continuing review.

Termination of CPHS approval. A termination of CPHS approval is either:
   a. A decision by the convened CPHS to stop permanently the activities in a previously approved research study; or
   b. CPHS acknowledgement of a notification from a researcher that all study activities have been stopped permanently.

Terminated studies are considered closed and no longer require continuing review.

External Review. External review means that a designated CPHS member determines whether or not to accept the review of another IRB for a particular research project. An external review procedure occurs when the College delegates its responsibility for review to the IRB of another institution or a commercial IRB for research conducted under the auspices of the College or its affiliates.

2.3 Human Subjects Research Determination

The responsibility for an initial determination as to whether an activity constitutes human subjects research rests with the investigator. The investigator should make this determination based on the definitions of “human subject” and “research” in Section 1.1. Because the College will hold them responsible if the determination is not correct, investigators should request a confirmation that an activity does not constitute human subjects research from the CPHS Office*. The request may be made verbally, by phone contact, by email, or through a formal written communication. All requests must include sufficient documentation of the activity to support the determination.

Determinations as to whether an activity constitutes human subjects research will be made according to the definitions in Section 1.1 with reference to the relevant sections of the regulations and the “Human Subject Regulations Decision Charts” dated September 24, 2004 or any updated information available on the OHRP web site.

Determinations regarding activities that are either clearly or clearly not human subjects research may be made by the CPHS Director or other CPHS staff who are CPHS members. Determinations regarding less clear-cut activities are referred to the CPHS Chair, who may make the determination or refer the matter to a convened meeting of the CPHS.

Documentation of all determinations made through the CPHS Office will be recorded and maintained in the CPHS Office. Formal submissions will be responded to in writing and a copy of the documents and determination letter/email will be kept on file.
2.4 Exempt from Further CPHS Review

All research involving human subjects in which College-affiliated investigators are engaged should be reviewed by the CPHS. Certain categories of research are exempt from further CPHS review and approval. Exempt research is subject to institutional review and exempt status is determined by the CPHS. Investigators should not make the determination whether or not a study is exempt.

It is the investigator’s responsibility to obtain a determination of Exemption from Review from the CPHS Office. The investigator sends to the CPHS Office a description of the research study, including information regarding the identification and recruitment of human subjects, confidentiality or anonymity of data, the consent process, and any special issues to be considered. The CPHS staff may communicate extensively with the researcher to gather the necessary information and revise study documents (e.g. an information sheet) into a mutually acceptable format.

The CPHS Director and CPHS Analysts as designated by the CPHS Chair and in consultation with the CPHS Chair as necessary, make the determination that the research is exempt from review.

If a project submitted for exemption presents ethical issues or does not meet appropriate standards for exemption, the project will be reviewed by the CPHS. The designation of exemption is made upon receipt of sufficient information for review. Determinations of exemptions are communicated to investigators via a letter from the CPHS Office.

Exemption determinations are documented in the CPHS database and CPHS paper file with a letter to the investigator. The regulatory category under which the exemption determination was made is documented in the determination letter, the CPHS database, and the paper file in the CPHS Office. Studies determined to be exempt from further CPHS review, like any expedited action, are reported to the full CPHS committees in the minutes of the next meeting scheduled after the date the approval letter is issued.

The exempt from review letters and study documents are filed alphabetically by the investigator’s last name in the CPHS Office or archived.

Continuing renewal of exempt studies is not required. The exemption letter explains to the investigator the designation of exemption and indicates if the study is modified so that the exemption designation is no longer applicable, the project requires CPHS review to continue. Revisions that may affect the exempt status of the study are sent to the CPHS Office for review.
2.4.1 Limitations on Research Subjects

Vulnerable Populations: The CPHS Director or CPHS Analyst, in consultation with the CPHS Chairs, determines whether or not research involving vulnerable populations is eligible for exemption from further review on a study by study basis.

Children: The exemption for research involving survey or interview procedures or observations of public behavior does NOT apply to children, except for research involving observations of public behavior when the investigator does not participate in the activities being observed.

Prisoners: The exemptions do NOT apply. CPHS review is required.

2.4.2 Categories of Exempt Research

With the above exceptions, research activities not regulated by the FDA (see Section 2.4.3 for FDA Exemptions) in which the only involvement of human subjects will be in one or more of the following categories are exempt from CPHS review:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as:
   a. Research on regular and special education instructional strategies, or
   b. Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
   a. Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
   b. Any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability; be damaging to the subject's financial standing, employability, or reputation; or result in a loss of insurability.

3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (2), if:
   a. The human subjects are elected or appointed public officials or candidates for public office; or
   b. Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
4. 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.

NOTE: In order to be eligible for this exemption, all of the materials have to exist at the time the research is proposed.

5. Research and demonstration projects which are conducted by or subject to the approval of federal Department or Agency heads, and which are designed to study, evaluate, or otherwise examine:
   a. Public benefit or service programs;
   b. Procedures for obtaining benefits or services under those programs;
   c. Possible changes in or alternatives to those programs or procedures; or
   d. Possible changes in methods or levels of payment for benefits or services under those programs.

Such projects must be conducted pursuant to specific federal statutory authority. In addition, there must be no statutory requirements for CPHS review, the research must not involve significant physical invasions or intrusions upon the privacy of subjects, and the exemption must be invoked only with authorization or concurrence by the funding agency.

6. Taste and food quality evaluation and consumer acceptance studies,
   a. If wholesome foods without additives are consumed; or
   b. 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 FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

2.4.3 FDA Exemptions

The following categories of FDA-regulated clinical investigations are exempt from CPHS review:

1. Emergency use of a test article, provided that such emergency use is reported to the CPHS within 5 business days. Any subsequent use of the test article at the institution is subject to prior CPHS review. [21 CFR 56.104(c)] (See Section 6.3.4 for a detailed discussion of emergency use)

2. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or 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 FDA or
approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [21 CFR 56.104(d)]

2.4.4 Additional Protections

Although certain research is exempt from further CPHS review, this research is subject to the ethical principles of the Belmont Report and institutional ethical standards. Research that is exempt from CPHS review is held to the following ethical standards:

a. Research entails no more than minimal risk to participants.
b. Selection of subjects is equitable.
c. Adequate confidentiality provisions for research data (if collecting identifiable data) as appropriate.
d. Respect for the privacy of participants.
e. Informed consent of participants is obtained or informed consent may be acceptably waived.

The individual making the determination of exemption will determine whether to require additional protections for subjects in keeping with these standards.

In the process of making exempt determinations, the CPHS Director or CPHS Analyst evaluates whether these standards are satisfied and, if not, requests appropriate modifications to the study prior to making a final determination.

2.5 Expedited Review

The CPHS may use the Expedited review procedure to review either or both of the following:

a. Some or all of the research appearing on the list of categories of research eligible for Expedited review and found by the reviewer(s) to involve no more than minimal risk.
b. Minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

2.5.1 Categories of Research Eligible for Expedited Review

The research activities listed below should not be determined to be minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects. [63 FR 60364-60367, November 9, 1998]

The categories in this list apply regardless of the age of subjects, except as noted.
The expedited review procedure may not be used where identification of the subjects or their responses would reasonably place them at risk of criminal or civil liability, or be damaging to the subjects' financial standing, 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 no greater than minimal.

The expedited review procedure may not be used for classified research involving human subjects.

The standard requirements for informed consent (or its waiver or alteration, or other exception) apply regardless of the type of review, expedited or at a convened meeting, utilized by the CPHS.

Research categories one (1) through seven (7) pertain to both initial and continuing CPHS review:

(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
(a) From healthy, non-pregnant 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. [Children are defined in the DHHS regulations as "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."] [45 C.F.R. 46.402(a)]

(3) Prospective collection of biological specimens for research purposes by noninvasive means.
Examples: (a) hair and nail clippings in a non-disfiguring 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 gum base 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.

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (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.) Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). [NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See exempt categories and 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.] 

[NOTE: Expedited category #5 is considered to include information and specimens previously collected for research purposes, relying on information from OHRP published in 72 FR 60848-60851 (October 26, 2007).]

(6) Collection of data from voice, video, digital, or image recordings made for research purposes.

(7) 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.

[NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See exempt categories and 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.]
Continuing review of research previously approved by the convened CPHS as follows:
(a) When (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; or
(b) When no subjects have been enrolled and no additional risks have been identified; or
(c) When the remaining research activities are limited to data analysis.

Of note, category (8) identifies three situations in which research that is greater than minimal risk and has been initially reviewed at a convened meeting of the CPHS may undergo subsequent continuing review by the expedited review procedure. For a multi-center study, an expedited review procedure may be used by the CPHS at a particular site whenever the conditions of category (8)(a), (b), or (c) are satisfied for that site. However, with respect to category 8(b), while the criterion that "no subjects have been enrolled" is interpreted to mean that no subjects have ever been enrolled at a particular site, the criterion that "no additional risks have been identified" is interpreted to mean that neither the investigator nor the IRB at a particular site has identified any additional risks from any site or other relevant source.

Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the CPHS has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Under Category (9), an expedited review procedure may be used for continuing review of research not conducted under an investigational new drug application or investigational device exemption where categories (2) through (8) do not apply but the CPHS has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified. The determination that "no additional risks have been identified" does not need to be made by the convened CPHS.

2.5.2 Expedited Review Procedures

Under an expedited review procedure, the review may be carried out by the CPHS Chair or by one or more reviewers designated by the Chair from among members of the CPHS. CPHS members who serve as designees to the CPHS Chair for expedited review will be matched with their field of expertise to the study.

The Chairs delegate authority to the CPHS Director and CPHS Analysts in the CPHS Office to select members for expedited reviews from the official rosters of the entire CPHS membership. The CPHS Director or a CPHS Analyst selects reviewers with appropriate expertise and experience. A CPHS member is considered experienced after the member has completed a CPHS member orientation; has observed at least
one convened meeting; is proficient at ethical and regulatory analysis; has expertise specific to the study being reviewed; and is willing to review the study. CPHS members with a conflict of interest regarding a particular study (see section 1.5.4) will not be selected. Reviewers have appropriate qualifications, experience, and technical knowledge about the study to be reviewed and are aware of the regulatory criteria for the review. Of note, the regulatory criteria for review are the same for expedited and full committee reviews.

When reviewing research under an expedited review procedure, the CPHS Chair, or designated CPHS member, should receive and review all documentation that would normally be provided for a full committee review and determine whether the research meets the criteria allowing review using the expedited procedure. The expedited review procedure for proposed study amendments includes evaluating whether the proposed amendment is appropriately characterized as “minor”, using the definition of a minor change in section 2.2. If the research does not meet the criteria for expedited review, then the reviewer indicates that the research requires review by the CPHS at a convened meeting, and the study is placed on the next appropriate meeting agenda.

In reviewing proposed research, an expedited reviewer follows the review procedures described in sections 2.7 and 2.8 and may exercise all of the authorities of the CPHS except that the reviewer may not disapprove the research. A research activity may be disapproved only after review in accordance with a non-expedited procedure set forth below.

Expedited reviewers communicate approval, modifications necessary prior to approval, or a referral to a convened committee meeting to the CPHS staff. The investigator is notified in writing of the outcome of the expedited review. Approval is valid starting on the date of the approval for the interval indicated in the letter sent to the investigator.

If modifications are necessary prior to approval, the CPHS staff typically informs the investigator by e-mail. The modified study documents or additional information is sent back to the original reviewers for further review.

In the event more than one CPHS member performs an expedited review and the reviewers disagree, the CPHS Director or CPHS Analyst, in consultation with the CPHS Chair, may make a final determination. At the discretion of the CPHS Director or CPHS Chair, the study will be submitted to the CPHS for review at a convened meeting.

2.5.3 Informing the CPHS

Members of the CPHS are notified of expedited review approvals in a list at the next scheduled meeting. Any CPHS member can request to review the study documents by contacting the CPHS staff.
2.6 External Review

External review occurs when the College has formally delegated its responsibility for review to the IRB of another institution or a commercial IRB. The College typically agrees to delegate review for certain multi-center studies to reduce the administrative burden of multiple review processes and to support efforts to standardize the outcome of IRB review across multiple institutions. The College may also delegate review to the IRB of a facility where the interaction or intervention with research participants will take place and when that facility is not within the College or its affiliates.

The purpose of CPHS external review is to provide the CPHS, the College, and institutions affiliated with the College with a record and understanding of the research activities occurring under the auspices of the College.

2.6.1 Delegation of review

Delegation of review occurs through the execution of a formal agreement signed by the Institutional Officials of the College and the institution to which review is delegated or commercial IRB. This agreement describes the respective roles and responsibilities of the institutions regarding the protection of research participants under the Federal Wide Assurance (FWA) of each institution or organization. It includes arrangements for review activities, notice and reporting obligations and procedures, compliance, and access to copies of the meeting minutes from the reviewing IRB.

2.6.2 External review procedure

The CPHS Chair or any member with adequate subject area expertise and experience as a CPHS member may perform an external review. The Chairs delegate authority to the CPHS Director and CPHS Analysts to select members for external reviews from the official rosters of the entire CPHS membership. The procedure for selection is the same as that for expedited review described in section 2.5.2.

An external review relies on the information about the research provided to the reviewing IRB by the lead PI, study correspondence, plus other relevant local documents. An external review procedure applies to initial and continuing review by another IRB and any amendments to the study that require IRB review. In general, an external review conforms to the procedures for expedited initial reviews described in section 2.5.2 and continuing review in section 2.11.3, although the CPHS reviewers typically presume that the review criteria of 45 C.F.R. 46.111 in the DHHS regulations or 21 C.F.R. 56.111 in the FDA regulations have been satisfied through the procedures of the reviewing IRB.

Once an investigator makes study information available, the CPHS staff will arrange an external review as if the study was to receive expedited review. For continuing review
of research that receives CPHS external review, the expiration date of the reviewing IRB will be used by the CPHS.

Local oversight of a study by the CPHS also includes the review of compliance with state law and institutional policies and procedures; reports of protocol deviations and serious adverse events occurring locally; complaints about the conduct of the study; and any actions taken to suspend or restrict the activities of the local study team.

2.6.3 CPHS actions resulting from external review

The CPHS reviewer performing an external review may: 1) accept the review of the other IRB to which review was delegated, 2) request additional information about the research from the local principal investigator or from the reviewing IRB, or 3) reject the review of the other IRB. If the other IRB’s review is rejected, the study will be scheduled for review at the next convened meeting of the CPHS with an open agenda. Notice of rejection is typically provided to the other IRB that performed the initial review. This notice is accompanied by an explanation of the reasons for rejecting the initial review.

2.6.4 Criteria for accepting another IRB’s review

Criteria for accepting the review of another IRB are:
   a. Appropriate qualifications, standing, and available time of the local principal investigator to conduct the research.
   b. Adequate local resources for the conduct of the research, including those services necessary to support or protect research participants.
   c. Acceptance of the research activity by the local principal investigator’s department or section.
   d. Adequate safeguards incorporated into the research activities and consent process for the protection of the welfare and rights of research participants.

2.6.5 Notice to the local principal investigator

The CPHS sends a letter to the local principal investigator stating the outcome of an external review. This outcome may be: the acceptance of the other IRB’s review or the result of review by the CPHS at a convened meeting.
2.6.6 Notice to the CPHS of external reviews

Members of the CPHS receive notice of the results from external reviews in a list at the next scheduled CPHS meeting. Any member may review the study receiving external review by requesting the study documents from the CPHS Office.

2.7 Convened CPHS Meetings

Except when an expedited review procedure is used, the CPHS conducts initial and continuing reviews of all non-exempt research at convened meetings at which a quorum (see below) of the members is present.

2.7.1 CPHS Meeting Schedule

The College has four panels of the CPHS: A, B, C, and D. The rosters are registered with the Office of Human Research Protections (OHRP) and are updated whenever changes in membership occur. All four panels meet the federal requirements for IRB membership and may share members. For example, a primary member on one committee may also be listed as an alternate on another committee’s roster if his or her expertise is comparable.

Panels A, C and D each meet once per month. Panel B meets infrequently, only when a special request is received from an investigator to review a study in a timeframe that does not meet the schedule of the standing meetings and the review may be in the best interest of a potential subject. Any of the committees may meet on an ad hoc basis as necessary.

CPHS Panels A, C and D: These panels are comprised of members with appropriate expertise to review all types of studies. Based on the availability of complete study information, a particular study may be assigned to any panel. When the study application documents are ready for review, the study is added to the next agenda for either CPHS A, CPHS C or CPHS D, whichever meets next.
  - CPHS D meets the first Thursday of each month.
  - CPHS A meets the third Thursday of each month.
  - CPHS C meets the fourth Thursday of each month.

CPHS B: This panel handles special requests to review a study when a deadline exists that is not accommodated by standing CPHS meetings, such as a situation when review is needed to provide study participation as a medical treatment option to a potential subject and for certain time sensitive categories of research.

If any FDA-regulated studies are assigned to a meeting agenda, the CPHS staff involved with preparations for the meeting confirm that at least one licensed physician will be present as a voting member for the meeting.
2.7.2 Preliminary Review

When an application for review arrives in the CPHS Office, it is reviewed for completeness by CPHS staff. This administrative review includes an evaluation of application documents for consistency, accuracy, completeness, compliance with regulations on human subjects protection, state law, institutional requirements, and CPHS standards.

If an application is incomplete, the CPHS staff works with members of the research team to complete the application prior to scheduling or assigning the study for review.

2.7.3 Primary and Secondary Reviewers

A primary reviewer system consisting of two CPHS members is utilized for initial study review. Reviewers are selected by the CPHS Analyst in consultation with the CPHS Director according to the nature of each study and the expertise of the CPHS committee members. Any CPHS member may request a change to the assignments.

One primary reviewer is selected for expertise related to the scientific nature of each study. Expertise is assured by an advanced degree or applicable experience. Upon occasion the primary reviewer is designated because of a specific subject population or a particular issue requiring review. The second reviewer may be a member with additional expertise related to the nature of the study or be a non-scientist or a non-affiliated member providing an additional viewpoint to that of the primary reviewer. The criteria for designating the primary reviewers include ensuring there is no conflict of interest. When there is not adequate expertise in the committee to review a study, a consultant who is an expert in that discipline reviews the study and makes a report and recommendation to the committee (see Section 2.9).

The primary reviewers are responsible for:

a. Acquiring a thorough knowledge of the details of the proposed research.

b. Performing an in-depth review of the proposed research.

c. Leading the discussion of the proposed research at the convened meeting and presenting any ethical issues with the research.

d. Making suggestions for modifications to the proposed research, when appropriate.

An absent reviewer can submit written comments for presentation at the convened meeting.

All members are expected to review all of the studies on the meeting agenda, regardless of primary and secondary reviewer assignment.
2.7.4 Pre-Meeting Distribution of Documents

The CPHS staff is responsible for providing the meeting documents to CPHS members in advance of the meeting. Members are expected to allow sufficient time before meetings to review study documents to assure that CPHS reviews are completed on a timely basis.

One week in advance of the meeting, the CPHS staff provides CPHS members with meeting materials, including the agenda, minutes from prior meetings, continuing education materials, notices, and the information available for the studies that will be reviewed during the meeting. Some of the study materials are provided electronically and some materials are provided in paper form, depending on member preference and material availability.

The meeting documents are delivered to members’ offices or designated drop-off points approximately one week before the meeting.

A committee member is expected to contact the CPHS staff if his or her meeting materials do not arrive on time; a replacement copy is made available immediately.

Additional updated documents relating to agenda items are provided to CPHS members when they become available by e-mail prior to the day of the meeting.

2.7.5 Study information received by the CPHS

The application for review of a new study by the CPHS is intended to be a comprehensive and detailed description of the research study. The documents for full committee review include:

a. Human Subjects Review Form (HSRF)
b. Departmental Scientific Review Form (DSRF)
c. CPHS Study Plan document with attachments as applicable:
   - Attachment A: Medical Device
   - Attachment B: Placebo
   - Attachment C: Genetic Research
   - Attachment D: Employees and Students
   - Attachment E: Illiterate Participants
   - Attachment F: Research Involving Children
   - Attachment G: Research Involving Incompetent Participants
   - Attachment H: Request for Waiver of Participant Consent
   - Attachment I: Request for Waiver of Signed Consent Form
   - Attachment J: Investigational New Drug (IND)
   - Attachment L: International Research Form
   - Attachment M: Pregnant Women, Fetuses and Neonates
d. Consent form(s), assent form(s), parental permission forms, verbal consent scripts and information sheets as applicable
e. Supplemental documents - as applicable:
    Survey instruments, telephone scripts, advertisements
    Copy of the grant proposal
    Site agreement
    Investigator's Brochure
    Billing grid
    Conflict of Interest Committee recommendation form
    Model consent form
    Complete protocol

f. Any other relevant documents

The primary reviewers receive all of the study documents as described above. If any of these documents are only available as paper copies, the copies are included in a notebook for the primary reviewers. Typically each of the study documents are available electronically to CPHS members. Any CPHS member may request any of the materials provided to the primary reviewers and the CPHS staff will arrange to make the requested materials available.

If a CPHS member requires additional information to complete the review, they may contact the investigator directly or may contact the CPHS staff to request the information from the investigator.

2.7.6 Quorum

The quorum consists of a simple majority of the voting membership, including at least one member whose primary concern is in a non-scientific area. If research involving an FDA-regulated article is involved, a licensed physician is included in the quorum. When studies from VA investigators are being reviewed, at least one VA representative is included in the quorum. If research involves participants who may be vulnerable to coercion or undue influence, one or more individuals who are knowledgeable about or experienced in working with such participants are included in the quorum.

The CPHS staff establishes attendance at scheduled committee meetings approximately two weeks prior to the meeting. Efforts are made to ensure there is at least one non-affiliated member in attendance at each Committee meeting. The CPHS staff also ensures the confirmed attendees will meet quorum and have the adequate expertise to review the studies on the agenda.

The CPHS Chair, with the assistance of the CPHS staff, will confirm that an appropriate quorum is present before calling the meeting to order. The CPHS staff is responsible for ensuring that quorum is maintained throughout the meetings and a nonscientist is consistently present.

Members are considered present if participating through teleconferencing or videoconferencing. In that case, the member must have received all pertinent study
documents prior to the meeting and must be able to participate actively and equally in all discussions.

Opinions of absent members that are transmitted by mail, telephone, facsimile, or e-mail may be considered by the attending CPHS members, but may not be counted as votes or to satisfy the quorum for convened meetings.

2.7.7 Meeting Procedures

The Chair begins the meeting when quorum has been established and a nonscientific member is present. The Chair reminds the members about the CPHS COI Policy and announces any notifications that need be made. Studies are generally reviewed in agenda order, although studies may be taken out of order to accommodate reviewers’ schedules as necessary at the discretion of the Chair.

The CPHS reviews and discusses the minutes from the prior meeting and determines whether there are any revisions or corrections to be made. If there are no changes to be made, the minutes will be accepted as presented and considered final. If it is determined that revisions or corrections are necessary, the minutes may be approved as amended.

The CPHS reviews applications for initial and continuing review, as well as requests for modifications to previously approved studies. The primary reviewers present an overview of each research study. The members present at a convened meeting have voting rights, except in the case of a conflict of interest (see below). In order for the research to be approved, it must receive the approval of a majority of those voting members present at the meeting.

CPHS staff members attend each meeting in order to assist the committee. CPHS Staff members record the meeting minutes, vote counts, assure that quorum is not lost, and that a nonscientist is consistently present. A CPHS staff member records the vote for each study to confirm the vote counts in the meeting minutes. Generally, the CPHS Director is present for assistance and guidance during each meeting, including on institutional policies.

2.7.8 Guests

At the discretion of the CPHS, the local Principal Investigator may be invited to the CPHS meeting to answer questions about his or her proposed or ongoing research. Typically a local Principal Investigator is only invited if substantial revisions are needed upon first review and the Committee has asked to review the study again. The local Principal Investigator may not be present for the discussion or vote on his or her study.

Other guests may be permitted to attend CPHS meetings at the discretion of the CPHS Chair and the CPHS Director. Guests may not speak unless requested by the CPHS and must sign a confidentiality agreement.
2.8 Criteria for CPHS Approval of Research

In order for the CPHS to approve human subjects research under the DHHS regulations at 45 C.F.R. 46.111 or a clinical investigation under FDA regulations at 21 C.F.R. 56.111, it must determine that the following requirements are satisfied:

a. Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purpose.

b. 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. In evaluating risks and benefits, the CPHS should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The CPHS should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

c. Selection of subjects is equitable. In making this assessment, the CPHS should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

d. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by 45 C.F.R. 46.116 (DHHS) or 21 C.F.R. 50.20 (FDA).

e. Informed consent will be appropriately documented, in accordance with and to the extent required by 45 C.F.R. 46.117 (DHHS) or 21 C.F.R. 50.27 (FDA).

f. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

g. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

h. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

In order to approve research in which some or all of the subjects are children, the CPHS should determine that the research is in compliance with 45 C.F.R. 46, subpart D and 21 C.F.R. 50, subpart D and determine the applicable risk level.
2.8.1 Risk/Benefit Assessment

The identification and measurement of risk is based on the information included in the application for review including the investigator's statements about the risks, benefits and any mitigating factors, as well as the Committee's expertise. The purpose of this section is to describe the process by which the CPHS evaluates the adequacy of human subjects protections.

The CPHS must judge whether the anticipated benefits, either of new knowledge or potentially improved health for the research participants, justifies asking any person to undertake the risks. The CPHS should disapprove research in which risks are judged unreasonable in relation to anticipated benefits.

2.8.1.1 Definitions

Risk: The probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study. Both the probability and magnitude of possible harm may vary from minimal to significant.

Minimal risk: The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those encountered in daily life or during the performance of routine physical or psychological examinations or tests in reference to a healthy person in a safe environment.

Note: The definition of minimal risk is different for research involving prisoners. See Section 5.7.2 for that definition.

Benefit: A valued or desired outcome; an advantage. The benefits of research fall into two major categories: benefits to participants and benefits to society. Some research has therapeutic intent, e.g., research that evaluates a procedure that may ameliorate participants' medical conditions or provide a better understanding of their disorders. Some research has no immediate therapeutic intent, but is designed principally to increase the understanding and store of knowledge about human physiology and behavior. Non-therapeutic research may benefit society as a whole by increasing knowledge and improving safety, technological advances, and health.

2.8.1.2 Procedure

The CPHS considers the following questions and issues when analyzing the risks and benefits of proposed research:

a. What risks will participants be exposed to that are different from those of everyday life or standard therapy if participants are currently suffering from or being treated for any condition? Risks might include: physical (pain, discomfort, risks to health), economic (damage to reputation, loss of insurance, impact on employability), legal, psychological, emotional, social or other.
b. Risks should be evaluated for frequency, severity, specificity, reversibility, and possible late effects.

c. CPHS committees should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies participants would receive even if not participating in the research).

d. CPHS committees should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within its responsibility.

e. Are risks clearly and accurately identified in the study documents?

f. Do study participants include children or other vulnerable populations and are there are special risks for these vulnerable groups? How are these risks addressed?

g. If deception will be used, is it necessary and justified and will debriefing be adequate?

h. If study is blinded, is there an appropriate plan for unblinding?

i. Are risks kept to a minimum with measures such as:
   
   i. Using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk.
   
   ii. Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
   
   iii. Using appropriate eligibility criteria (to screen out any especially vulnerable participants).
   
   iv. Assuring that proposed participant population is appropriate to the research.
   
   v. Determining whether recruitment excludes those participants for whom the risks are more likely to occur or are unacceptable.
   
   vi. Assuring that recruitment is free of coercion and undue influence.
   
   vii. Assuring that there is no status relationship between research team members and participants.
   
   viii. Measures to make study procedures as comfortable as possible for participants, i.e., no unnecessary or excessive testing.
   
   ix. Study-wide monitoring of safety and data integrity, as well as appropriate lab tests and other individualized monitoring.
x. Good study design, so that the risks participants take result in usable information (the riskier the research, the more safeguards the study design must incorporate).

xi. There are provisions for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects or additional resources for participants.

xii. An appropriate plan for management of incidental findings.

xiii. Obtaining a Certificate of Confidentiality to minimize legal risk.

d. Is the research personnel qualified to perform the research or, in the case of student research, is the level of supervision adequate?

e. What will study participation require of the participant? How many visits and how long will they take; what kinds of procedures are involved; how do the study procedures differ from standard care?

f. Will subjects be compensated for participating in the study, and if so, how?

g. Are there any unusual, invasive, or sensitive procedures (e.g., excessively long or frequent visits; many injections, infusions, or blood samples; genetic testing)?

h. Will the participant be told about the study in a way he or she can understand, so the participant can make an informed choice about taking part? Consent form content and readability are key considerations. Are there procedures for obtaining consent and having ongoing dialogue with participants about their study involvement? Are risks identified clearly and accurately for participants? What provisions are made if the participant does not understand English?

i. Are there provisions to protect the privacy of the subjects and confidentiality of the data and research records, including for recording and coding of the data, de-identification of the data, and security for the transmission and storage of the data?

   i. If data is stored electronically, are there adequate firewall and other electronic protections in place.

   ii. Are there provisions to protect the privacy of the subjects and confidentiality of data associated with subject samples like saliva, blood, and tissue?

   iii. If data will be shared, are there formal agreements needed and used?

   iv. Is a Certificate of Confidentiality needed?

   v. Are the research procedures being performed in a location that protects the privacy of participants and in a way that preserves their dignity?
p. What are the expected benefits?
   i. Benefits can take the form of potential therapy, education, information, resources, attention, or empowerment.
   ii. Benefits can be directed to participants or their community or society.
   iii. If there is no benefit to participants, is the issue being researched important to society?
   iv. If the stated intent is to benefit participants, is it a truly a benefit from the perspective of the participants?
   v. Benefit may exist from participation in study even if the actual research does not provide a participant benefit: e.g., participants’ medical conditions are more closely monitored, free medical treatment is provided to participants which they otherwise could not access.
   vi. If participation in the study will provide no possibility of benefit to participants, the study documents, especially the consent form, must say so.

q. Are the risks of the research reasonable in relation to the benefits? Whether the balance is reasonable may require consideration of type of risks: physical, psychological, social, economic, or legal.

Achieving this evaluation requires balancing the potential risks to participant or to others, such as disclosure of genetic information, with potential benefits to a participant and to society. A sliding scale of risk may be used ranging from:
   a. Little or no benefit to participants should entail little or no risk.
   b. High risk studies may require a showing of significant benefit to participants or the potential for an advance in knowledge in the absence of beneficial alternatives to research participation.
   c. Long-term effects should be considered.

Additional considerations for clinical research often involve an evaluation of physical risks and may include the possibility of death. If the participant is currently being treated for a medical condition, the CPHS expects that the research will use procedures currently being used to diagnose or treat the participants’ condition, whenever possible; if these procedures are not included, specific justification should be made in the study documents. Such additional considerations include:
   a. The phase of the research with respect to a particular drug, device or procedure.
   b. The medical condition of the participants (how ill are the participants?).
   c. Are there other appropriate medical treatments for the condition, the effectiveness and availability of these alternative treatments, and the comparative risks they present?
d. Possible late effects of participation (e.g., secondary cancers).

e. What drugs or therapies are being used and at what dose levels?

f. Are samples of blood, tissue, or other biospecimens collected? Are they banked for future research use?

g. If the research is a more than minimal risk, interventional study, is there an adequate data and safety monitoring plan in place?

### 2.8.1.3 Additional Considerations for CPHS Committees

Social and behavioral science and education research risks involve primarily social, psychological, economic, or legal risks, and only rarely physical risks.

Some research presenting little or no benefit to an individual participant will not be approved, unless the study presents low risk to participants and the prospect of considerable societal benefit.

If a study is risky (e.g., involves sensitive information), an investigator is required to show how he or she will mitigate the potential risks through confidentiality protection measures or other assurances of anonymity, provided these assurances are actually possible to fulfill.

In international research, an investigator must address the potential social, cultural, political and economic risks inherent in the country in which the research is being conducted.

If a research study is likely to reveal sensitive information about a participant that is unnecessary to the research purpose, the intended data collection should be altered.

### 2.8.1.4 Scientific Merit

In order to assess the risks and benefits of the proposed research, the CPHS determines that:

a. The research uses procedures consistent with sound research design;

b. The research design is sound enough to reasonably expect the research to answer its proposed question; and

c. The knowledge expected to result from this research is sufficiently important to justify the risks, time, and effort invested by participants.

In making this determination, the CPHS may draw on its own knowledge and disciplinary expertise, or the CPHS may draw on the knowledge and disciplinary expertise of others, such as reviews by a funding agency or departmental scientific review.
The signature of an official responsible for the local investigator's research unit documents departmental scientific review on new study applications. For full committee studies, the Departmental Scientific Review Form (DSRF) is used as documentation. For expedited studies, the Human Subjects Review Form (HSRF) documents this review. For student projects, the faculty advisor’s signature documents this review. Review of the department from which study participants are drawn is also be required if different from the investigator's research unit.

2.8.2 Selection of subjects is equitable

The CPHS determines by reviewing the study documents that the selection of subjects is equitable with respect to gender, age, socioeconomic status, and any other relevant classification such as active military or veteran status. The CPHS will not approve a study that does not provide adequately for the equitable selection of subjects or has not provided appropriate scientific and ethical justifications for excluding classes of persons who might benefit from the research. In making its determination about equitable selection, the CPHS evaluates: the purposes of the research; the setting in which the research occurs; the scientific and ethical justifications for including vulnerable populations such as children, prisoners, pregnant women, mentally disabled individuals, or economically or educationally disadvantaged individuals; the scientific and ethical justifications for excluding classes of individuals who might benefit from the research; plus the inclusion and exclusion criteria for study participation.

There may be special circumstances in which an ad-hoc committee will need to be formed to address selection issues involved in the review of a study. The purpose of the ad-hoc committee would be to illuminate certain issues requiring fuller discussion on a specific study or a specific issue. If such discussion is needed, the CPHS office staff will assemble a committee consisting of study population and community representatives such as veterans or students, CPHS members, and researchers to resolve the issues.

2.8.2.1 Recruitment of Subjects

The local investigator is expected to provide the CPHS with any recruiting materials used in identifying and contacting potential participants, including recruitment methods, advertisements, and payment arrangements. See Section 2.9.7 for a discussion of the CPHS review of advertisements and payments to study participants.

2.8.3 Informed Consent

The CPHS ensures that informed consent will be sought from each prospective subject or the subject’s legally authorized representative, in accordance with and to the extent required by 45 CFR 46.116 and 21 CFR 50.20. In addition, the CPHS ensures that informed consent will be appropriately documented in accordance with and to the extent required by 45 CFR 46.117 and 21 CFR 50.27. See Chapter 4 below for detailed CPHS policies and procedures on informed consent.
2.8.4 Data and Safety Monitoring

The CPHS determines that, where appropriate, the research plan makes adequate provision for monitoring the data to ensure the safety of subjects. Local investigators are asked to provide the following information in the CPHS application for its initial review of their research:

a. The potential risks to subjects of participation in the study, including the expected frequency, severity, specificity, and reversibility of the major risks identified and possible late effects of participation (e.g., secondary cancers or reputational harm).

b. If the study is more than minimal risk, a description of the data and safety monitoring plan for interventional studies.

c. The Data and Safety Monitoring (DSM) plan must be commensurate with the level of risk, size and complexity of the study.

As part of the CPHS primary reviewer’s assessment of the application for review of the study, he or she reviews the proposed DSM plan and the administration and composition of the monitoring entity, when applicable. The CPHS reviewer ensures that the DSM plan includes appropriate elements, and that reporting to the CPHS is addressed. If the CPHS primary reviewer does not have adequate expertise to assess the DSM plan or the monitoring entity (if one is specified in the plan), the reviewer is encouraged to consult with individuals with appropriate clinical, scientific, or statistical expertise.

The CPHS committee may consider the following issues when evaluating whether a DSM plan is necessary and appropriate:

a. Level of risk of the research.

b. Phase of the study, if it involves drugs, biologics or devices.

c. Other factors such as blinding of participants and performance site investigators, multiple sites, vulnerable research participants, high-risk interventions, or new, unfamiliar interventions not otherwise categorized as a phase III clinical trial.

The CPHS makes its determinations about the sufficiency of the DSM plan on a study-by-study basis. In addition, the CPHS may consider the following issues when evaluating whether a DSM plan is necessary:

a. Whether study presents risks of breach of confidentiality and privacy.

b. Whether it can be anticipated that the research may reveal a risk of suicide or homicide by a research participant, based either on the population being studied or the nature of the questions being asked. The study documents should describe the procedures that will be followed if the research reveals such a risk.

c. Whether it can be anticipated that the research may reveal neglect or abuse of a vulnerable individual, based either on the population being studied or the nature of the questions being asked. The study documents should describe the procedures that will be followed if the research reveals such a risk.
The CPHS may consider the following issues when evaluating whether a DSM plan is adequate:

a. The data to be monitored.
b. The frequency of the monitoring.
c. Who will conduct the monitoring, such as a data monitoring committee, data and safety monitoring board (DSMB), medical monitor, investigator, independent physician, or the CPHS.
d. Reporting channels.
e. Procedures for communication from the data monitor to the IRBs and sites.

DSM plans should provide for reports to be made by the investigators to the CPHS at appropriate intervals and immediately if monitoring reveals a problem requiring re-evaluation of study.

Regarding the content of reports, the CPHS may request at any time an affirmative statement from the DSMB or other monitor that there are no safety problems that have been identified with the research.

CPHS recognizes that conflicts of interest are inherent when monitors who are chosen by research sponsor conduct data and safety monitoring. If the CPHS believes the sponsor DSM plan is inadequate, the CPHS may:

a. Request changes by the sponsor,
b. Request the investigator to conduct additional data and safety monitoring, or
c. Not approve the study.

For DoD regulated research, an independent research monitor is required for studies involving more than minimal risk. The CPHS may appoint a research monitor for studies involving no more than minimal risk if necessary to satisfy this requirement. According to DoD regulations, the research monitor must be appointed by name and has the authority to stop a research study in progress, remove individuals from the study, and take whatever steps are necessary to protect the safety and well-being of research subjects until the CPHS can assess the research monitor’s report.

2.8.5 Privacy and Confidentiality

The CPHS will determine whether adequate procedures are in place to protect the privacy of subjects and to maintain the confidentiality of the data.

2.8.5.1 Definitions

Privacy: Having control over the extent, timing, and circumstances of sharing oneself (physically, psychologically, emotionally, behaviorally, or intellectually) with others.

Confidentiality: Methods used to ensure that information obtained by researchers about their subjects is not improperly divulged.
**Private information:** 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).

**Identifiable information:** Information where the identity of the subject is or may readily be ascertained by the investigator or is associated with the information.

### 2.8.5.2 Privacy

The CPHS determines whether the research activities constitute an invasion of privacy. In order to make this determination, the CPHS obtains information regarding how the investigators make contact with subjects or use subjects’ private, identifiable information and reasonable expectations of privacy in the situation. In developing strategies for the protection of subject privacy, consideration should be given to:

a. Methods used to identify and contact potential participants.
b. Settings in which an individual will be interacting with an investigator.
c. Appropriateness of the personnel present for research activities.
d. Methods used to obtain information about participants and the nature of the requested information.
e. Information that is obtained about individuals other than the “target participants,” and whether such individuals meet the regulatory definition of “human participant” (e.g., a subject provides information about a family member for a survey).
f. The appropriate amount and extent of information is necessary to complete the study.

Maintaining the confidentiality of information, especially health information, may support the protection of privacy. As a result, investigators should obtain appropriate permission or a CPHS granted waiver or alteration for the use of health information that is ordinarily considered to be private.

### 2.8.5.2.1 Participant Contact

If the population of interest for a study is identified by its medical condition, investigators should have appropriate authorization to make contact with subjects, unless a partial waiver of authorization has been granted.

If the population of interest for a study is identified by their medical condition, then access to other information in the medical record should be limited to appropriately supervised and trained personnel. In addition, the CPHS typically recommends that first contact about research participation be from someone involved with the person’s medical care and so has legitimate access to the person's medical records.
The CPHS retains the ability to increase or decrease the level of interventions or data collection prior to potential participant contact depending on the nature of the information to be obtained for research purposes.

If the research consists of a written survey only, an explanatory letter or introductory paragraph should be included that provides the researcher’s name, affiliation with Dartmouth, specific method of obtaining the potential participant's contact information, the voluntary nature of responses, level of confidentiality that may be expected, and a description of purpose of the study.

If the research consists of a telephone survey, the CPHS recommends the following procedures:

- Telephone interviewers should be well versed and sensitive to issues of privacy. The telephone script should include at least the following information: the interviewer's name, affiliation with Dartmouth, method of obtaining potential participant's contact information, the voluntary nature of responses to survey questions, and extent of confidentiality that may be expected.

- A letter should be sent to potential participants prior to the telephone interview that describes the study and indicates when the telephone survey is scheduled. The letter should include the means by which the potential participant's name was obtained, and, if applicable, the name of the physician who cares for the individual.

- The letter should contain instructions for declining participation, such as a telephone number or stamped postcard with notice that participation has been declined.

### 2.8.5.3 Confidentiality

If the investigator can readily ascertain the identity of the subjects from collected research data or will meet participants in person, then the research is not de-identified and the CPHS determines if appropriate protections are in place to minimize the likelihood that the information will be inappropriately divulged. The extent of confidentiality protections should be commensurate with the potential of harms from inappropriate disclosure.

At the time of initial review, the CPHS evaluates whether the privacy and confidentiality of information about research participants are adequately protected. The CPHS does this through an evaluation of the methods used to obtain, use or disclose, and maintain the study information, including but not limited to research data:

- About the research participants,
- About individuals who may be recruited to participate in studies,
- Reliance on individually identifiable records,
- Methods employed to protect the confidentiality of research data,
e. Appropriate permissions from research participants, or investigator requested alteration or waiver of individual permissions from the CPHS for the use of information that is ordinarily considered to be private, and

f. An Investigator's or research staff member's activities preparatory to research.

The investigator provides information regarding the protection of privacy and maintenance of confidentiality for research participants at the time of initial review through the application for review and other relevant study documents. The CPHS reviews the information received from the investigator and determines whether or not the confidentiality of research subjects is sufficiently protected. In some cases, the CPHS may also require that a Certificate of Confidentiality be obtained from NIH as additional protection for research data.

In reviewing confidentiality protections, the CPHS considers the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research. It evaluates the effectiveness of proposed de-identification techniques, coding systems, encryption methods, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections.

Confidentiality is not “guaranteed” to any research participant, either verbally or in the consent and authorization forms as applicable.

2.8.6 Vulnerable Populations

At the time of initial review, the CPHS considers the scientific and ethical reasons for including vulnerable participants in research. The CPHS may determine and require that, when appropriate, additional safeguards are put into place for these participants, such as those lacking decision-making capacity. For a more extensive discussion about the CPHS review and approval process for individual populations of vulnerable subjects, please refer to Section 5.

2.9 Additional Considerations during CPHS Review and Approval of Research

2.9.1 Determination of Risk

At the time of initial and continuing review, the CPHS makes a determination regarding the risks associated with the research studies. Risks associated with the research are classified as either “minimal” or “greater than minimal” based on the definition of minimal risk as the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests in reference to a healthy person in a safe environment. Risks that are greater than minimal may be further characterized as low, moderate, or significant. The meeting minutes reflect CPHS determinations regarding risk levels.
2.9.2 Period of Approval

At the time of initial review and at continuing review, the CPHS makes a determination regarding the frequency for review of each research study. All research studies are reviewed by the CPHS at intervals appropriate to the degree of risk or other factors, but no less than once per year if federally conducted or supported. Studies involving no more than minimal risk that are not federally conducted or supported and involve research procedures for which expedited review is appropriate may be reviewed every two years. In some circumstances, a shorter review interval (e.g., biannually, quarterly, or after accrual of a specific number of participants) may be required (see below). The meeting minutes reflect the CPHS determination regarding the frequency of review.

2.9.2.1 Review More Often Than Annually

Research that meets any of the following criteria typically will require review more often than annually:

a. Significant risk to research subjects (e.g., death, permanent or long lasting disability, morbidity, or severe toxicity) without the possibility of direct benefit to the subjects.

b. The involvement of especially vulnerable populations likely to be subject to coercion or undue influence (e.g., terminally ill individuals).

c. A history of serious or continuing non-compliance on the part of the PI.

The following factors are also considered when determining which studies require review more frequently than on an annual basis:

a. The probability, frequency, and magnitude of anticipated risks to subjects.

b. The medical condition of the proposed subjects, if any.

c. The overall qualifications of the PI and other members of the research team.

d. The specific experience of the local investigators and other members of the research team in conducting similar research, if any.

e. The nature and frequency of adverse events observed in similar research at this and other institutions.

f. The novelty of the research if unanticipated adverse events may be made more likely by its novelty.

g. Any other factors that the CPHS concludes are relevant.

In specifying an approval period of less than one year, the CPHS may define the period with either a time interval or a maximum number of subjects either studied or enrolled. If a maximum number of subjects studied or enrolled is used to define the approval period, it is understood that the approval period in no case can exceed 1 year and that the number of subjects studied or enrolled determines the approval period only when that number of subjects is studied or enrolled in less than 1 year.
2.9.3 Independent Verification That No Material Changes Have Occurred

In general, the CPHS relies on the accuracy and completeness of information provided by the investigator. Nevertheless, the CPHS recognizes that protecting the rights and welfare of subjects may sometimes require the CPHS to act independently to verify study information that no material changes occurred during the CPHS-designated approval period by utilizing sources other than an investigator. Independent verification may be necessary at times; for example, in cooperative studies or other multi-center research.

The CPHS determines the need for verification from outside sources on a case-by-case basis and according to the following criteria:

a. Research studies where concern about possible material changes occurring without CPHS approval have been raised based on information provided in continuing review reports or from other sources.

b. Research studies conducted by local investigators who have previously failed to comply with federal regulations and the requirements or determinations of the CPHS.

c. Research studies randomly selected for internal audit.

d. Any other circumstance in which the CPHS concludes verification from outside sources is relevant.

The following factors will also be considered when determining which studies require independent verification:

a. The probability and magnitude of anticipated risks to subjects.

b. The medical condition of the proposed subjects, if applicable.

c. The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed.

In making determinations about independent verification, the CPHS may prospectively require that such verification take place at predetermined intervals during the approval period, or may retrospectively require such verification at the time of continuing review, review of amendments, adverse events, and unanticipated problems involving risks to subjects or others.

If any material changes have occurred without CPHS review and approval, the CPHS will decide what corrective action should be taken.

2.9.4 Consent Monitoring

In reviewing the adequacy of informed consent procedures for proposed research, the CPHS may, on occasion, determine that special monitoring of the consent process by an impartial observer (consent monitor) is required in order to reduce the possibility of coercion and undue influence.
Such monitoring may be particularly warranted when the research presents significant risks to subjects, or if subjects are likely to have difficulty understanding the information to be provided. Monitoring may also be appropriate as a corrective action where the CPHS has identified problems associated with a particular PI, group of investigators, research staff members, or a research project. See Section 4.5 for a detailed discussion of consent monitoring.

2.9.5 Investigator Conflict of Interests

The CPHS application for review asks study-specific questions regarding conflict of interest for the investigators and key personnel conducting the research. As part of its review process, the CPHS makes a determination as to whether to accept the recommendation of the COI Committee at Dartmouth College to manage any conflicts with regard to the research under review. Certain management plan recommendations are eligible for expedited review, such as the addition of a disclosure to the consent form. When a conflict of interests exists, the CPHS approval letter for a study notes that an approved conflict management plan that adequately protects study participants is in place.

*For VA Studies:* The CPHS notifies the VA R&D Committee for the facility that a COI management plan has been incorporated in the study through the CPHS approval letter. The VA R&D Committee may ratify the COI management plan approved by the CPHS by its approval of the study. The VA R&D Committee may also request further modifications to the study before granting its final approval. In this case, the investigator applies for CPHS review of the study as amended by the VA R&D Committee. The VA R&D Committee only approves a study that has prior CPHS approval.

2.9.6 Significant New Findings

During the course of research, significant new knowledge or findings about the test article or the condition under study may develop. The PI reports any significant new findings to the CPHS and the CPHS reviews them with regard to the impact on participants' rights and welfare. As part of this review, the CPHS requests the local PI's comment on whether the new information should be provided to currently enrolled participants. Since the new knowledge or findings may affect the risks or benefits to participants or their willingness to continue in the research, the CPHS may require that the PI notify the currently enrolled participants about the new information. The CPHS communicates this requirement to the PI. Ordinarily the consent form should be updated and consent newly obtained from the currently enrolled participants to acknowledge receipt of this new information and affirm their continued willingness to participate in the research.
2.9.7 Recruitment of Subjects

2.9.7.1 Advertisements

The CPHS approves any and all advertisements prior to posting or distribution for studies that are conducted under its review. Prior to use of the advertisements for the research, the CPHS reviews:

a. The information contained in the advertisement.
b. The mode of its communication.
c. The final version of printed advertisements.
d. The final version of scripts for or audio or video recordings.
e. Any images associated with the advertisements.

This information should be submitted to the CPHS with the initial application or as an modification to the study. The CPHS reviews advertisements to assure that the information is accurate and not coercive or unduly optimistic. The impact of the advertisement should not create undue influence on the subject to agree to participate in the research. The review precludes the following influences:

a. Statements implying certainty of a favorable outcome or other benefits beyond what was described in the consent form and the other study documents.
b. Claims, either explicit or implicit, that a drug, biologic substance, or medical device was safe or effective for the purposes under investigation.
c. Claims, either explicit or implicit, that a test article is known to be equivalent or superior to any other drug, biologic substance, or medical device.
d. The use of terms like “new treatment”, “new medication”, or “new drug” without explaining that a test article is investigational or that a placebo is involved.
e. Promising “free medical treatment” when the intent is only to say participants will not be charged for taking part in the investigation.
f. Emphasis on payment, such as bold type or larger font on printed media, or inclusion of the amount to be paid,
g. The inclusion of exculpatory language.

Any advertisement to recruit subjects should be limited to the information the prospective participants need to determine their eligibility and interest. When appropriately worded, the following information may be included in advertisements for research participants:

a. The name and address of an investigator and research facility.
b. The condition being studied, if applicable, and the purpose of the research.
c. In summary form, the criteria that will be used to determine eligibility for the study.
d. The time or other commitments required of the subjects.
e. The location of the research activities and the person or office to receive further information.

f. A clear statement that the activity is research and not treatment for a condition, if applicable.

g. A brief list of potential benefits (e.g., no cost for a health exam).

Clinical Trials Listings. CPHS review and approval of listings of clinical trials on the internet would provide no additional safeguards for research participants and is not required when the listing format limits the information provided to basic trial information, such as: the title and purpose of the study; a study summary; basic eligibility criteria; study site locations; and how to obtain further information about the study. Examples of clinical trial listings that do not require prospective CPHS approval include the National Cancer Institute’s cancer clinical trial listing (PDQ), the government-sponsored AIDS Clinical Trials Information Service (ACTIS), and ClinicalTrials.gov. If the opportunity to add additional descriptive information is not precluded by such database systems, CPHS review and approval may assure that any additional information does not promise or imply a certainty of cure or other benefit beyond what is contained in the study documents, including the consent form.

For FDA regulated clinical trials, the CPHS consent form template includes a description of the information that will be available on www.clinicaltrials.gov.

2.9.7.2 Payment to Research Subjects

Payment to research subjects may be an incentive for participation or a way to reimburse a subject for travel and other experiences incurred due to participation. Payment for participation, however, is not considered to be a research benefit. Regardless of the form of remuneration, economic coercion of subjects should be avoided. Payments may reflect a certain degree of risk, inconvenience, or discomfort associated with participation. The amount of compensation should be proportional to the risks and inconveniences posed by participation in the study. Ordinarily, compensation is not offered when research activities are integrated with usual medical care.*

Investigators who wish to pay research subjects should justify payments in their application for review. Such justifications should:

a. Substantiate that proposed payments are reasonable and commensurate with the expected contributions of the participants;

b. State the terms of agreement to research participation and the amount of payment in the consent form; and

c. Substantiate that payments are fair and appropriate, and that they do not constitute (or appear to constitute) undue influence on the individuals in the potential study population to participate in the research study.
The CPHS reviews both the amount of payments and the proposed method of disbursement to assure that neither entails coercion or undue influence.

Credit for payment should accrue and not be contingent upon the participant completing the entire study. The CPHS does not allow the entire payment to be contingent upon completion of the entire study. Any amount paid as bonus for completion of the entire study may not be so great that it becomes economically coercive on study participants.

The consent form should describe the terms of payment and the conditions under which subjects would receive partial payment, e.g., if they withdraw from the study before their participation is completed, or no payment, e.g., they are ineligible to participate in the study.

If certain identifying information is needed to issue checks, cash, gift certificates, or other forms of payment to participants, the consent form should contain information about these disclosures.

2.9.7.3 Recruitment Incentives

Payment arrangements among sponsors, organizations, investigators, and those referring research participants should not place participants at risk of coercion or undue influence, cause inequitable selection, or promote a sponsor’s products. The CPHS does not permit payment in exchange for referrals of prospective participants or payments designed to accelerate recruitment that are tied to the rate or timing of enrollment (“bonus payments”).

2.9.8 Compliance with Applicable State and Local Laws

CPHS review includes the evaluation of research activities for compliance with applicable state and local laws in the jurisdictions where the research is taking place. The CPHS may rely on the Office of General Counsel at Dartmouth College and available legal expertise among its members for the interpretation and application of New Hampshire and Vermont state laws. *The CPHS also may rely on advice from the VA Regional Counsel for guidance on the federal law specifically applicable to the VA facilities.

Arrangements for outside legal counsel with appropriate credentials and expertise are made as necessary to obtain advice about compliance with the law of other jurisdictions as it applies to human subjects research where research may be conducted. In addition, the CPHS relies on reviewing IRBs at other sites to evaluate multi-site research activities for compliance with applicable state and local laws.

The CPHS evaluates each study for consistency with applicable state and local laws regarding the participation of minors and individuals lacking capacity to consent to participation in research activities; the reporting of infectious diseases; the reporting of child and elder neglect and abuse; the confidentiality of medical records and receipt of
certain services; “experimental treatment” of individuals with mental disabilities; contractual indemnification for research-related injury or illness; and other legal issues as may arise in connection with specific research activities.

2.9.9 Collaborative Research Projects

The College assures that the facilities involved in a study receive adequate documentation about the study to protect the interests of participants. Before a study begins, the IRB for each participating facility should approve it, as well as, when appropriate, the IRB for any coordinating facility.

For collaborative research, the lead PI should identify all institutions participating in the research, contact information for the IRBs of those institutions, and specific procedures for the dissemination of study information among the participating institutions. Relevant study information includes, but is not limited to IRB initial and continuing approvals, reports of unanticipated problems involving risks to subjects or others, and study modifications.

When the CPHS relies on another IRB, the CPHS Chair or Director reviews the policies and procedures of that IRB to ensure that they meet College standards.

When another institution relies on the CPHS as its reviewing IRB, the CPHS facilitates the necessary arrangements, including acquisition of a Federal-wide Assurance for the other institution if necessary, the execution of an appropriate IRB authorization agreement, and documentation of the respective roles and responsibilities of the institutions for the protection of human research participants.

When the CPHS reviews research conducted at another institution, the particular characteristics of each institution’s local research context is considered, either (i) through knowledge of its local research context by the CPHS or (ii) through information gathered by the CPHS office, Director, Chair, or other members.

If the College is a research coordinating facility, the PI documents how information about human subject protections will be communicated to the other participating facilities engaged in the research. The PI serves as the single liaison with outside regulatory and funding agencies, other participating facilities, and for internal review and oversight procedures.

The PI takes responsibility for the participating facilities obtaining review and approval from their IRBs and adopting all study modifications in a timely fashion. The PI arranges for the research to be reviewed and approved by other appropriate committees at the coordinating facility as necessary and at each participating facility prior to the enrollment of participants.

The PI is advised to follow the following procedures when the College is a coordinating facility:
a. In the initial application for CPHS review of the multi-site study, the PI indicates in writing on the application form or in a letter that the College is the coordinating facility for a multi-site study.

b. The PI includes the following information in the application for CPHS review:
   i. Name of each participating facility.
   ii. FWA number for each participating facility.
   iii. Contact information for the investigator at each participating facility.
   iv. Contact information for the IRB at each participating facility.
   v. The research activities conducted at each participating institution.
   vi. Method of distribution to participating facilities of the most current versions of the study documents.
   vii. Method for confirming that amendments and modifications in the study documents have been communicated to participating sites.
   viii. Method for communicating to participating facilities any serious adverse events and unanticipated problems involving risks to subjects or others.
   ix. Method of communicating regularly with participating sites.

c. The PI includes approval letters from each IRB for all participating sites.

d. The PI maintains copies of correspondence between participating sites and their IRBs.

The CPHS reviews the procedures for the communication and management of information among the sites and determines if they are suitable for the proposed research project.

2.9.10 Adequacy of Resources to Protect Subjects

At the time of initial review and at continuing review, the CPHS determines whether the investigator has sufficient resources available that are necessary to protect human subjects in the study, including:

a. Access to a population that would allow recruitment of the required number of subjects.

b. Sufficient time to conduct and complete the research.

c. Adequate numbers of qualified staff.

d. Adequate facilities.

e. A process to ensure that all persons assisting with the research are adequately informed about the study and their research-related duties and functions.

f. Availability of medical or psychological resources that subjects might require as a consequence of the research.
2.10 Possible CPHS Actions

Approval: The study is approved as presented.

Minor Revisions Required for Approval: There are no substantive issues or concerns with the study. Nevertheless, the Committee requires simple concurrence by the investigator with minor modifications to certain aspects of the study documents. Study activities are not initiated until the CPHS has received and approved the requested modifications and has provided a final letter of approval. The approval date is the date of CPHS approval after all modifications have been reviewed and accepted.

In order to receive CPHS approval for a study in which minor modifications have been requested the following conditions apply.

a. For studies reviewed by the full committee, one or more CPHS members review the investigator’s response and any revised documents. Responses may be given to the CPHS Chair, reviewer, the CPHS Director, a CPHS Analyst, or a designee of the CPHS for review. The reviewer(s) may approve the study upon receipt and approval of the revisions without further action by the full committee.

b. For studies receiving expedited review, one or more CPHS members review the investigator’s response and any revised documents. The reviewer(s) may approve the study upon receipt and approval of the revisions.

c. Approval of the study will not be granted until modifications are corrected to the satisfaction of the reviewer(s).

d. Approval is communicated to the investigator in writing and to the Committee in the minutes of the next meeting following the approval.

Substantive Revisions Required for Approval: The concerns of the Committee are substantive in content. The magnitude and number of concerns, questions, or problems are more than minor. A designation of Substantive Revisions Required indicates that the convened Committee will again review the revised study documents.

In order to receive approval for a study for which substantive revisions are required:

a. For studies reviewed by the full committee, the investigator’s response should be sent for review at a convened meeting of the same CPHS panel that conducted the initial review. The CPHS office staff provides the investigator’s response and any revised documents for the second review. The study is placed on the agenda at the next meeting if the modifications made by the investigator are available.

b. For studies receiving expedited review, an investigator’s response and the revised documents are reviewed by the same CPHS members who performed the initial review.

c. Approval of the study is not granted until any modifications made by the investigator satisfy CPHS reviewers.
d. Final approval of the study is communicated to the investigator in writing.

e. The review of the response and revised documents is documented in the minutes of the next CPHS meeting or in the file of studies eligible for expedited review.

**Disapproved**: The CPHS has determined that the research cannot be conducted at the College.

The CPHS declines to review and approve grant proposals as it is permitted to do under 45 CFR 46.118.

### 2.11 Study Suspension, Termination and Administrative Hold

#### 2.11.1 Study Suspension or Termination

The CPHS may decide to suspend or terminate approval of research that is not being conducted in accordance with CPHS or regulatory requirements or that has been associated with unexpected problems or serious harm to subjects. (See Section 7 for a discussion of unexpected problems and non-compliance).

Suspension of CPHS approval temporarily stops previously approved research activities. Suspended studies remain open and require continuing review.

A CPHS Chair or the CPHS Director may ask an investigator to temporarily suspend study activities under any circumstances that apparently increase risks or decrease benefits to participants. The CPHS at its next convened meeting ratifies or rejects the suspension after review of the circumstances and updated information about the study's activities.

A sponsor-imposed or institutional suspension alone does not constitute a suspension, as it is not an action by the CPHS to withdraw its approval of a previously approved study. Similarly, an action by the investigator that halts or materially changes the activities of one or more of the investigator’s studies as previously approved by the CPHS does not constitute a study suspension. Any change to research activities, including temporary suspension, should be reported by the PI to the CPHS as an amendment to the study. The CPHS reviews any suspension of research activities for its effects on research participants and evaluates the proposed procedures by the investigator for mitigating those effects.

Termination of CPHS approval permanently stops all activities in a previously approved research study. Terminated studies are considered closed and no longer require continuing review. Only a determination by the CPHS at a convened meeting can terminate approval for a previously approved study, including terminations of studies approved under expedited review. Termination of CPHS review at the request of an investigator when study activities are completed is handled administratively in the CPHS Office.
The CPHS notifies the PI in writing of suspensions or terminations and includes a statement of the reasons for these actions. The terms and conditions of a suspension are made explicit. The investigator is provided with an opportunity to respond to the CPHS in person or in writing. When study approval is suspended or terminated, the convened CPHS or a designee, if appropriate, considers whether proposed procedures for the withdrawal of enrolled participants are necessary to protect their rights and welfare. These procedures may include: transferring responsibility for the study to another investigator; making arrangements for medical care or other monitoring of participants outside the research context; allowing continuation of some research activities under the supervision of an independent monitor; or requiring or permitting monitoring of participants for safety reasons.

If a suspension of the study activities involves the withdrawal of participants from the study or other modification affecting current participants, the CPHS may direct the investigator to notify participants to provide the following information:

- An explanation, after review and approval of the explanation by the CPHS.
- A description of any monitoring for safety reasons that may be necessary.
- Contact information for the PI and the CPHS for the participant to report any adverse events or unanticipated problems.

All suspensions and terminations will be reported promptly to the appropriate institutional officials and regulatory agencies according to the procedures described in section 7.6.

2.11.2 Administrative Hold

A PI may request an administrative hold on a study when the investigator wishes to temporarily or permanently stop some or all approved research activities. An administrative hold may be initiated by an investigator or may be in response to a request by the convened CPHS or CPHS designee to take such action. Administrative holds are not suspensions or terminations.

The meaning of the term “administrative hold” is restricted when applied to VA studies.*

2.11.2.1 Procedures

Investigators implementing an administrative hold should notify the CPHS in writing. This notice should include:

- A statement that the investigator is voluntarily placing a study on administrative hold in response to a request by the convened CPHS or CPHS designee, if appropriate.
- A description of the research activities that will be stopped.
- Any proposed actions necessary to protect current study participants.
d. Any actions taken prior to CPHS approval of proposed changes in order to eliminate apparent immediate harm to current study participants.

Upon receipt of written notification from the investigator, the CPHS office staff arranges to place the research project on the next available agenda for review of the changes to study activities.

The CPHS Director, in consultation with the investigators and CPHS Chair, determines whether any additional procedures need to be followed to protect the rights and welfare of current study participants as described in “Protections for Currently Enrolled Study Participants” below. The CPHS Director, in consultation with the investigators and CPHS Chair, also determines how and when currently enrolled participants will be notified of the administrative hold.

Investigators may request a change to an administrative hold by requesting an appropriate modification to the previously approved research.

2.11.3 Protection of Currently Enrolled Participants

Before an administrative hold, termination, or suspension takes effect, the convened CPHS or its designee should consider whether any additional procedures are needed to protect the rights and welfare of current study participants. Such procedures may include:

a. Transferring responsibility for the participants to another investigator.

b. Making arrangements for clinical care outside the research.

c. Allowing continuation of some research activities under the supervision of an independent monitor or another investigator.

d. Arranging for follow-up of participants for safety reasons.

e. Continuing adverse events or outcomes reporting to the CPHS and the sponsor.

f. Notification of current participants.

g. Notification of former participants.

2.12 Continuing Review

The CPHS conducts continuing review of ongoing research at intervals that are appropriate to the level of risk and other factors for each research study, but not less than once per year for federally funded or conducted research. Continuing review occurs as long as the research remains active for long-term monitoring or follow-up of study participants, even when the research is permanently closed to the enrollment of new participants and participants have completed the research-related interventions. Continuing review of research also occurs when the remaining research activities are limited to the analysis of identifiable private information.
2.12.1 Approval Period

At the College, a determination of the approval period is made by the CPHS on a study-by-study basis. Certain studies may be subject to continuing review after a few months of enrollment or after enrollment of the first several research participants.

For each initial or continuing review, the CPHS indicates an approval period with an approval expiration date specified. CPHS approval is considered to have lapsed at midnight on the expiration date of the approval. For a study approved by the convened CPHS, the approval period starts on the date of the convened meeting. If the convened CPHS requests specific minor revisions to a study prior to approval, then the approval action date is when a CPHS member confirms these revisions as having been satisfactorily made by the investigator.

For a study approved under expedited review, the approval period begins on the date the CPHS Chair or CPHS member(s) designated by the Chair approves the study.

The approval action date and approval expiration date are clearly noted on all CPHS approval letters.

Review of a change in a study does not alter the date by which continuing review should occur, because continuing review is review of the entire study, not simply a change to one or more of its activities.

Federal regulations and guidance make no provision for a grace period extending the conduct of research beyond the expiration date of CPHS approval. Therefore, continuing review and re-approval of research should occur by midnight of the date when CPHS approval expires. If the CPHS performs continuing review within 30 days prior to date when CPHS approval period expires, the CPHS may retain the anniversary date as the date by which the continuing review should occur.

Research that is not federally funded, has been determined by the CPHS as minimal risk, and is eligible for expedited review may receive continuing review every two years rather than annually. Eligibility for continuing review biennially is determined on a study-by-study basis provided the three conditions stated above are satisfied and no circumstances have come to the attention of the CPHS that would preclude biennial review. Such circumstances could include, but are not limited to complaints about the research activities, or other indications of problems associated with the research.

2.12.2 Continuing Review Process

To assist investigators, the CPHS office staff sends out renewal notices as reminders to investigators up to three months in advance of the expiration date; however, it remains the investigator’s responsibility to ensure that continuing review of ongoing research receives approved prior to the expiration date.
Investigators are asked to send the following information to the CPHS for continuing review:

a. The initial application review as updated with any changes;
b. The current consent form(s);
c. Any newly proposed consent form;
d. Any progress reports plus other relevant documents; and
e. A CPHS renewal application form.

In conducting continuing review of research not eligible for expedited review, the CPHS office staff makes available to reviewers the complete study documents, including any modifications previously approved by the CPHS. The CPHS staff also obtains any additional related information that a CPHS member may request.

In the case of studies eligible for expedited review, the CPHS members may request the CPHS staff to provide them with any study documents required for their review.

Review of currently approved or newly proposed consent forms occurs during the scheduled continuing review of research by the CPHS. Nevertheless, consent forms are also reviewed whenever new information becomes available that requires modification of information in the consent form.

2.12.3 Continuing Review of Studies Currently Eligible for Expedited Review

In conducting expedited continuing review, CPHS reviewers receive the information listed above in the previous section. The reviewers determine whether the research meets the criteria for an expedited review process, and if so, whether the research continues to meet the criteria for approval.

Generally, if research did not qualify for expedited review at the time of initial review, it would not qualify for expedited review at the time of continuing review, except in limited circumstances described by expedited review categories (8) and (9) at 63 FR 60364-60367 (See the expedited review categories of research activities.). It is also possible that research activities that previously qualified for expedited review in accordance with 45 CFR 46.110 have changed or will change such that expedited CPHS review would no longer be appropriate for continuing review.

2.12.4 Lapse in Continuing Review

Federal regulations and guidance do not permit a grace period or approval extension after expiration. Research activities that continue after the approval period has expired is research conducted without CPHS approval. If continuing review does not occur within the timeframe set by the CPHS, all research activities must stop, including recruitment (media advertisements should be withdrawn), enrollment, consent
processes, interventions, interactions, and data collection, unless the CPHS finds that it is in the best interests of the study participants to continue certain research activities. The cessation of research activities should occur even if the investigator has provided the necessary information to the CPHS before the expiration date. Therefore, it is the responsibility of investigators to allow sufficient time for CPHS review before the expiration date.

The CPHS office staff is responsible for notifying the investigator of the expiration of approval and that all research activities must stop.

If research participants are currently enrolled in the research project and their participation is ongoing, once notified of the expiration of approval, the PI should immediately send to the CPHS Chair and Director a list of research subjects for whom suspension of the research would cause harm. Enrollment of new subjects should not occur and continuation of research interventions or interactions for already enrolled subjects may only continue when the CPHS Chair and Director or their designees find that it is in the best interest of individual research participants to do so.

Once approval has expired, CPHS review and approval of the study must occur prior to re-initiation of research activities. If study approval has lapsed and the PI has not provided the required information, the study activities are suspended by the CPHS and the PI is reminded by the CPHS office staff to make an application for continuing review. This reminder and study suspension notice is sent to the PI promptly once approval has lapsed. If study approval has been suspended for 6 months or more and the PI has not provided the required information for continuing review, the PI is notified by the CPHS office of its intent to terminate review of the study in two weeks unless the PI responds with additional information about the status of the study.

If a research study requires modifications prior to approval at the time of the continuing review and the approval expires before the PI responds to the requested modifications, the PI may not conduct any research activities after the expiration date. Once the PI responds, the existing study will receive continuing review. If the PI does not respond for an extended period, the CPHS office may administratively close the study to further CPHS review. Decisions of this kind are be made in a manner that ensures that closure will not harm any participants previously enrolled who may require ongoing medical care or other attention in connection with the research activities.

### 2.13 Amendment of an Approved Study

Investigators may wish to modify or amend approved research activities. Investigators should seek CPHS approval before initiating any changes in approved research activities unless the change is necessary to eliminate an immediate hazard to a subject (in which case, the CPHS should then be notified at once).

In determining whether a proposed change should be reviewed as an amendment or as a new study, the PI may wish to consult with the CPHS Director or a staff Analyst and
consider whether the changes involve the study’s purpose, procedure, or population. If changes are proposed in all three of these areas, it is often most appropriate to prepare an application for CPHS review of a new study. For example, if a researcher wishes to add a population to an existing study, but not alter the study procedures or purpose, modifying the original study is usually acceptable. Likewise, modifying a procedure without changing the study’s purpose or study population may also be acceptable as a modification. If, however, the researcher wishes to add a population and also revise the study procedures, typically, these changes should be presented as a new study.

Certain modifications may be reviewed by expedited procedures if they include no more than minor changes as defined in Section 2.2. For study amendments determined to be eligible, the modifications are typically reviewed using the expedited procedure.

Investigators submit various types of documentation to inform the CPHS about changes in the status of the study, including, but not necessarily limited to:

a. Completed “Revision or Additions Review” form.

b. Revised CPHS Study Plan or sponsor’s protocol (if applicable).

c. Revised versions of approved consent forms, parental permissions, or assent documents (if applicable) or any other documentation that would be provided to subjects when the modifications requested may impact willingness to continue to participate in the study.

d. Revised or additional recruitment materials.

e. Any relevant documents used for communicating with study participants.

A CPHS staff Analyst in consultation with the CPHS Director and Chair makes the initial determination as to whether the proposed changes may be approved by an expedited review process, if the changes are minor as defined in this document, or whether the modification warrants full committee review. The reviewer for the expedited procedure has the responsibility for determining that the proposed changes are suitable for expedited review and, if not, refer the study for review at a convened CPHS meeting.

2.13.1 Expedited review of Study Modifications

The CPHS may use expedited review procedures for minor changes in previously-approved research [See Section 2.2 for the definition of a minor change]. An expedited review may be carried out by the CPHS Chair or a designee.

The reviewer determines whether the requested modifications satisfy the criteria that allow expedited review, and if so, whether the research activities, including the proposed modifications, meet regulatory criteria for approval. The revision may then be approved through expedited review.
2.12.2 Full Committee Review of Study Modifications

When a proposed change in a research study is not minor as determined by a CPHS reviewer, then the CPHS reviews the proposed change at a convened meeting before the change is implemented. If doubt exists about whether a proposed change is minor, a convened Committee makes this determination. [45 C.F.R. 46.110 and 46.111] The only exception is a change necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the CPHS should be promptly informed by the PI of the change following its implementation and should review the change to determine that it is consistent with ensuring the welfare of the study participants.

CPHS members receive and review the application for review of the study modifications and any revised study documents provided by the investigator. At a CPHS meeting, the primary reviewer presents an overview of the study modifications and leads the CPHS through a discussion of them. As applicable, the CPHS considers whether the information about those modifications might relate to participants' willingness to continue to take part in the research and, if so, whether to provide additional information to participants.

Possible CPHS actions on study modifications reviewed at a convened meeting are the same as those for an initial review of a study, as described in Section 2.10.

2.14 Closure of Studies

The completion or termination of review of a study is a change in the research activities and should be promptly reported to the CPHS by the investigator. Although study participants may no longer be "at risk" from research interventions, a final report from the investigator to the CPHS allows it to close its files as well as providing information that may be used by the CPHS in its evaluation and approval of related studies.

The CPHS Renewal or Termination application form contains the criteria for termination of CPHS review. Investigators are expected to promptly notify the CPHS of their intent to end study activities and terminate CPHS review. The investigator should include a final report with a study closure notice.

The CPHS Analysts and Director review requests for termination of CPHS review to determine whether the criteria for termination are satisfied. When a study can be appropriately closed, the investigator's request for termination of review is acknowledged and the CPHS file is closed and archived.

2.15 Reporting CPHS Actions

CPHS actions are promptly communicated to the PI and any designated contact person for the study in writing in a letter prepared by the CPHS office staff and signed by the CPHS Chair or an appropriate designee. Along with the approval letter, a copy of the
approved consent form with a stamped approval date on each sheet of paper is sent to the investigator.

When a study needs modifications prior to approval, the letter states the requested modifications along with the basis for requesting those modifications in most cases. For a disapproval or suspension of research activities, the CPHS letter includes the basis for making that decision.

Copies of letters to investigators are filed in the study files maintained by the CPHS.

The CPHS reports its findings and actions to the institution through its minutes, which are distributed by CPHS office staff to College's Institutional Official. Copies of meeting minutes are stored permanently and securely in the CPHS Office.

2.16 Appeal of CPHS Decisions

When a research project presented at a convened CPHS meeting is disapproved or requires minor or substantive modifications prior to approval, the CPHS notifies the PI in writing about the specific modifications that are necessary to obtain CPHS approval. The CPHS includes in its written notification to the PI a statement of the reasons for its decisions in most cases and gives the PI an opportunity to respond in person and in writing if the study is disapproved or needs substantive revisions.

When there is disagreement between the CPHS and the PI regarding the nature or extent of CPHS requested changes, and these disagreements are not resolved in an informal manner, the PI or the CPHS may appeal to the Institutional Official (IO) for assistance with resolution of the disagreement. The IO may organize a special CPHS meeting to facilitate discussion between the CPHS and the PI. While the IO may provide guidance and make recommendations to the CPHS for expeditious resolution of the matter, final approval of the research remains with the CPHS.

2.17 Study Audits

The CPHS may decide to have studies audited for a variety of reasons, including for cause, random selection as part of an on-going audit program, or as a result of some specific characteristic of a study. Such characteristics are, for example, a vulnerable study population, the specific risks presented by the study procedures to participants, or other circumstances associated with the conduct of the study. Only studies that are active or for which some cause has been identified are subject to audit; no audits are performed on studies that are exempt from further CPHS review. The time period that an audit may cover extends from study initiation through closure. The PI and research staff members of a study are expected to cooperate with CPHS audit procedures. If feasible, reasonable accommodations will be made to schedule audit activities at times that are mutually convenient for the auditor and the research staff.
When the CPHS decides to audit a study, an auditor is assigned who has the requisite knowledge of research ethics, the regulations applicable to the study, and institutional resources for research activities. The auditor may be a CPHS chair, member, or a consultant whose activities are supported by the CPHS office staff. The CPHS delegates its audit authority for studies conducted in VA facilities to the Research Compliance Officer (RCO) of the facility. Audits of VA projects by the RCO are conducted according to the Office of Research Oversight (ORO) Guidance Regarding Research Officer Audit and Training Requirements for the applicable time period.*

Both study procedures and documents are subject to audit. The documents may be maintained in any media. These documents may include, but are not limited to, those listed below.

- Recruitment documents,
- Consent and authorization documents,
- Grant proposals and financial records,
- Clinical trial agreements and budgets,
- Documents provided by the sponsor or funding agency,
- Correspondence from the sponsor, funding agency, coordinating center, federal officials, and CPHS,
- Data records, including databases, as well as medical records and other source documents,
- Reports to the sponsor, funding agency, federal officials, and CPHS, including those about unanticipated problems involving risks to subjects or others, serious adverse events related to research activities, complaints about the study from any individual, protocol deviations, and non-compliance with regulatory standards or CPHS requirements,
- Records of interactions or interventions with study participants,
- Monitoring or audit reports by sponsors, funding agencies, or other institutional officials,
- Pharmacy records, if applicable, and
- Other documents relevant to the conduct of the study, such as research staff training records.

The study procedures that are subject to audit include, but are not limited to, those listed below.

- Consent process,
- Compliance with applicable regulations, the study plan or protocol, and CPHS requirements, including eligibility criteria for study participants,
- Sufficiency of study documentation,
- Study data management, including security safeguards and maintenance of confidentiality,
- Timeliness and responsiveness of the PI and research staff members to CPHS review processes and requirements, and
- Other study activities relevant to protection of study participants.
g. Staff training records.

Documentation of audit activities includes a database that tracks the audit history of each study and written reports that include, if appropriate, recommendations for remedial actions. Reports of audit results are placed in the CPHS study file and, as appropriate, are sent to each of the following individuals.

a. PI,
b. Dean or department chair of the PI,
c. The CPHS Director and Chairs,
d. The CPHS at convened meetings.

Once an audit report is completed, the CPHS at a convened meeting determines remedial actions resulting from the audit report, if any. These actions may be reported to appropriate institutional and regulatory officials as required or determined by the CPHS. Reports of routine VA research project audits are provided to the CPHS quarterly.*
Section 3: Documentation and Records

3.1 Policy

The College prepares and maintains adequate documentation of CPHS activities. Records are accessible for inspection and copying by authorized representatives of the FDA, OHRP, DoD, the Environmental Protection Agency (EPA), sponsors, and other entities at reasonable times and in a reasonable manner, during normal business hours with appropriate notice. In addition, copies of CPHS records are made available as required by law.

3.2 CPHS Records

CPHS records include, but are not limited to:

a. Descriptions of research projects, e.g., protocol.

b. Investigator brochures, if any.

c. Recruitment materials.

d. Scientific evaluations, if any, of the project.

e. Approved consent forms, including DHHS-approved or other sample consent forms when one exists.

f. HIPAA Privacy Rule authorization if separate from the consent form.

g. Records of continuing review activities, including progress reports from investigators and reports made in connection with the data safety monitoring plan for the study.

h. Any proposed study amendments and the CPHS action on each amendment.

i. Reports of unanticipated problems involving risks to subjects, including research-related injuries or illness and serious, unexpected adverse events related to research participation occurring in studies under review by the CPHS.

j. Documentation of protocol deviations.

k. Documentation of any non-compliance with applicable regulations and CPHS or other IRB determinations.

l. Statements of significant new findings provided to research participants.

m. CPHS membership rosters.

n. CPHS meeting minutes.

o. Copies of correspondence between the CPHS and investigators.

p. Copies of correspondence with the R&D Committee at VA facilities.

CPHS records also document CPHS determinations required by regulations and study-specific findings supporting those determinations, including:
a. Eligibility for exemption or expedited review.
b. Waiver or alteration of the consent process and authorization for research use of health information.
c. Research involving pregnant women, fetuses, and neonates.
d. Research involving prisoners.
e. Research involving children.

3.3 CPHS Membership Rosters

The CPHS maintains a resume for each of its members as well as a list that identifies each member and describes the member's expertise and chief anticipated contributions to CPHS deliberations. The list typically contains the following information about members:

a. Name.
b. Gender.
c. Earned degrees.
d. Affiliated or non-affiliated status (Neither the member nor an immediate family member of the member may be affiliated with the College if non-affiliated status applies.)
e. Status as scientist or non-scientist. For purposes of its rosters, CPHS members with research experience are designated as scientists, including any student member. Research experience includes scientific training and current involvement in the conduct of research. Students being trained in research fields are designated as scientists.
f. Credentials, such as board certifications or licenses that may describe each member's anticipated contributions to CPHS deliberations.
g. The representative capacities of each CPHS member, including identification as a CPHS member who is a prisoner representative as required by Subpart C, and each member who is knowledgeable about or experienced in working with children, pregnant women, mentally impaired individuals, and other potentially vulnerable, local populations involved in research activities.
h. Any special role on the CPHS, such as Chair or Vice Chair.
i. Voting status. Any ex officio members are non-voting members.
j. Alternate status, including corresponding regular members for whom each alternate may substitute.
k. Relationship between the CPHS member and the College. E.g., employment.

The CPHS office staff keeps the CPHS membership list current. The CPHS Director or a designee promptly reports changes in CPHS membership to OHRP.
3.4 CPHS Meeting Minutes

A CPHS Analyst or the CPHS Director generates minutes for each meeting that describe the proceedings. A summary of expedited reviews is included in the CPHS minutes each month. "Rapid review" CPHS B panel convened meetings occur on an ad hoc basis and the minutes are recorded separately. Minutes of the CPHS A, C, and D panels are reviewed and approved at the next meeting of the same Committee. Minutes of the CPHS B panel are reviewed and approved by the Chair and other voting members who attended the CPHS B panel meeting. After being reviewed and approved, the minutes are distributed electronically to designated administrators at the College, Geisel School of Medicine, Dartmouth–Hitchcock Medical Center, affiliated VA facilities, and other institutions for which the CPHS is the reviewing IRB. Minutes of CPHS meetings contain sufficient detail to describe the actual meeting proceedings as they occur. The minutes may include the following information:

a. Attendance, including the names of CPHS members who are present.
b. Names of CPHS members or alternate members who are participating through videoconference or teleconference.
c. Names of alternate members and the absent member for whom they are substituting (See Section 1.5.3).
d. Names of consultants present, if any.
e. Name of investigators present, if any.
f. Names of guests present, if any.
g. The presence of a quorum throughout the meeting, including the presence of one member designated as a non-scientific member.
h. Business items discussed, if any.
i. Continuing education.
j. The action taken on each research project, including separate deliberations and vote for each study undergoing initial review, continuing review, or review of modifications by the convened CPHS.
k. Votes on each action (total number voting; number voting for; number voting against; number abstaining; number of those excused, number of those recused).
l. Basis or justification for the CPHS action including any modifications to the research prior to approval.
m. Summary of controverted issues and the resolution.
n. Approval period for initial and continuing approved studies.
o. Risk level for approved studies.
p. Review of investigator reports, e.g., adverse event or safety reports, study deviations.
q. Review of available data and safety monitoring board (DSMB) reports and recommendations.

r. Review of plans for data and safety monitoring.

s. Investigator responses to requested, specific minor or substantive revisions, as applicable.

t. Justification of modifications to information concerning risks or alternative procedures contained in the sample consent forms, including DHHS or other sample consent forms.

u. Study-specific documentation that the research meets regulatory criteria [45 CFR 46.116(d) and 164.512(i)(2)(ii)] for approving a consent procedure that may not include or alters some or all of the required elements of informed consent and authorization, or when waiving informed consent and authorization.

v. Study-specific documentation that the research meets the required regulatory criteria [45 CFR 46.117©] when the requirements for documentation of consent are waived.

w. When approving research that involves populations covered by Subparts B, C, or D of 45 CFR 46, the minutes document CPHS reasoning and findings for the determinations stated in the Subparts or agreement with the findings and reasoning presented by the investigator.

x. Determination of the risk level for investigational devices and the rationale for such determinations.

y. Acceptance of the management plan for any investigator conflict of interest.

z. Verification from sources other than the investigator that no material changes have been made since the previous review (e.g., cooperative studies, or other collaborative research).

aa. Relevant considerations underlying the conclusion that a study population may be vulnerable.

bb. Special protections in specific research projects for subjects who are likely to be vulnerable to coercion, undue influence, legal risks, or susceptibility to other harms such as children, prisoners, pregnant women, people with mental disabilities, victims of crime, or people who are economically or educationally disadvantaged, regardless of source of support for the research.

cc. Special protections for study data including security measures for personally identifiable information such as social security numbers.

dd. A list of research projects approved since the last meeting under expedited review procedures.

e. Documentation of approval by the Chair or a designee of research contingent on the resolution of specific minor conditions appears in the minutes for the next available meeting.
ff. An indication that, when a CPHS member has a conflicting interest (See Section 1.5.4.) with the research under review, the CPHS member did not vote on the proposal, and that the quorum was maintained.

Information provided by consultants may be documented in the minutes.

The CPHS minutes, once approved, may not be altered except by the CPHS Chair or Director with the concurrence and approval of the convened CPHS. This statement does not apply to typographical and administrative errors.

Note: The initial attendance list shall include those members present at the beginning of the meeting. The minutes indicate, by name, those members who enter or leave the meeting. The vote on each action reflects those members absent for and recused from the vote on that action. See section 1.5.4 about CPHS member conflicts of interest.

3.5 Documentation of Exemptions

Documentation for exemptions consists of the specific exemption category and a letter to the investigator stating that the activity described in the investigator’s application for review satisfies the conditions of the cited exemption category. The exempt determination is reported at the next convened CPHS meeting through documentation in the minutes.

3.6 Documentation of Expedited Reviews

For initial and continuing review by the expedited procedure, CPHS records include: the applicable regulatory category(s); a description of any specific action requested by the reviewer; the approval period; and any determinations required by the regulations, including study-specific findings supporting those determinations.

3.7 Record Retention

Records in any medium are available for inspection and copying by authorized representatives of the OHRP, FDA, sponsors, and other entities at reasonable times and in a reasonable manner during normal business hours and with appropriate advance notice.

Paper or digital copies of records are maintained securely and are made available to CPHS members, CPHS staff, and others as appropriate and by specific request.

Some older CPHS paper files, as well as copies of past meeting minutes and full committee meeting agendas, are stored offsite by Dartmouth College Records Management. This Dartmouth College department provides inactive records storage and maintenance, including record retrieval and disposition services. In general, CPHS files are shredded or otherwise destroyed after 10 years.
Section 4: Informed Consent and Documentation of Consent

4.1 Policy

The CPHS evaluates both the consent process and the procedures for documenting informed consent to ensure that adequate informed consent is obtained from research participants, unless a waiver of consent has been approved by the CPHS in accordance with Section 4.6 of these procedures. Except as provided in Section 4.7 of these procedures, the use of a written consent form approved by the CPHS, which is expected to be signed and dated by each research participant, is used for documentation of informed consent (See Section 4.4).

The following procedures describe CPHS review of the consent process, if any, and documentation of consent when it is obtained.

4.2 Definitions

Legally Authorized Representative. A legally authorized representative is an individual or agency authorized by law to provide permission on behalf of a prospective subject to the subject’s participation in the procedures involved in the research. A legally authorized representative may include a person appointed as a health care agent under a Durable Power of Attorney for Health Care (DPAHC), a court-appointed guardian of the person, or next-of-kin in the following order of priority: spouse, adult child (18 years of age or older), parent, adult sibling (18 years of age or older), grandparent, or adult grandchild (18 years of age or older). The biological or adoptive parent of a minor child is a legally authorized representative of the child, unless parental rights have been terminated by a court with appropriate jurisdiction to do so.

Legal guardian. An individual or agency appointed as the guardian of a person for a ward by a court with appropriate jurisdiction.

4.2.1 Review of the Informed Consent Process

In an application for CPHS review, the investigator describes the consent process used in the research and how the process meets each of the following criteria. The CPHS reviews the proposed consent process and determines that it meets the criteria listed below.

a. Informed consent may only be obtained from potential subjects who possess both the legal and mental capacity to consent, i.e., to make an informed decision whether or not to participate in the research. For potential subjects without such capacity, consent may be obtained from a legally authorized representative provided the CPHS has approved this alternative source of permission for research participation.
b. Informed consent should be sought under circumstances that provide a potential subject or a legally authorized representative with sufficient opportunity to consider whether or not to participate in the research.

c. Informed consent should be sought under circumstances that minimize the possibility of coercion or undue influence from any source in the consent process.

d. Information about the research is presented in language that is understandable to the subject or a legally authorized representative. In general, the language used should approximate an 8th grade reading level and use non-technical terms.

For subjects whose native language is not English, information should be presented in a language that is understandable to the subject or the subject’s legally authorized representative. The CPHS may specify that the informed consent process include a reliable translator who is not a family member.

e. The informed consent process should not include any exculpatory information through which the subject is made to waive, or appear to waive, any of the subject’s rights or through which the investigator, the sponsor, or the research institution and its employees or agents are released from liability for negligence or appear to be released.

f. The PI is responsible for adequately informing each prospective subject about the research.

4.3 Basic Elements of Informed Consent

In an application for CPHS review, the investigator describes the information provided to prospective subjects during the consent process, which should include the following elements.

a. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

b. A description of any reasonably foreseeable risks or discomforts to the subject;

c. A description of any benefits to the subject or to others which may reasonably be expected from the research;

d. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

e. A statement describing the extent, if any, to which the confidentiality of records identifying the subject will be maintained;

f. For research involving more than minimal risk, an explanation as to the availability of medical treatment in the case of research-related injury or illness, including who will pay for the treatment, whether other financial compensation is
available, and any special provisions for research-related injury or illness exist as
specified by a funding agency such as the VA or DoD;

g. An explanation of whom to contact for answers to questions about the research
or to express concerns or complaints about the research, and whom to contact in
the event of a research-related injury to the subject;

h. Contact information for the CPHS so study participants can obtain answers to
questions about the research or their rights as research participants; express
concerns or complaints about the research; or talk to someone other than
research staff;

i. A statement that research participation is voluntary, refusal to participate will
involve no penalty or loss of benefits to which the subject is otherwise entitled,
and that the subject may discontinue participation at any time without penalty or
loss of benefits to which the subject is otherwise entitled;

j. For FDA-regulated studies, the possibility that the FDA may inspect and copy the
research records;

k. For studies conducted by VA investigators or involving VA patients, records, or
facilities, the VA provides necessary medical treatment to any participant who
experiences a research-related injury,*

l. For studies conducted by VA investigators or involving VA patients, records, or
facilities, a statement that no payment for services received in connection with
research participation, excluding standard of care medical services, is expected
from research participants who are veterans, except in accordance with federal
law;*

m. For studies conducted by VA investigators or involving VA patients, records, or
facilities, a statement that certain veterans are expected to make co-payments
for services received as standard medical care;*

n. For studies conducted by VA investigators or involving VA patients, records, or
facilities, a statement that medical care services received in connection with
research participation will be provided and paid for by the Department of
Veterans Affairs;*

The following additional elements of informed consent should be used when appropriate
for the proposed research.

a. A statement the particular treatment or procedure may involve risks to the subject
that are currently unforeseeable. For example: Include such information when
the research involves investigational products or procedures for which the risks
to subjects are not yet well known.

b. A statement if the subject is or becomes pregnant, the particular test product or
procedure may involve risks to the embryo or fetus that are currently
unforeseeable. For example: Include such information when the research involves pregnant women or women who can become pregnant and the risk to fetuses of the drugs, devices, or other procedures involved in the research are not well known. Such information may be appropriate for male research participants as well.

c. A description of anticipated circumstances under which the subject’s participation may be terminated by the investigator without regard to the subject's consent.

d. Any additional costs to research participants that may result from their participation in the research.

e. The consequences of a participant’s decision to withdraw from the research, including a description of any options for limited participation such as data collection without receiving study interventions.

f. Procedures for safely withdrawing from participation.

g. A statement that significant new findings developed during the course of the research that may relate to the subject’s willingness to continue participation will be provided to the subject. For example: Include such information when the research is of long term duration and interim information is likely to be developed during the conduct of the research.

h. The approximate number of subjects involved in the study.

i. Information about research use of public data resources if applicable.

j. When the proposed research includes the research use or disclosure of individually identifiable health information, an authorization for research use of Protected Health Information (PHI) in accordance with the HIPAA Privacy Rule is typically required. The CPHS consent form templates include the required elements of authorization. The VA requires use of an authorization as a separate document from the consent form.*

The CPHS reviews the information provided to prospective and current subjects, including any changes to the conditions of study participation, and determines whether appropriate elements are included in the process and documents for obtaining permissions from research participants.

4.4 Documentation of Informed Consent

In an application for CPHS review, the investigator describes how informed consent will be documented. Except as provided in Sections 4.6 and 4.7 of this document, a written consent form approved by the CPHS is used to document informed consent. See also the VA requirements for consent form documentation.*

Informed consent is typically documented by the use of a written consent form approved by the CPHS that is signed and dated by the subject or the subject's legally authorized representative. Once approved by the CPHS, consent forms are date-stamped with the
date at the conclusion of the most recent review, including reviews of study amendments involving changes to the information contained in the consent form. Investigators are responsible for tracking the version of the most recently CPHS approved consent form within each approval period for the entire study. In addition, investigators are responsible for providing each study participant with a copy of the consent form that he or she signed and dated.

The consent form may be either of the following:

a. A written document that embodies the basic and any required additional elements for informed consent. A consent form may be read to the potential participant or a legally authorized representative, but in any event, the potential participant or representative should be given adequate opportunity to read it before it is signed; or

b. A short form written consent document stating that appropriate elements of informed consent have been presented orally to the potential participant or a legally authorized representative. When this method is used the following conditions should be satisfied.

   i. There should be a witness to the oral presentation fluent in both the non-English language used and in English; and

   ii. The CPHS should approve a written summary of the information presented to the potential subject or legally authorized representative that includes the basic and any appropriate additional elements of consent; and

   iii. The potential participant or legally authorized representative should sign and date only the short form; and

   iv. The witness should sign and date both the short form and a copy of the summary; and

   v. The person actually obtaining consent should sign and date a copy of the summary; and

   vi. A copy of the summary should be given to the participant or representative, in addition to a signed and dated copy of the short form.

   vii. The CPHS has reviewed both the summary and short form and determined whether these documents contain adequate information to inform the decision making of non-English speaking, potential study participants.

4.5 Consent Monitoring

In reviewing the informed consent process and procedures for proposed research, the CPHS may, on occasion, determine that monitoring of the consent process by an impartial observer (consent monitor) is needed to reduce the possibility of coercion and undue influence or to ensure that the approved consent process is being conducted.
Such monitoring may be warranted for:

a. High risk studies
b. Studies that involve particularly complicated research procedures or interventions,
c. Studies involving vulnerable populations, e.g., newly diagnosed patients or children,
d. Studies involving study staff with little experience in conducting the consent process with potential study participants, or
e. Other situations when the CPHS has concerns about the consent process.

Monitoring may also be appropriate as a corrective action where the CPHS has identified problems associated with a particular investigator or research project.

If the CPHS determines that consent monitoring is required, the CPHS Chair and the Director develop a monitoring plan and present it to the CPHS at a convened meeting for approval. The consent monitoring may be conducted by CPHS staff, CPHS members, or another individual who may or may not be affiliated with the institution. The PI is notified of the CPHS determination that consent monitoring should occur and the reasons for the determination. Arrangements are made with the PI for the monitoring of the consent process for a specified number of subjects. When observing the consent process, the monitor determines:

a. Whether the informed consent process was appropriately conducted and documented,
b. Whether the participant had sufficient time to consider study participation,
c. Whether the consent process controlled or eliminated coercive or undue influences,
d. Whether the information was accurate and conveyed in an understandable manner, and
e. Whether the subject appeared to understand the information provided and voluntarily consented to research participation.

Following the consent monitoring, the monitor reports her or his observations to the CPHS, which then decides whether any additional actions need to be taken to protect potential and enrolled study participants.

4.6 Waiver of Informed Consent

The CPHS may approve a consent procedure that does not include or that alters some or all of the elements of informed consent, or waive the requirements to obtain informed consent, provided the CPHS finds and documents that:
a. The research involves no more than minimal risk to the subjects;
b. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
c. The research could not practicably be carried out without the waiver or alteration; and
d. Whenever appropriate, the subjects must be provided with additional pertinent information after participation.

In addition, the CPHS may approve a consent procedure that does not include or that alters some or all of the elements of informed consent or waive the requirement to obtain informed consent, provided the CPHS finds and documents that:

The research project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:

a. Public benefit or service programs
b. Procedures for obtaining benefits or services under those programs
c. Possible changes in or alternatives to those programs or procedures; or
d. Possible changes in methods or levels of payment for benefits or services under those programs; and

The research could not practicably be carried out without the waiver or alteration.

FDA regulations do not provide for waivers of informed consent except in emergency situations. See Section 6.3.4.2.

DoD regulations do not provide for waivers of informed consent if the research participant meets the definition of “experimental subject”, unless a waiver is obtained from the Secretary of Defense. Research involving a human being as an "experimental subject" is defined by DoD regulations as an activity for research purposes where there is an intervention or an interaction with a human being for the primary purpose of obtaining data regarding the effect of the intervention or interaction [32 CFR 219.102(f), reference (c)]. This reference includes examples of such interventions or interactions and also describes certain exclusions.

4.7 Waiver of Documentation of Informed Consent

The CPHS may waive the requirement for the investigator to obtain a signed consent form for some or all subjects* if it finds that:
a. The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality; or

b. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

Procedures such as surveys, questionnaires and interviews collecting non-sensitive information generally do not require written consent when conducted by non-researchers. Research participants should be asked whether they want documentation linking them with the research, and their wishes should govern. For example: Domestic violence research in which the primary risk is discovery by the abuser that the subject is talking to researchers about experience of being abused.

In order to waive written documentation of consent where the only record linking the participant and the research would be a consent document, the CPHS should determine that the research is not FDA-regulated.

In the event documentation of consent is waived, the CPHS typically asks the investigator to provide a written summary of any information about the research that will be communicated to potential participants. The CPHS considers whether the investigator should provide participants with a written statement about the research for their reference.
Section 5: Vulnerable Subjects in Research

5.1 Policy

When some or all of the participants in research conducted under the auspices of the College are likely to be vulnerable to coercive or undue influences in the consent process or have diminished decision-making capacity, the research should include additional safeguards to protect the rights and welfare of such participants. The CPHS applies the regulatory requirements for the protection of vulnerable subjects and may create additional protections for research involving vulnerable participants.

The VA does not permit research that involves certain classes of participants without a waiver by the VA Chief Research and Development Officer.*

The following procedures describe the review of research involving vulnerable participants by the CPHS.

5.2 Definitions

Children are individuals who have not attained the legal age allowing them to consent to treatments or procedures involved in the research. New Hampshire law defines minors as individuals under the age of eighteen years old. Therefore, the CPHS generally regards children as individuals under eighteen years of age. Certain New Hampshire statutes and case law, however, provide minors with a right to consent to their own medical care in some circumstances.

Under both Federal and New Hampshire law, under certain circumstances minors of varying ages under 18 years old may consent to treatment for drug abuse and sexually transmitted infections; to blood donation; to the use of contraceptive drugs and devices; and to abortion procedures. In addition, New Hampshire common law recognizes both emancipated (in general by marriage, military service, and the law of another state) and mature minors (for the purpose of consent to medical treatment). Because New Hampshire law does not specifically address consent by children with special legal status to research participation, the CPHS reviews issues of consent related to enrollment of these children in research activities on a case-by-case basis.

NOTE: For research conducted in jurisdictions other than New Hampshire, research activities should comply with the laws regarding the legal age of consent in relevant jurisdictions. The Office of General Counsel at the College provides assistance with regard to the law in other jurisdictions.

Guardian means an individual who is authorized under applicable State law to consent on behalf of a child or an adult ward to general medical care. In New Hampshire, a guardian of a minor has the duty and authority to act in the best interests of the minor, subject to any residual parental rights and responsibilities, to make important decisions in matters affecting the life and development of the minor and his or her general welfare.
For research conducted in jurisdictions other than New Hampshire, the research complies with the laws regarding guardianship in each relevant jurisdiction. The Office of General Counsel of the College provides assistance with regard to the laws in other jurisdictions.

**Delivery** means complete separation of the fetus from a woman by expulsion, extraction, or any other means.

**Fetus** is the product of conception from the time of implantation until delivery.

**Dead fetus** is a fetus which exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord if still attached.

**In vitro fertilization** is any fertilization of human ova that occurs outside the body of a woman.

**Neonate** means a newborn.

**Viable neonate** means being able, after delivery, to survive to the point of independently maintaining a heartbeat and respiration given the benefit of available medical therapy.

**Pregnancy** is the period of time from confirmation of implantation through any of the presumptive signs of pregnancy, such as missed menses, or by a medically accepted pregnancy test, until delivery.

**Prisoner** is any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

**Surrogate Consent** is consent to research participation obtained from a legally authorized representative on behalf of a participant who lacks the legal or decision-making capacity to consent on her or his own behalf.

### 5.3 Involvement of Vulnerable Populations

When some or all of the participants in research are likely to be vulnerable to coercive or undue influences, the CPHS includes additional safeguards to protect the rights and welfare of these participants. Some of the vulnerable populations that may be involved in research include children, prisoners, adults who lack the ability to consent, students, employees, active military personnel, or homeless persons.
If the CPHS reviews research that involves categories of participants vulnerable to coercive or undue influences, the review process includes one or more individuals who are knowledgeable about or experienced in working with these participants.

45 CFR 46 has subparts designed to provide additional protections for vulnerable populations that also include requirements for CPHS determinations.

Subpart B: Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

Subpart C: Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Subpart D: Additional Protections for Children Involved as Subjects in Research

DHHS-funded research that involves any of the above populations should comply with the requirements of the relevant subparts. The subparts may or may not apply to research funded by other federal agencies. For studies conducted by VA employees or at VA facilities, additional protections should include those required by the VA for vulnerable populations.*

Under the College’s FWA, the 45 CFR 46 subparts only apply to DHHS-funded research and any research funded by any other federal agency that requires compliance with the subparts, such as the FDA, whose regulations include 45 CFR 46 Subpart D. The following policies and procedures, which are based on the subparts, apply to all research regardless of funding agency. The individual sections also describe how the subparts apply to DHHS-funded research.

For DoD regulated research involving active military personnel, special protections apply to minimize undue influence. These protections recognize the relationship between officers and other military personnel and provide for separate recruitment procedures. In addition an independent ombudsman is present during unit recruitment procedures.

In general, for federally funded research involving federal employees such as active military personnel, individuals may not receive compensation for research during duty hours, but may be compensated if the individuals are involved in the research when not on duty. If questions arise about this requirement, the research team and the CPHS office staff should plan to seek legal advice.

For DoD regulated research, prisoners of war may not be included in the study population. The definition of prisoner of war varies depending on which branch of the DoD funds the study.

For EPA regulated research, intentional exposure of pregnant women, nursing women, or children to any substance is prohibited. EPA regulated research that involves pregnant women or children should comply with 40 CFR 26 Subparts C and D, which refer to portions of 45 CFR 46 Subparts B and D. In addition to the above prohibition of
intentional exposure, special regulatory protections apply to pregnant women, nursing women, and children involved in observational research. The EPA regulations define observational research as any human research that does not meet the definition of research involving intentional exposure of a human subject in 40 CFR 26.202(a).

5.4 Responsibilities

The PI is responsible for identifying a potential to enroll vulnerable subjects in the research. The PI is also responsible for identifying patients who are at risk for impaired decisional capacity as a consequence of psychiatric illness and who are being asked to participate in a research study presenting greater than minimal risk to participants.

The CPHS includes representation, either as members or ad hoc consultants, of individuals interested in or who have experience with vulnerable populations involved in a research proposal under review.

The CPHS reviews the PI’s justifications for including vulnerable populations in proposed research.

The CPHS ensures that additional safeguards have been included in each study to protect the rights and welfare of vulnerable subjects, as needed, at the time of initial review of the research proposal.

The CPHS continues to review research at intervals appropriate to the degree of risk and determine whether the proposed research continues to meet criteria for approval.

For studies that do not have or are not required to have a Data and Safety Monitoring Board or a Data Monitoring Committee and have enrolled vulnerable subjects, the CPHS carefully reviews the data and safety monitoring plan.

The CPHS is knowledgeable about and experienced in reviewing studies involving populations who may be vulnerable to coercive and undue influences. If the CPHS requires additional expertise to review a study, the CPHS Director or an Analyst arranges to obtain an expert consultant.

5.5 Procedures

**Initial Review of Research Proposal:** In proposed research when a PI identifies a potential to enroll vulnerable subjects in an application for initial review, the PI also provides a justification for the inclusion of such participants.

The CPHS evaluates the proposed plan for obtaining consent from the specific vulnerable populations. If the research involves adults unable to provide consent, the CPHS evaluates the proposed plan to obtain the permission of a legally authorized representative.

The CPHS evaluates and approves a proposed plan for obtaining initial and continuing assent, as appropriate, from participants who are minor children and legally incapable of providing consent.
The CPHS evaluates the research to determine the need for additional protections for vulnerable study participants and considers the use of a data and safety monitoring board or data monitoring committee if appropriate.

Additional safeguards to protect the rights and welfare of vulnerable subjects may involve the appointment of an independent monitor. This monitor is a qualified individual not involved in the research study who independently determines each subject’s capacity to provide voluntary informed consent.

Examples of studies that may warrant independent monitoring include those involving schizophrenic patients who will be exposed to placebo use, a medication washout period, or treatment with drugs that are not approved by the FDA. Populations requiring independent consent monitoring may also include individuals with psychotic disorders or conditions characterized by lack of reality testing (i.e., psychosis).

CPHS review assesses the type and adequacy of additional protections for vulnerable populations proposed by the PI. For studies conducted by VA employees or at VA facilities, additional protections include those required by the VA for vulnerable populations.* The CPHS does not approve a study unless the PI has incorporated adequate protections and, as applicable, those required by DHHS and the VA for vulnerable populations in the study.

**Continuing Review and Monitoring.** At continuing review, the CPHS identifies the enrollment of any vulnerable subjects, reassesses the need for an independent monitor, and evaluates the effectiveness of any additional protections incorporated into the study procedures.

### 5.6 Research Involving Pregnant Women, Human Fetuses and Neonates

#### 5.6.1 Research Involving Pregnant Women or Fetuses

##### 5.6.1.1 Research Not Funded by DHHS or Any Other Federal Agency

For research not funded by DHHS, no additional safeguards are required and there are no restrictions on the involvement of pregnant women in research where the risk to the fetus is no more than minimal.

Pregnant women or fetuses may be involved in research not funded by DHHS involving more than minimal risk to fetuses if the following conditions, as applicable, are met and documented by the CPHS.

a. When scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.
b. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus.

c. Risks are minimized to the extent possible for achieving the objectives of the research.

d. If the research holds out the prospect of direct benefit to the pregnant woman or the prospect of a direct benefit both to the pregnant woman and the fetus, then the consent of the pregnant woman is obtained in accord with the usual conditions for informed consent.

e. If the research holds out the prospect of direct benefit solely to the fetus, then the consent of the pregnant woman and the father is obtained in accord with the usual conditions for informed consent, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity, or the pregnancy resulted from rape or incest.

f. Each individual who provides consent under paragraph e. or d. of this Section is informed about the reasonably foreseeable impact of the research on the fetus or neonate.

g. For children who are pregnant, assent and parental permission are obtained in accord with the usual conditions for parental permission and assent.

h. No inducements, monetary or otherwise, are offered to terminate a pregnancy.

i. Those individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.

j. Those individuals engaged in the research will have no part in determining the viability of a neonate.

5.6.1.2 Research Funded by DHHS or Another Federal Agency

For EPA regulated research, special considerations apply. See Section 5.3.

Under 45 CFR Part 46 Subpart B, pregnant women or fetuses may be involved in research funded by DHHS if the following conditions as applicable, are met:

a. When scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risk to pregnant women and fetuses.

b. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

c. Any risk is the least possible for achieving the objectives of the research.
d. If the research holds out the prospect of direct benefit to the pregnant woman, to both the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus, when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, then the consent of the pregnant woman is obtained in accordance with the usual conditions for informed consent.

e. If the research holds out the prospect of direct benefit solely to the fetus, then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity, or the pregnancy resulted from rape or incest.

f. Each individual who provides consent under paragraph e. or d. of this Section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.

g. For children who are pregnant, assent and permission are obtained in accord with the usual conditions of permission and assent in Section 5.8.1.

h. No inducements, monetary or otherwise, will be offered to terminate a pregnancy.

i. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.

j. Individuals engaged in the research will have no part in determining the viability of a neonate.

5.6.2 Research involving neonates

Neonates of uncertain viability and nonviable neonates may be involved in research if the following conditions as applicable are met:

a. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

b. Each individual who provides consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

c. Individuals engaged in the research will have no part in determining the viability of a neonate.

d. The requirements for neonates of uncertain viability or nonviable neonates in the following Sections have been satisfied as applicable.

Neonates of Uncertain Viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research unless the following additional conditions have been met.

a. The CPHS determines that:
i. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or

ii. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and

b. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with the usual conditions for parental permission, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

**Nonviable Neonates.** After delivery, nonviable neonates may not be involved in research unless the following additional conditions are met.

a. Vital functions of the neonate will not be artificially maintained.

b. The research will not terminate the heartbeat or respiration of the neonate.

c. There will be no added risk to the neonate resulting from the research.

d. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.

e. The legally effective informed consent of both parents of the neonate is obtained in accord with the usual conditions for parental permission, except that waiver and alteration of consent do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet this requirement, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet these requirements.

**Viable Neonates.** A neonate that has been determined to be viable may be involved in research only to the extent permitted by and in accord with the CPHS review processes and procedures for research involving children.

**After Delivery, Research Involving the Placenta, a Dead Fetus or Fetal Material.** After delivery, research involving the placenta, a dead fetus, or fetal material consisting of cells, tissue, or organs excised from a dead fetus, is evaluated for conduct in accordance with applicable Federal, State, or local law and regulations regarding human remains.
If information associated with materials described above is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, these individuals are research subjects and other Sections of these procedures apply.

**5.6.3 Research Not Otherwise Approvable Affecting Pregnant Women, Fetuses, or Neonates**

**Research Not Funded by DHHS.** If the CPHS finds that proposed research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates, and the research is not approvable under this Section of CPHS procedures, then the CPHS may decide to consult with one or more experts in pertinent disciplines, such as science, medicine, ethics, and law. Based on the recommendation of these experts if applicable, the CPHS may approve the research based on either:

a. That the research in fact satisfies the conditions of Section 5.6.1.1, as applicable;

Or

b. The following conclusions:
   i. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;
   ii. The research will be conducted in accord with sound ethical principles; and
   iii. Informed consent will be obtained in accord with the usual conditions for informed consent and other applicable sections of these procedures.

**Research Funded by DHHS.** DHHS-funded research that is not otherwise approvable and involves pregnant women, fetuses, and neonates must be approved by the Secretary of Health and Human Services prior to initiation of the research activities.

If the CPHS finds the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates, and the research is not approvable under the above procedures in this section, then the CPHS arranges to send the research proposal to OHRP for DHHS review.

**5.7 Research Involving Prisoners**

Prisoners are one of three classes of potential subjects identified as vulnerable to exploitation in research in 45 C.F.R. 46 and there are special rules for their protection. In the past, prisoners were viewed as a convenient research population. They are housed in a single location, constitute a large and relatively stable population, and live a routine life. Unfortunately, all the things that make a prison and prisoners a convenient research population also make prisoners ripe for exploitation.
The concern of 45 C.F.R. Part 46, Subpart C, and policies based on it is whether prisoners have any real choice about participation in research, or whether incarceration effectively eliminates voluntary choice.

This section applies to research involving prisoners, regardless of funding source with the following exception. For research not supported by the DHHS or the VA, Subpart C is not applied to any incidental involvement of a prisoner in research activities that planned only to involve a non-prisoner population as participants. The FWA entered into by the Trustees of Dartmouth College applies 46 C.F.R. 46 only to DHHS funded research and permits this exception for the incidental involvement of prisoners in research funded by other sources.

Research conducted in prisons or jails do not satisfy the conditions of this limited exception. The CPHS may identify additional protections for individual participants in research activities that may only incidentally involve prisoners.

The requirements in this Section are consistent with Subpart C of 45 CFR 46, which applies solely to DHHS-funded research.

5.7.1 Applicability

This policy applies to biomedical and behavioral research conducted under the auspices of the College that is planned to involve prisoners as subjects. Even though the CPHS may approve a research study involving prisoners as subjects according to this policy, investigators are still subject to the regulations of the New Hampshire Department of Corrections and other applicable State or local law. [45 CFR 46.301]

5.7.2 Minimal Risk

The definition of minimal risk in the Subpart C is different than in the rest of the federal regulations. According to 45 CFR 46.303, minimal risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

5.7.3 Composition of the CPHS [45 CFR 46.304]

In addition to satisfying the general requirements described in the Sections of these procedures on the membership of the CPHS, when reviewing research involving prisoners, the CPHS should also meet the following requirements:

a. A majority of the CPHS members (exclusive of prisoner representatives) should have no association with the prison involved, apart from their membership on the CPHS.

b. At least one member of the CPHS should be able to represent prisoners and have the appropriate background and experience to serve in that capacity.
5.7.4 Additional Duties of the CPHS [45 CFR 46.305]

In addition to its other responsibilities, the CPHS approves research involving prisoners if it finds that the research is permitted by one of the following categories [45 CFR 46.306]:

a. A study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.

b. A study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.

c. Research on conditions particularly affecting prisoners as a class. For example, research on social and psychological problems, such as alcoholism, drug addiction, and sexual assaults.

d. Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject;

In addition, the CPHS should make each of the following determinations prior to its approval of research involving prisoners as subjects.

a. Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired.

b. The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers.

c. Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the CPHS justification in writing for following some other procedures, control subjects should be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project.

d. Information about the research is presented in language which is understandable to the subject population.
e. Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole.

f. If the CPHS finds there may be a need for follow-up examination or medical care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

5.7.5 Waiver for Epidemiology Research

The Secretary of DHHS has waived the applicability of 45 CFR 46.305(a)(1) [research involves a permissible category of research involving prisoners] and 46.306(a)(2) [list of the permissible categories of research involving prisoners] for certain research conducted or supported by DHHS consisting or epidemiologic studies that meet the following criteria.

a. Research in which the sole purpose is:
   i. To describe the prevalence or incidence of a disease by identifying all cases, or
   ii. To study potential risk factor associated with a disease, and

b. The CPHS has approved the research, made the determinations needed under 45 CFR 46.305(a)(2)–(7), and documented that:
   i. The research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects.
   ii. Prisoners are not a particular focus of the research.
   iii. The research consists of epidemiological studies on chronic diseases, injuries, or environmental health and uses epidemiologic methods, such as interviews and the collection of biologic specimens that generally entail no more than minimal risk to the subjects.

In order for a study to be approved under this waiver, the CPHS should find that, among other things, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the data.

5.8 Research Involving Children*

For EPA regulated research, special considerations apply. See Section 5.3.

The following section applies to research involving children regardless of funding source. The requirements in this section are consistent with Subpart D of 45 CFR 46, which applies to DHHS-funded research and Subpart D of 21 CFR 50, which applies to FDA-regulated research involving children.
Categories of Research

Research on children should be reviewed and characterized by the CPHS into one of the following categories:

a. Research not involving risks greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (i.e., research presenting only minimal risk to participants). The CPHS may find that the permission of one parent is sufficient.

b. Research involving greater than minimal risk, but presenting the prospect of direct benefit to individual subjects.
   i. The risk is justified by the anticipated benefit to the subjects;
   ii. The CPHS may find that the permission of one parent is sufficient;
   iii. Assent of the child is obtained, provided each child is capable of providing assent.

c. Research involving greater than minimal risk and no reasonable prospect of direct benefit to individual subjects, but is likely to yield generalizable knowledge about the subjects’ disorder or condition.
   i. The risk represents a minor increase over minimal risk;
   ii. The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
   iii. Permission of both parents or a legal guardian should be obtained, unless one parent is deceased, unknown, incompetent, or not reasonably available, or only one parent has legal responsibility for the care and custody of the child;
   iv. Assent of the child is obtained, provided each child is capable of providing assent.

d. Research that is not otherwise approvable, but which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children.
   i. DHHS-funded and FDA regulated research in this category should be approved by the Secretary of Health and Human Services, and permission to participate in the research is obtained from either both parents or a legal guardian.
   ii. For non-federally-regulated research, the CPHS may consult with a panel of experts in pertinent disciplines during its review, such as experts in the science, medicine, ethics, and law relevant to the research. Based on the recommendation of the panel, the CPHS may approve the research if it determines:
1) The research in fact satisfies the conditions for one of the previous categories;

Or

2) The research satisfies the following criteria:
   a) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
   b) The research will be conducted in accord with sound ethical principles; and
   c) Consent is obtained in accord with the usual conditions for informed consent to research participation.

5.8.1 Parental Permission and Assent

5.8.1.1 Parental Permission

The CPHS determines whether adequate provisions have been made for soliciting the permission of each child’s parent or guardian for each research project it reviews.

Parents or guardians should be provided with the basic elements of consent and any additional elements that may be necessary, as described in Section 5.5.

The CPHS may find that the permission of one parent is sufficient for research to be conducted under categories a. and b. above. The CPHS’s determination of whether permission should be obtained from one or both parents is documented in its approval letter when a study receives review.

Permission from both parents is obtained for research conducted under categories c. and d. above unless:
   a. One parent is deceased, unknown, incompetent, or not reasonably available;
   or
   b. Only one parent has legal responsibility for the custody of the child.

The CPHS may waive the requirement for obtaining permission from a parent or legal guardian if:
   a. The research meets the criteria for a waiver of consent in Section 4.6,
b. If the CPHS determines that the research study is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects. For example, research that involves neglected or abused children. The CPHS should assure that an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and that the waiver is not inconsistent with Federal, State or local law. The choice of an appropriate protection depends upon the nature and purpose of the activities described in the study materials, the risks and anticipated benefits to research participants, and their age, maturity, status, and condition.

Permission from a parent or legal guardian is documented as described in Section 4.4 and 4.7.

5.8.1.2 Assent from Children

Because “assent” means a child’s affirmative agreement to participate in research, the child should actively show his or her willingness to participate in the research, rather than just complying with directions and not resisting in any way. When judging whether children are capable of assent, the CPHS takes into account the ages, maturity, and psychological state of the children involved. The CPHS uses its discretion to judge the capacity to assent for the children involved in a proposed research activity or may rely on the investigator to determine capacity for each individual child.

The CPHS evaluates the proposed assent procedure and the form and content of the information conveyed to prospective subjects. For research activities involving adolescents whose capacity to understand may be similar to that of adults, the assent procedure should include information similar to that provided for informed consent by adults or for parental permission. For children whose age and maturity level limits their ability to comprehend the nature of the research activity, but who should be consulted about participation in research, an accurate picture of the actual experience of participation in research should be conveyed. For example, what the experience will be like, how long it will take, whether it might involve any pain or discomfort. The assent procedure should reflect a reasonable effort to enable the child to understand, to the degree they are capable, what their participation in the research involves.

Ordinarily, the CPHS presumes that children ages 7 and older should be given an opportunity to provide assent. Generally, oral assent with the use of a script may be obtained from children 7 - 11 years of age. Assent using a written document for the children to sign may be used with older children.

At times, there may be an inconsistent outcome between parental permission and a child’s assent. Usually a "no" from the child overrides a "yes" from a parent, but a child legally cannot decide to be in research over the objections of a parent. There may be individual exceptions to these guidelines, such as when the use of an experimental product for a life threatening disease is being considered. In general, a child can refuse participation in research, even if parental permission has been obtained.
If the CPHS determines that the capacity of the children who would participate in proposed research is so limited that they cannot reasonably be consulted, or the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children as individuals and is available only in the context of the research, then assent by the children is not a necessary condition for the research. The CPHS may determine assent may be waived, provided the criteria for a waiver are met, even when the children who are potential subjects are likely to have the capacity to assent.

5.8.1.3 The Assent Form

When the assent of children who are the intended participants in research should appropriately occur, the CPHS determines whether and how assent should be documented.

Investigators should develop information about the research that is age appropriate and study specific, taking into account the typical child's experiences and level of understanding. The assent process should treat the child respectfully and convey essential information about the study. An assent form should contain those basic elements for consent that are appropriate for the age of the children and the study.

For younger children, an assent form should be limited to about one page if possible. Illustrations are helpful and larger font makes a form easier to read. Studies involving older children or adolescents should include more information and may use more complex language.

5.8.2 Children Who Are Wards

Children who are wards of the State or any other governmental agency, institution, or entity may be included in research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition, only if such research is:

a. Related to their status as wards; or
b. Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

If the research meets the conditions above, an advocate should be appointed for each child who is a ward in addition to any other individual acting on behalf of the child as legal guardian or in loco parentis. One individual may serve as the advocate for more than one child.
The advocate should be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child’s participation in the research. The advocate should not be associated in any way with the research, the investigators, or the guardian organization, except in the role as advocate or member of the CPHS.

5.9 Adults with Impaired Decision Making Capacity

This Section applies to research involving adults with physical or mental disabilities that result in impaired decision-making capacity.

Prospective research participants lacking decision making capacity may not be enrolled in a study unless the CPHS has approved the enrollment of such participants. The CPHS approves research involving persons with impaired decision-making capacity only when each of the following conditions applies:

a. Individuals with impaired decision making capacity are suitable as research subjects and other individuals are not. Individuals with impaired decision-making capacity should not be included as subjects in research simply because they may be available.

b. The investigator presents to the CPHS a compelling reason to include individuals with impaired decision-making capacity as research subjects.

c. The proposed research entails no significant risks, or if the research presents some probability of harm, there is a greater probability of direct benefit to individual participants.

d. Assent by participants is obtained continuously throughout the duration of research activities. In the event assent is not present, then the preferences of the study participant are respected and prevail regardless of surrogate permission for research participation.

e. Research procedures have been designed to inform each participant’s representative regarding their role and obligations to protect the participant. Health care agents appointed under Durable Power of Attorney for Health Care (DPAHC), next-of-kin, or guardians should be given written descriptions of the proposed research study that include their obligations as a surrogate decision maker. Representatives of potential study participants should be informed about their obligation to determine what the prospective participant would do, or if the these wishes cannot be determined or are unknown, what the representative believes is in the potential participant’s best interests based on knowledge of and personal experience with the participant.

5.9.1 CPHS composition
When a study population is intended to include adult participants who will lack decision making capacity, the CPHS membership reviewing the proposed research should include at least one member who has expertise in the specific area of the research. Consideration may be given to adding an ad hoc member or consultant who is a member of the proposed study population, a family member of such a person, or a representative of an advocacy group for that population. The CPHS may utilize ad hoc consultants or members as necessary to ensure appropriate scientific expertise and and representational experience.

5.9.3 Determination of Decision-Making Capacity

The decision-making capacity of a potential research participant should be evaluated by a qualified practitioner when there is reason to believe that an individual may lack the capacity to make a voluntary and informed decision about research participation. When an investigator anticipates encountering potential participants who lack decision making capacity, the investigator should present to the CPHS a plan for assessing the decision making capacity. The CPHS will evaluate whether the proposed plan to assess capacity is adequate.

For research involving potential participants with physical or mental disorders that may affect decision-making capacity, the CPHS may determine that capacity assessments are necessary, unless the investigator can justify why such assessments would be unnecessary.

For research that presents greater than minimal risk, the CPHS may require investigators to have independent, qualified professionals to assess whether potential participants have the capacity to give voluntary, informed consent. Even in research involving only minimal risk, the CPHS may require that the study include a capacity assessment if there is reason to believe that potential participants may lack such capacity.

For research involving subjects who may have fluctuating, potentially diminishing, or limited decision making capacity, the CPHS may request that the investigator establish and maintain ongoing communication with involved caregivers. Periodic re-consent and assent, as appropriate, may be considered as CPHS requirements for some studies to assure continuing agreement about participation. Consent monitors may be used during recruitment and the consent process or waiting periods may be used to allow more time for the potential participant to consider the information that has been presented.

It is often possible for investigators and others to enable individuals with decisional impairment to make voluntary and informed decisions about participation in research. Potential enabling measures include teaching, group sessions, audiovisual presentations, and oral or written tests of recall. Other measures may include subsequent questions to assess subject comprehension, video or audio recording of the consent process, second opinions, use of independent consent observers, allowing a
waiting period before enrollment, or involvement of a trusted family member or friend in the decision making process.

For potential or enrolled participants with fluctuating decision making capacity or those with a known diminishing capacity to consent, a re-consenting process involving surrogate permission may be necessary.

Although lacking capacity to provide informed consent, some individuals may resist participating in a research study approved by a representative. Under no circumstances should unwilling adult participants be involved in research activities.

If it is anticipated that research participants may lose decision making capacity after enrollment, the PI should notify the CPHS. The PI is expected to develop a monitoring plan for enrolled subjects under these circumstances. The PI should be encouraged to obtain advance directives for research participation that appoint a surrogate decision maker from individuals within a study population having known fluctuating or diminishing decision making capacity. Such advance directives should be obtained during the initial consent process from those individuals within the eligible study population who possess decision making capacity.

5.9.3 Determining Capacity to Consent

Decision making capacity in the research context has been interpreted by the American Psychiatric Association as involving the following abilities:

a. To evidence a choice,
b. To understand relevant information,
c. To appreciate the situation and its likely consequences, and
d. To manipulate information rationally.

A range of professionals and methods may assess decision making capacity. In general, a researcher or consultant familiar with the conditions that impair decision making capacity and qualified to assess and monitor capacity and consent in such individuals should make evaluations on an ongoing basis. The CPHS considers the qualifications, independence from the research, and the institutional affiliation of each individual proposed by the PI to assess decision making capacity.

The majority of studies conducted at the College enroll only study participants who have the capacity to consent. For studies approved to enroll participants who may lack capacity to consent, a qualified individual should assess the capacity of each potential participant to consent. The PI may determine that a prospective research participant lacks decision-making capacity and is unlikely to regain it within a reasonable period of time. If the reason for lack of capacity is a mental illness or condition, then a
psychiatrist or licensed clinical psychologist should confirm any diagnosis and document it.

A person who has been determined to lack capacity to consent to research participation should be notified of that determination before permission is obtained from a legally authorized representative. If permission is given by a legally authorized representative to enroll such a person in the study, the participant should be informed that such permission has been obtained. Should the participant object to any aspect of involvement in the study, this objection should be respected and prevail.

5.9.4 Informed Consent and Assent

In general, adults are presumed to have the capacity to provide consent. When there is reason to believe prospective participants may lack the capacity to give consent, an investigator may obtain consent from the legally authorized representative of a potential participant, which is referred to as surrogate consent and described in the Section below.

A person who has been determined to lack capacity to consent to participate in a research study should be informed about the research to the extent compatible with the person's ability to understand the information provided. Under most circumstances the potential participant should also assent to participation by signing and dating the written consent form or a separate assent form. If the person objects to participating, this objection should be respected and prevail.

The decision-making capacity of some subjects may fluctuate or be expected to diminish over time. For individuals who have fluctuating decision making capacity or those with diminishing capacity to give consent, re-consent involving a surrogate decision maker may be necessary. Although lacking capacity to provide informed consent, some individuals may refuse to participate in a research study approved by a representative. Under no circumstances should a person be involved in the research if explicitly unwilling to do so.

5.9.4.1 Surrogate Consent

In general, an investigator obtains informed consent from each adult study participant. Under appropriate conditions, investigators may obtain informed consent from a legally authorized representative of a subject, a process which is known as surrogate consent.

**Definition:** Legally authorized representative means an individual or judicial or other entity authorized under applicable law to consent on behalf of a prospective study participant to the individual's participation in the procedures involved in the research [45 CFR 46.102(c)].
Surrogate consent is designed to protect human research participants from exploitation and harm and, at the same time, make it possible to conduct essential research on problems that are unique to persons who lack decision-making capacity.

Under certain conditions, surrogate consent may be obtained from a court appointed guardian of the person or a health care agent who has been appointed by an individual in a Durable Power of Attorney for Health Care (DPAHC). In New Hampshire, a guardian ordinarily has to return to court to obtain authority to provide surrogate consent to research participation for a ward. For example, an individual might have designated a person to provide consent with regard to health care decisions through a DPAHC that specified the designated attorney also has authority to make decisions about research participation.
Section 6: Investigational Drugs & Devices in Research

6.1 Policy

Use of investigational drugs should be conducted according to FDA's IND regulations, 21 CFR 312, and other applicable FDA regulations. Use of an investigational device in a clinical trial to obtain safety and effectiveness data should be conducted according to FDA's IDE regulations, 21 CFR 812, 813, and other applicable FDA regulations. The CPHS reviews the use of investigational drugs and devices for compliance with FDA regulations and ethical conduct of the research in which they are used.

The following procedures describe CPHS review of the use of investigational drugs and devices in research conducted under the auspices of the College.

6.2 Definitions

Investigational Drug. An investigational drug is one for which the PI or a sponsor has filed an IND application to the FDA under 21 CFR 312, or a drug that the FDA has previously approved and is being studied for an unapproved or approved indication in a clinical trial.

Investigational Device. A medical device is a healthcare product that has not been previously approved by the FDA for commercial distribution and is being used in a clinical trial designed to evaluate the effectiveness, safety, or both of the device, or any healthcare product that does not achieve its primary intended purpose by chemical action or by being metabolized.

IND. IND means an investigational new drug application or assigned number in accordance with 21 CFR 312.

IDE. IDE means an investigational device exemption application or assigned number in accordance with 21 CFR 812.

Emergency Treatment Use. Emergency treatment use is the use of a test article on a human subject in a life-threatening situation in which no standard, acceptable treatment is available and there is not sufficient time to obtain CPHS approval. See 21 CFR 56.102(l) for the definition of test article.

Significant Risk (SR) Device. Significant risk device means an investigational medical device that:

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

(2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or
(3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
(4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

**Non-Significant Risk (NSR) Device.** A non-significant risk device is an investigational medical device that does not meet the criteria for a significant risk device.

**Humanitarian Use Device (HUD).** Humanitarian use device is one that is intended to benefit patients by treating or diagnosing a disease that affects fewer than 4,000 individuals in the United States per year.

**Substantially Equivalent Device.** A medical device is substantially equivalent if it has the same intended use as a predicate device and the same or different technological characteristics, provided the information about the device is substantially equivalent to the predicate device and demonstrates that the device is as safe and effective as a legally marketed device plus does not raise different questions of safety and effectiveness than the predicate device. "Different technological characteristics" means that there is a significant change in the materials, design, energy source, or other features of a device from those of the predicate device.

**510(k) Clearance.** A 510(k) clearance is a form of FDA approval for marketing a substantially equivalent medical device.

### 6.3 IND and IDE Requirements

The PI should indicate on the CPHS application for review whether the research involves an investigational drug or medical device. If it does, then the PI should state whether the drug or device is used for the indication approved by the FDA. If not, the PI should provide information about the regulatory status of the investigational or unlicensed test articles. If there is a FDA assigned IND or IDE number for the study, documentation of the IND or IDE number could be:

- a. An industry sponsored protocol with an identified IND or IDE number.
- b. A letter from FDA containing the IND or IDE number.
- c. A letter from industry sponsor identifying the IND or IDE number.
- d. Other document or communication verifying the IND or IDE number.

For any study involving a NSR investigational medical device, an IDE application or assigned number approved by the FDA is not required. If a sponsor has identified a device as used in a study as NSR, then the investigator should provide an explanation of the determination. If the FDA has determined the device as used in the study is an NSR device, documentation of that determination should be provided.
If the research involves an investigational drug or medical device and there is no FDA assigned IND or IDE number respectively, the PI should provide justification of why FDA approval is not required.

The CPHS reviews the application for review for studies involving investigational drugs or medical devices and determines:

a. Whether there is an IND or IDE number associated with the study and, if so, whether there is appropriate supporting documentation verifying the number assigned.

b. If the research involves an investigational drug or medical device without an assigned IND or IDE number and whether the research satisfies the applicable criteria listed below.

6.3.1 IND Exemption

For investigational drug use, an IND number assigned by the FDA is not necessary if each of the following conditions is satisfied.

a. The drug being used in the research is lawfully marketed in the United States;

b. The results of the research are not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;

c. The research is not intended to support a significant change in the advertising for the product;

d. The research does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks or decreases the acceptability of the risks associated with the use of the drug;

e. The research is conducted in compliance with the requirements for IRB review and informed consent (21 CFR parts 56 and 50, respectively);

f. The research is conducted in compliance with the requirements concerning the promotion and sale of drugs (21 CFR 312.7);

g. The research will not be conducted under an exception from informed consent requirements for emergency research in 21 CFR 50.24.

The following research activities are also exempt from the IND requirements.

a. A clinical investigation involving use of a placebo, if the investigation does not otherwise require submission of an IND; and

b. A drug intended solely for tests in vitro or in laboratory research animals, if it is shipped in accordance with 21 CFR 312.160.
For clinical investigations involving an in vitro diagnostic biological product, an IND number is not necessary if:

a. It involves one or more of the following: (i) blood grouping serum, (ii) reagent red blood cells or (iii) anti-human globulin;

b. It is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and

c. It is shipped in compliance with 312.160.

6.3.2 Exempted IDE Investigations

In research on medical devices, an IDE number assigned by the FDA is not necessary if one of the following categories of devices is involved.

a. The research involves a medical device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.

b. The research involves a medical device that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of 21 CFR 807 in determining substantial equivalence.

c. The research involves a diagnostic medical device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
   i. Is noninvasive,
   ii. Does not require an invasive sampling procedure that presents significant risk,
   iii. Does not by design or intention introduce energy into a subject, and
   iv. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

d. The research involves a device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

e. The research involves a device intended solely for veterinary use.

f. The research involves a device shipped solely for research on or with laboratory animals and labeled in accordance with 21 CFR 812.5(c).

g. The research involves a custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.
6.3.3 CPHS Review of Investigational Drugs and Devices

The CPHS reviews research involving investigational drugs and medical devices using the same criteria it would use in considering approval of any research involving an FDA-regulated product (21 CFR 56.111).

In general, for research involving investigational medical devices:

a. Unless the FDA has already made a risk determination for the use of the investigational medical device in the study, the CPHS reviews proposed studies using investigational medical devices and may determine if the device represents significant or non-significant risk and reports its findings to the PI in writing. The CPHS considers the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures. The FDA considers the investigational use of NSR medical devices to have approved applications for an IDE and applies only the abbreviated IDE requirements at 21 CFR 812.2 to the sponsor of the study. These requirements include CPHS review of the study and the informed consent of study participants, unless a waiver of consent is granted. If the medical device as used in the study is considered SR, the CPHS may approve the study, but the study may not begin until an IDE number assigned by the FDA is obtained for the study.

b. The CPHS does not review studies involving SR medical devices under expedited review.

c. The CPHS records in its meeting minutes and provides to the PI the rationale for its determination whether a medical device should be classified as NSR or SR.

d. If the FDA has already made the SR or NSR determination for the investigational medical device used in a study, the agency’s determination is final and the CPHS does not need to make a specific risk determination for the device as used in the study.

6.3.4 Emergency Treatment Use

6.3.4.1 Emergency Treatment Exemption from Prior CPHS Review

The FDA defines emergency use as the use of a test article, i.e., investigational drug, biological product, or medical device, on a human subject confronted by a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval. If the conditions described in 21 CFR 56.102(d) exist, then the emergency exemption from prior IRB approval found at 21 CFR 56.104(c) may apply. Informed consent to the use of the test article is required unless the conditions for an exception at 21 CFR 50.23 are satisfied.

An investigator should notify the CPHS within 5 business days whenever an emergency use of a test article occurs. Any subsequent use of the test article at the institution is subject to prior CPHS review. An investigator should not construe notification of the
CPhS about an emergency use of a test article, with or without reliance on an exception to the requirement to obtain informed consent, as approval for the emergency use by the CPhS. The CPhS Director, Chair, or a designee reviews each notice of emergency use of a test article and any request for an exception to the requirement to obtain informed consent for the use of a test article. This review verifies that the circumstances conform to the requirements of the applicable FDA regulations.

An emergency use of a test article does not constitute a systematic investigation designed to develop or contribute to generalizable knowledge. Nonetheless, emergency use of a test article is considered a research activity involving a human subject under FDA regulations, and safety information may be collected about the individual receiving the test article under such circumstances.

### 6.3.4.2 Waiver of Informed Consent for Emergency Treatment Use

An exception under the FDA regulations at 21 CFR 50.23 permits the emergency use of an investigational drug, device, or biologic without informed consent when an investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing the following specific conditions.

a. The subject is confronted by a life-threatening situation necessitating the use of the test article;

b. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject;

c. Time is not sufficient to obtain consent form the subject’s legally authorized representative; and

d. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject’s life.

If time is not sufficient to obtain a determination by an independent physician before use of the test article, the actions of the investigator should be reviewed and evaluated in writing by an independent physician within 5 business days. The CPhS should be notified within 5 business days when an investigator relies on an emergency waiver of informed consent. This notification should not be construed as an approval by the CPhS. The CPhS Chair, Director, or a designee reviews a notice of reliance on an emergency waiver of informed consent to verify that circumstances conformed with the applicable FDA regulations.

### 6.3.4.3 Emergency Treatment Use

The FDA regulations at 21 CFR 312.310(d) provide for an investigational drug or biologic to be used as treatment in emergency situations when there is not enough time to make a formal, written request. The FDA may authorize shipment of the drug or biologic via electronic communications in such circumstances.
Prior CPHS review of emergency expanded access use ordinarily does not occur, because in an emergency the conditions for an exemption from CPHS review are likely to be satisfied under 21 CFR 56.104(c) and 56.102(d). Informed consent also may not occur, because often the conditions for an exception exist under 21 CFR 50.23. The circumstances of emergency treatment use should be carefully considered to determine applicable regulations in 21 CFR Parts 50 and 56, as well as 21 CFR 312.310(d).

6.3.4.4 Single Patient Treatment Use Including Emergency Treatment Use.
Access to investigational drugs or biologics for use by a single, identified patient is arranged either through the sponsor under a treatment protocol or through the FDA by obtaining the drug from the sponsor and submitting a treatment use request to the FDA. Review and approval of the treatment use by the CPHS is required. The FDA identifies the following special considerations as safeguards for expanded access use by a single patient. See also Section 6.3.4.1.

   a. Treatment is generally limited to a single course of therapy for a specified duration unless otherwise authorized by the FDA.

   b. At the conclusion of treatment, the attending physician or sponsor needs to provide the FDA with a written summary of the results of the expanded access use, including any adverse effects.

   c. The FDA may require sponsors to monitor an individual patient's expanded access use if the use is for an extended duration.

6.3.5 Expanded Access to Investigational Drugs

The FDA regulations at 21 CFR 312.300 allow certain individual patients not enrolled in clinical trials to obtain expanded access to investigational drugs, agents, or biologics through the following methods.

Compassionate Use. The term “compassionate use” is commonly used to refer to the use of investigational drugs outside of a clinical trial for a limited number of patients who are desperately ill and for whom no standard alternative therapies are available. The term “compassionate use” does not, however, appear in FDA or HHS regulations. It is preferable, instead, to use the names of the specific access programs when discussing the use of investigational articles outside of a clinical trial.

Group C Treatment IND. The FDA may permit the distribution by NIH under NCI treatment protocols of certain investigational drugs, agents, or biologics to oncologists for the treatment of cancer outside of controlled clinical trials. Group C drugs, agents, or biologics usually have shown sufficient evidence of relative and reproducible efficacy in a specific tumor type in early phase clinical trials. Although the FDA typically grants a waiver of IRB review for most drugs used in Group C Treatment IND protocols, the CPHS requires prior CPHS review and approval. Safety and efficacy data are ordinarily collected on the patients who receive these drugs.
**Open – Label Study:** A study designed to obtain additional safety data, typically done when the controlled trial has ended and treatment with an investigational agent continues. The purpose of such a study is to allow subjects to continue to receive the benefits of the investigational drug, agent, or biologic until marketing approval is obtained. Prior CPHS review and approval is required.

**Parallel Track:** This FDA program makes investigational drugs, agents, or biologics available as quickly as possible to persons with AIDS and other HIV-related diseases. These drugs, agents or biologics are used in separate protocols that "parallel" controlled clinical trials and remain important to establish the safety and effectiveness of these new drugs, agents, or biologics. Although the Secretary of the Department of Health and Human Services may, on a study-by-study basis, waive the provisions of 45 CFR Part 46 when adequate protections are provided through other mechanisms, prior CPHS review and approval is required by the CPHS.

**Treatment IND or Biologics:** A FDA regulatory category that provides eligible patients with investigational drugs or biologics as early in the development process as possible for the treatment of serious conditions and life-threatening diseases for which there are no satisfactory alternative treatments. In 21 CFR 312.300 the FDA defines an "immediately life-threatening disease" and "serious disease or condition" for the purposes of expanded access and treatment use. The FDA permits an investigational drug to be used under a treatment IND after sufficient data have been collected to show that the drug may be effective for its intended use in its intended patient population and does not have unreasonable risks associated with its use. Prior CPHS review and approval is required. See 21 CFR 312.320.

**General Criteria for Expanded Access Use.** There are four general FDA criteria for any expanded access use, including for a single patient, an intermediate-size patient population, or more widespread treatment use. Additional regulatory criteria also apply to each of these categories of patient populations, which define the types of expanded access use.

1. The drug is intended to treat a serious or immediately life-threatening disease or condition;
2. There is no satisfactory alternative treatment available;
3. The potential patient benefit justifies the potential risks of treatment use, which are not unreasonable in the context of the disease or condition to be treated;
4. The requested treatment use of the investigational agent will not interfere with the conduct of clinical investigations that could support expanded access use or otherwise compromise the potential development of expanded access use.

**Informed Consent.** Assuring informed consent may be important in treatment use situations, because a patient may be desperately ill and particularly vulnerable. The patient is receiving a drug or biologic that has not yet been proven either safe or
effective in a clinical setting. Both the situation of the patient and his or her condition may compromise the ability to make an informed assessment about the risks involved. The review of the CPHS determines whether a patient is likely to or can be well informed about the risks of the proposed treatment. See also Section 6.3.4.2.

Costs for Expanded Access Use. Under certain conditions, in general the FDA permits sponsors to charge for its direct costs of a drug, agent, or biologic that is approved for expanded access use. See 21 CFR 312.8.

The CPHS pays particular attention to issues of equity when considering the situation in which a patient is responsible for some costs of the drug or biologic. Expanded access use may preclude economically disadvantaged individuals as a class from access to test agents. The CPHS balances this potential lack of access against the possibility that the drug or biologic may not be available as therapy until it receives FDA approval when similar access barriers could exist.

6.4 Exception from Informed Consent for Planned Emergency Research

The FDA makes an exception to its general requirements to obtain the informed consent of subjects for planned research in life-threatening emergencies in 21 CFR §50.24. The research plan receives prior review and approval from the FDA or DHHS and the CPHS. The plan should be publicly disclosed to the community in which the research will be conducted. Such research are not allowed under the regulations covering the emergency use of a test article in a life-threatening situation (21 CFR §56.104(c)).

6.5 Humanitarian Use Devices (HUD)

Treatment with a HUD is ordinarily subject to CPHS initial and continuing review under 21 CFR 814.124. At the time of review, the CPHS determines if the written consent of patients for treatment use of the HUD is necessary.

If a physician is confronted with an emergency situation and determines that CPHS approval cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be used without prior CPHS approval. In this instance, approval may be obtained from the VA Chief of Staff, a departmental chair, or CPHS Chair. The physician should provide written notification of HUD use to the CPHS within five days. The notice to the CPHS should include identification of the patient, the date of use, as well as the circumstances and reason for the use of the HUD.

The investigator is responsible for notifying the FDA if the CPHS withdraws approval for use of a HUD within five days of receiving CPHS notice about withdrawal of its approval.
Section 7: Unanticipated Problems, Complaints and Non-Compliance

7.1 Policy

Dartmouth College complies with DHHS and FDA regulations stating that institutions have written policies on reporting unanticipated problems involving risks to subjects or others to the CPHS, institutional officials, relevant federal agencies and departments.*

The following procedures describe how unanticipated problems involving risk to subjects or others are handled in research conducted under the auspices of the College.

7.2 Definitions

Unanticipated problems involving risk to participants or others (UPR).*

Unanticipated problems involving risks to participants or others refer to any problem, event, incident, or new information that:

a. Is unexpected in terms of nature, severity, or frequency;
b. Is not included in the research procedures that are described in the study-related documents, such as the CPHS-approved documents including consent forms;
c. Is not characteristic of the subject population being studied; and
d. Indicates that subjects or others are at a greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Problems that should be reported to the CPHS include 1) changes made to the research without prior CPHS approval in order to eliminate apparent immediate harm to research participants, and 2) other unanticipated incidents, experiences, events, or outcomes that indicate research participants or others may be at an increased risk of harm.

Non-compliance. Non-compliance is a failure to conform to the applicable regulations and policies for the protection of human subjects as described in this document or failure to follow the study specific determinations of the CPHS. Non-compliance may be minor or sporadic or it may be serious or continuing.

Serious non-compliance. Serious non-compliance is non-compliance that, in the judgment of the CPHS Chair, Director, or the convened CPHS, increases risks to research participants, decreases the potential for benefits, or compromises the integrity of the human research protection program or the research project. Research being conducted without prior CPHS approval is considered serious noncompliance.
**Continuing non-compliance.** Continuing non-compliance is a pattern of non-compliance, in the judgment of the CPHS Chair, Director, or convened CPHS, suggesting the likelihood that instances of non-compliance will persist without CPHS intervention. Continuing non-compliance includes a failure to respond to or implement a request to resolve an episode of non-compliance.

**Allegation of Non-Compliance.** Allegation of non-compliance is an unproven assertion of non-compliance.

**Finding of Non-Compliance.** Finding of non-compliance is a determination by the convened CPHS that an allegation of non-compliance or a report of non-compliance is likely correct based on the available evidence developed during an investigation by the CPHS in consultation with appropriate institutional officials.

7.3 Unanticipated Problems Involving Risks to Subject or Others

7.3.1 Data Safety Monitoring (DSM) Plan

For interventional research projects that involve more than minimal risk, the initial research plan sent to the CPHS by the PI should describe procedures for safety monitoring, reporting of adverse events or unanticipated problems involving risks to subjects or others, interim safety reviews, and a plan for communicating the results of these activities to the CPHS. The DSM plan should contain a description of the Data and Safety Monitoring Board or Committee (DSMB or DSMC), if one exists, or an explanation why provision of an independent data safety monitor is not necessary. CPHS evaluates the DSM plan and determines if it is adequate for the proposed research project.

7.3.2 CPHS Procedures for Reports of Possible Unanticipated Problems

7.3.2.1 Review by CPHS Staff and Chair

Upon receipt of an Unanticipated Problem Reporting (UPR) Form or a Serious Adverse Event-Unanticipated Adverse Device Effect Reporting (SAE-UADE) Form from a PI, the CPHS office staff checks the form for completeness. If the form is incomplete or unclear, the CPHS staff works with the investigator or the designated contact person to obtain additional information. Clarifications and additional information are documented in the CPHS file, indicating the date, the investigator or research team member providing information, and the CPHS staff person involved.

The CPHS Director, in consultation with the Chair or other experienced member designated by the CPHS Chair as necessary to obtain appropriate expertise, reviews the report of the incident considered to be an unanticipated problem. The CPHS Chair or designee makes a determination whether the event should be regarded as an unanticipated problem based on the criteria contained in the definition of an unanticipated problem involving risks to subjects or others in section 7.2.
Based on the information received from the investigator, the CPHS Chair or designee may suspend research to ensure prompt protection of the rights and welfare of participants. Suspension decisions made by the CPHS Chair or designee should be reported to a meeting of the convened CPHS.

The CPHS Director, Chair, or designee may obtain, as necessary, more detailed information from the PI, the sponsor, the study coordinating center, or DSMB or DSMC about any adverse event occurring during a research study.

If a CPHS reviewer concludes that either (1) the problem was foreseen or (2) no participants or others were harmed, and participants or others are not at increased risk of harm, the reviewer indicates on the form that the problem is not an unanticipated problem. The form is filed in the CPHS study file, the determination is communicated to the investigator, and no further action is taken.*

If the CPHS reviewer concludes that the problem is an unanticipated problem, but that the risk is no more than minimal, the reviewer evaluates the following information.

a. The currently approved study documents including the consent form,
b. The CPHS Study Plan,
c. The protocol,
d. The investigator’s brochure, if any,
e. Previous reports of unanticipated problems involving risks to research participants or others, if any, and
f. Other relevant information available in the CPHS study file or obtained from the investigator.

After reviewing the above information, the CPHS reviewer takes appropriate action depending on the nature of the risk involved, which may include recommending modifications to the study and the consent form to the convened CPHS. The final results of the CPHS review are recorded, communicated to the investigator, and reported to the convened CPHS if not included in meeting minutes. Events determined to be unanticipated problems are reported to the relevant regulatory agencies and institutional officials according to the procedures in section 7.6.

A meeting of the convened CPHS reviews reported unanticipated problems when the risk may be more than minimal, serious adverse events, or unanticipated adverse device effects.*

7.3.2.2 CPHS Full Committee Review
The primary reviewer evaluates the CPHS study file, event report, and any recommendations from the CPHS director, Chair, or designee, as appropriate. All
CPHS members in attendance receive the event report, copies of the currently approved study documents, including the consent form, the CPHS Study Plan, the protocol, the investigator’s brochure if any, and other relevant information available in the CPHS study file or obtained from the investigator.

After review of the study documents and event report, the CPHS makes findings and takes actions based on the following considerations.

a. Whether the reported event is an unanticipated problem involving risks to research participants or others according to the definition stated earlier in this section.

b. What response to the report, if any, should be made, such as modifications to the research procedures or additional training of research personnel.

c. Whether suspension or termination of CPHS approval is warranted.

d. Whether further reporting to institutional or federal officials is required.

If the CPHS finds that the event is not an unanticipated problem involving risks to participants or others, according to the definition in this section, the CPHS may respond to the event with any of the following actions.

a. No action,

b. Modifications to the study protocol,

c. Revision of the continuing review timetable,

d. Modification of the consent process,

e. Modification of the consent form,

f. Providing additional information to current research participants whenever this information may relate to the participant’s willingness to continue their participation,

g. Providing additional information to past research participants,

h. Arranging additional training of the investigator or study staff, and

i. Any other appropriate actions.

If the CPHS finds that the event is an unanticipated problem involving risks to participants or others, according to the definition in this section, the CPHS may respond to the event with any of the following actions.*

a. Modification of the protocol,
b. Revision of the continuing review timetable,
c. Modification of the consent process,
d. Modification of the consent form,
e. Providing additional information to current research participants whenever this information may relate to the participant’s willingness to continue their participation,
f. Providing additional information to past research participants,
g. Arrangements for additional training of the investigator or study staff,
h. Reconsideration of CPHS approval for the study,
i. Arrangements for current research participants to have a special opportunity to consent again to their participation,
j. Monitoring of the research,
k. Monitoring of the consent process
l. Referral to other institutional officials (e.g., legal counsel, risk management, institutional official),
m. Suspension of the research activities,
n. Termination of the research project,
o. Any other appropriate actions.

If a UPR or SAE-UADE report suggests that participant safety is at risk, the CPHS may immediately suspend or terminate the research. Any suspension or termination of research by the CPHS is promptly reported to the Institutional Official, OHRP, FDA (if FDA-regulated research), and the VA R&D Administrative Office (if the study involves a VAMC). The CPHS Director is responsible for making such a report in writing.

If, after reviewing an investigator’s report, the CPHS finds that the reported incident is an unanticipated problem involving risks to research participants or others or that suspension or termination of CPHS approval is warranted, the CPHS Director:

a. Notifies the investigator in writing of the CPHS findings, with copies to the chair of the investigator’s department or section,
b. Immediately notifies the Research Compliance Officer at a VAMC who is the designee for reporting to ORO within 48 hours of the determination of a serious, unanticipated and related event, and
c. Reports the CPHS findings and recommendations to the Institutional Official and appropriate federal officials, including OHRP, FDA, and, if applicable, a VA Research Compliance Officer* and the Director of a VAMC*. See sections 7.5
7.3.2.3  Reconsideration of the CPHS Decision

The notice to the PI of the CPHS determination that an incident is an unanticipated problem involving risks to research participants or others (UPR) informs the PI that he or she has ten (10) business days from receipt of the notice to request reconsideration of the CPHS decision. The PI should send to the CPHS office a written request for reconsideration that includes the rationale for the request.

If a PI requests reconsideration, the PI’s written request is considered at the next CPHS meeting and the CPHS makes a determination whether to uphold, reverse, or modify its original decision. The CPHS notifies the PI of the final outcome reached by the CPHS and its reasons for that outcome.

If the CPHS receives a request for reconsideration from the PI and the study involves a VAMC, the CPHS notifies a VA R&D Administrative Office of the receipt of such a request and of the final outcome determined by the CPHS after its reconsideration.*

7.4 Complaints

The CPHS Director, in consultation with the Chair, promptly handles (or delegates to the CPHS office staff for handling) and, if necessary, investigates all complaints, concerns, suggestions, and appeals (complaints) received by the CPHS office. These communications include complaints, concerns, suggestions, and appeals from investigators, research participants and staff, and any other individual somehow associated with a study or research facility such as a VAMC.*

Upon receipt of the complaint, the CPHS Director or Chair makes a preliminary assessment whether the complaint warrants immediate suspension of the research project. If a suspension is warranted, the procedures in Section 2.11 are followed.

If the complaint constitutes non-compliance as defined above, it is considered an allegation of non-compliance according to section 7.5. If the complaint constitutes an unanticipated problem involving risk to subjects or others as defined above, it is handled according to Section 7.3.

The CPHS requests a summary of any complaints received by the investigator for each study at the time of continuing review.

7.5  Non-compliance
Investigators and their study staff routinely report instances of non-compliance to the CPHS as protocol deviations. Nevertheless, reports of unanticipated problems involving risks to subjects or others and serious adverse events or unexpected adverse device effects may also involve non-compliance. The PI is responsible for promptly* reporting non-compliance by study personnel to the CPHS. Commonly reported protocol deviations most often are instances of non-compliance that are neither serious nor continuing. Any individual, however, may report observed or apparent instances of non-compliance to the CPHS. In each case, the reporting individual is responsible for making the report in good faith, maintaining the confidentiality of the report until any investigation is completed, and cooperating with any CPHS or institutional review of these reports.

If an individual, whether investigator, study staff, or other, is uncertain whether a report is necessary or the circumstances involve non-compliance, he or she may contact the CPHS Director or Chair directly to discuss the situation informally.

The CPHS expects reports of non-compliance to be sent to the CPHS Office within 5 business days of discovery. The report should include a complete description of the noncompliance and specifically identify the study and personnel involved. The Director of the CPHS assists individuals in providing the information necessary for CPHS consideration of the report.

7.5.1 Review of Allegations of Non-compliance

Reports of protocol deviations and other allegations of apparent non-compliance are reviewed by the CPHS Director and Chair, who review:

- a. Available documents relevant to the allegation;
- b. The last approval letter from the CPHS;
- c. The last approved CPHS application for review and associated information;
- d. The last approved consent form;
- e. The grant, if applicable; and
- f. Other pertinent information (e.g., questionnaires, DSMB reports, clinical trial contract).

The CPHS Director and Chair review the allegation to make an initial determination about the credibility of the allegation in supporting apparent, serious, or continuing noncompliance. They may request additional information or an audit of the research in question.*

When the CPHS Director and Chair determine that the study was in compliance because the incident was consistent with the previous CPHS approval of the research, the determination is reported in writing to the PI and the reporting party. The
determination letter is copied to the Institutional Official in cases where the Institutional Official and any other parties had been notified at the outset.

If, in the judgment of the CPHS Director and Chair, the reported allegation of non-compliance is credible, the response occurs in accordance with Section 7.5.2.

In the judgment of the CPHS Director and Chair, if a report or allegation of non-compliance warrants suspension of the research before completion of a review or investigation to ensure protection of the rights and welfare of participants, the CPHS Director and Chair may suspend the research as described in section 2.11 with subsequent review at a meeting of the convened CPHS.

The CPHS Director and Chair may determine that additional expertise or assistance is required to make the necessary determinations and may establish an ad hoc committee to assist with the review and fact-gathering process. When an ad hoc committee assists in the review process, the CPHS Director is responsible for assuring that minutes of the meetings are generated and maintained to support the determinations or findings made by the ad hoc committee.

7.5.2 Review of Findings of Non-compliance*

Noncompliance is not serious or continuing:

When the CPHS Director and Chair determine that a protocol deviation or other report is non-compliance, but the non-compliance does not meet definition of serious or continuing non-compliance, these determinations are reported in writing to the PI and the reporting party. The CPHS Director and Chair work with the PI to develop a corrective action plan to prevent future non-compliance. The CPHS is notified about non-compliance that is not serious or continuing and any corresponding corrective action plans in a semi-annual summary report from the CPHS office. In the event a PI does not propose an appropriate corrective action plan, the matter is referred to a convened meeting of the CPHS with notification to the IO and, as applicable, a VA R&D Administrative Office at a VAMC*.

Serious or Continuing Non-compliance

When the CPHS Director and Chair determine that non-compliance has occurred and that the non-compliance may meet the definition of serious or continuing, the report is referred for review by the CPHS at the next convened meeting. The Chair may use her or his discretion, however, and call an ad hoc CPHS meeting should the circumstances warrant.

When non-compliance is referred to the CPHS for review at a convened meeting, the CPHS members receive the following information for review.

a. Available relevant documents regarding the incident of non-compliance;
b. The last approval letter from the CPHS;
c. The last approved CPHS study documents, including the consent form.

The convened CPHS may request additional information or find:

a. Non-compliance did not occur;
b. The incident of noncompliance is neither serious nor continuing and an adequate corrective action plan is in place;
c. Serious or continuing non-compliance has occurred and any modifications to the research proposed by the Chair and the Director or ad hoc committee should be approved; or
d. There may have been an incident of serious or continuing non-compliance and an inquiry (described below) should be made.

**Inquiry Procedure:** A determination may be made by the CPHS that an inquiry is necessary based on considerations that include but are not limited to:

a. Complaints that the rights of research participants were violated;
b. Reports that an investigator is not implementing the study as approved by the CPHS;
c. Unusual or unexplained adverse events occurring on a study;
d. Repeated failure of an investigator to report information requested by the CPHS.

A subcommittee of CPHS members, and non-members if appropriate, is established to ensure fairness and appropriate expertise. The charge to the subcommittee may include any of the following activities:

a. Review of study in question;
b. Review of monitoring or audit reports on the study, if applicable;
c. Review of relevant documentation, including consent forms, case report forms, as well as participants' research or medical files related to the conduct of the study;
d. Interviews of research or clinical personnel as necessary;
e. Preparation by the CPHS Director of a written summary report of the subcommittee’s findings, which is presented to the full CPHS at its next or an ad hoc meeting as necessary;
f. Recommendations for CPHS action as appropriate.

**7.5.3 Final Review of Non-Compliance**
The results of any inquiry into a report of non-compliance are reviewed at a convened CPHS meeting. A subcommittee’s inquiry report is available. If the results of the inquiry substantiate a finding of serious or continuing non-compliance, possible actions by the CPHS could include, but are not limited to:

a. Request a corrective and preventive action plan from the investigator.
b. Verify participant selection is appropriate and observation of the actual consent process.
c. Request increased data and safety monitoring of the research activity.
d. Request a directed audit for specific areas of concern.
e. Request a status report after each participant receives the initial or subsequent research interventions as appropriate.
f. Modify the frequency of continuing review.
g. Request additional education for the investigator and other research staff.
h. Notify current research participants, if the information about the non-compliance may affect their willingness to continue their participation.
i. Require modifications to the study procedures.
j. Require modifications to the information disclosed to potential participants during the consent process.
k. Require a special opportunity for current research participants to consent again to their participation.
l. Suspend some or all study activities (See below.); or
m. Terminate the study activities (See below.)

In the event the CPHS determines that the noncompliance is also an unanticipated problem involving risks to research participants or others, the procedures for CPHS review of such problems applies.

The investigator is informed in writing of any determinations made by the CPHS, their rationale, the basis for any action taken by the CPHS, and is given an opportunity to respond. If the CPHS determines that the non-compliance was serious or continuing, the results of the its final review will be reported as described below in section 7.6.

### 7.6 Reporting to Regulatory Agencies and Institutional Officials

CPHS office staff initiates these procedures promptly* when the CPHS takes any of the following actions:
a. Determines that an incident may be considered an unanticipated problem involving risks to research participants or others;
b. Determines that non-compliance was serious or continuing or both;
c. Suspends or terminates CPHS approval of research.

The CPHS Director or designee is responsible for preparing reports or letters that include the following information as applicable:

a. The nature of the event and its regulatory significance, namely an unanticipated problem involving risks to research participants or others, serious or continuing non-compliance, the suspension or termination of CPHS approval of research);
b. Name of the institution where the research is being conducted;
c. Title of the research project or grant proposal in which the incident occurred;
d. Name of the lead and site PIs for the study;
e. Number of the research project assigned by the CPHS office and the number of any applicable federal award, grant, contract, or cooperative agreement;
f. A detailed description of the incident, including the findings of the CPHS and the reasons for any CPHS determinations and actions;
g. Actions the investigator or the institution is taking, or plans to take, to address the incident, for example revise the study procedures, suspend enrollment, terminate the research activities, revise the consent form, inform enrolled participants, increase safety monitoring;
h. Plans, if any, for a follow-up or final report by the earlier of a specific date or when the corrective and preventive action plan has been implemented.

The CPHS Chair and the IO review the letter and revise the letter or report as needed.

The IO receives a copy of the correspondence or report. In addition, the CPHS Director or designee sends a copy of the report to *:

a. The CPHS, by including the letter in the next agenda as a notice.
b. The following Federal agencies:
   i. OHRP, if the study is subject to DHHS regulations or subject to a DHHS federal-wide assurance.*
   ii. FDA, if the study is subject to FDA regulation.
iii. If the study is conducted or funded by any Federal agency other than DHHS that is subject to the Common Rule, the report is sent to OHRP or the head of the agency as required by the agency.

iv. Reporting to a regulatory agency is not required if the incident occurred at a site that was not subject to direct oversight of the College and the agency has been notified of the incident by the PI, sponsor, another institution, or through other channels.

c. Lead and site PIs.

d. Sponsor, if appropriate.

e. Contract research organization, if the study is overseen by a contract research organization.

f. Department chairperson for the local PI;

g. The Privacy Officer of an involved covered entity, if the event involved unauthorized use, loss, or disclosure of individually identifiable patient information.

h. The Information Security Officer of an institution, if the event involved violations of applicable information security requirements.

i. Office of risk management, if appropriate;

j. Other appropriate institutional officials.

The report of the CPHS Director should be sent promptly after the final CPHS action*.

*In reporting serious or continuing non-compliance for VAMC studies, the report of the CPHS Director is reviewed and approved by the IO for Dartmouth College. The VAMC IO and R&D Administrative Office are responsible for sending copies of the report to the offices listed below.

a. OHRP in all cases.

b. If applicable, any funding agency other than DHHS subject to the Common Rule, unless the report to OHRP is sufficient under the agency's requirements.

c. Office of Research & Development for the Department of Veterans Affairs.

d. The Regional Office of the Office of Research Oversight in the Department of Veterans Affairs.

e. Director of the CPHS at the College.

f. The Director of the Veterans Integrated Service Network.

g. Other institutional officials, as applicable, including the FDA, CDC, Nuclear Regulatory Commission, NIH Office of Biotechnology Activities, and VA Network and Security Operations Center.